ORIGINAL RESEARCH

Maternal depression and antidepressant use during pregnancy and the risk of autism spectrum disorder in offspring

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Background: Results of some studies suggest that prenatal antidepressant exposure increases the risk of autism spectrum disorder (ASD) in offspring, while other studies suggest that depression independently increases the risk of having a child with ASD. Thus, confounding by indication is a concern.

Objective: The aim of this study was to estimate the risk of ASD in offspring of women who were exposed to antidepressants and/or had depression during pregnancy compared to unexposed women.

Materials and methods: We conducted a cohort study with nested sibling case–control analysis. Using the UK Clinical Practice Research Datalink (CPRD), we identified mother–baby pairs where the mother had ≥12 months of history before the delivery date and the child had ≥3 years of follow-up. Exposures during pregnancy were classified as 1) depression treated with antidepressants, 2) untreated depression, 3) other indications for antidepressant use, and 4) 4:1 match of unexposed women with no history of depression or antidepressant use. We calculated the prevalence of ASD and relative risk (RR) with 95% CI. In the sibling analysis, we compared exposure among ASD cases to that of non-ASD siblings born to the same mother. We calculated ORs and 95% CIs for women with treated and untreated depression, compared to unexposed.

Results: We identified 2,154 offspring with ASD among 194,494 mother–baby pairs. Compared to unexposed, the RR of ASD was 1.72 (95% CI 1.54–1.93) for treated depression and 1.50 (95% CI 1.28–1.75) for untreated depression, while the RR was not elevated in women who received antidepressants for other indications (RR =0.73, 95% CI 0.41–1.29). Additional analyses to assess the effects of severity of depression suggest that the risk of ASD in offspring increases with increasing severity, not with the antidepressant treatment. The results of the sibling analysis were similar to the main analysis.

Conclusion: Women with depression during pregnancy have an increased risk of having a child with ASD, regardless of antidepressant use.

Keywords: depression, pregnancy, antidepressants, autism, autism spectrum disorder

Plain language summary

Depression is a common condition in women, often occurring during childbearing years. Women may be given antidepressants by a doctor to treat depression during pregnancy. Results of prior studies suggest that antidepressant exposure during pregnancy increases the risk of having a child with autism spectrum disorder (ASD), while results of other studies suggest that depression itself increases the chance of having a child with ASD. This study, using the UK Clinical Practice Research Datalink (CPRD), was conducted to estimate the risk of

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ASD in children of women who took antidepressants and/or had depression during pregnancy compared to unexposed women. The results of this study suggest that women with depression during pregnancy, regardless of antidepressant use, have an increased risk of having a child with ASD compared to women who do not have depression.

Introduction

Depression is a common condition in women, with prevalence peaking during childbearing years.[1–3] Untreated depression during pregnancy may have a negative impact on the offspring,[4,5] including problems involving affect, cognition, and neuroendocrine and brain function.[6] Prescribing of antidepressants during pregnancy, currently estimated between 1% and 13% of pregnant women, increased steadily between 1990 and 2005 and have since remained stable.[7–13] Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed antidepressants during pregnancy. There are concerns regarding the impact of prenatal antidepressant use on offspring because these drugs are known to cross the placenta and serotonin is critical for fetal brain development.[14,15]

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by deficits in social function and communication with the presence of restricted or repetitive behavior, interests, or activities. Epidemiological studies have shown dramatic increases in the rate of ASD diagnosis,[16–18] now estimated to affect around 1% of children globally.[16] The etiology of ASD is not well understood; however, both genetic and environmental factors are thought to play an important role. It has been theorized that dysfunctional serotonin signaling is a potential causal mechanism for ASD.[15,19]

The results of epidemiological studies of maternal prenatal antidepressant medication use (primarily SSRIs) and the risk of ASD in offspring have been mixed.[20–32] Some studies found increased risks of 1.5–4.5-fold,[20–22,26,28] while the results of other studies suggest that depression independently increases the risk of having a child with ASD.[23–25] Thus, confounding by indication is a concern.

We conducted a cohort study using a large electronic database with mother–baby linkage to estimate the risk of ASD in offspring of women who were exposed to antidepressants and/or had depression during pregnancy compared to unexposed women. We also conducted a nested sibling case–control analysis to control for genetic risk factors, other potential confounders, and maternal predisposition to depression.

Materials and methods
Data source
This study was conducted using the CPRD, a large, population-based electronic medical database. Participating general practitioners (GPs) contributed de-identified data including medical diagnoses (recorded using Read codes), details of prescription drugs, symptoms, and specialist visits.[33,34] Results of validation studies indicated that the data were of high accuracy and completeness.[35–37] The mother–baby linkage has been used in previous studies on maternal drug exposures and outcomes in offspring.[38–42]

Source population
The source population consisted of mothers, aged 13–44 years, and their live-born, singleton infants born between 1989 and 2011. Mothers were required to have at least 12 months of recorded history before the baby's delivery date, and the children were required to have at least 3 years of follow-up after birth. We excluded mother–baby sets where the delivery date could not be identified.

Cohort identification
The exposure period for mothers was the year before the baby's delivery date. Cohort entry was the baby's delivery date minus 365 days. From the source population, we identified three cohorts of exposed women: 1) those with depression treated with antidepressants (diagnosis and ≥1 antidepressant prescription during the exposure period), 2) those with untreated depression (recent history of treated depression but no antidepressants during the exposure period), and 3) those who were prescribed antidepressants for other indications (women in this group had no history of depression). Other indications for antidepressant use included anxiety, bipolar disorder, manic disorder, schizophrenia, migraine, neuralgia, fibromyalgia, insomnia, smoking cessation, or pain. To each exposed mother, we matched (4:1) unexposed women who had neither depression nor prescriptions for antidepressants prior to the baby's delivery date and matched on mother's year of birth (±2 years), baby's year of birth (±2 years), and general practice attended (Figure 1).

Antidepressant exposure
We evaluated the timing of antidepressant use during the exposure period as follows: preconception (delivery date minus 281–365 days), first trimester (delivery date minus 191–280 days), second trimester (delivery date minus 101–190 days), and third trimester (delivery date minus 100
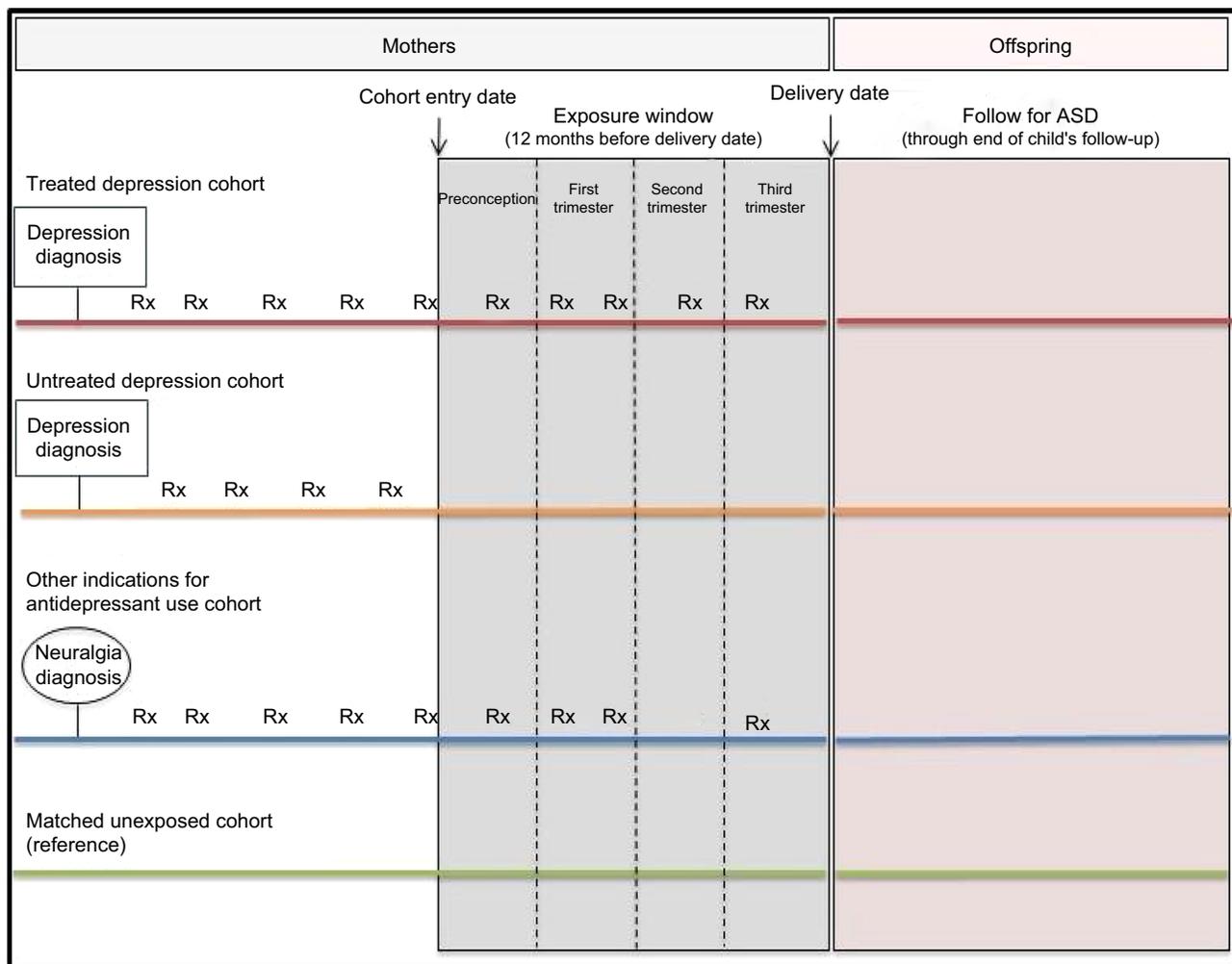
Figure I Diagram of cohort identification, exposure window definition, and follow-up period.
Note: Rx, antidepressant prescription.
Abbreviation: ASD, autism spectrum disorder.

days; Figure 1). We calculated the prescription duration as the total number of pills prescribed divided by the number of pills prescribed per day. We also evaluated antidepressant class: SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), other antidepressants (eg, monoamine oxidase inhibitors, tetracyclic antidepressants, and norepinephrine and dopamine reuptake inhibitors), and multiple classes.

ASD case identification

We identified all children with at least one Read diagnostic code indicating ASD recorded at any time, including codes for autism, Asperger's syndrome, and pervasive developmental disorder (PDD). Validation studies have indicated that over 90% of ASD diagnoses in the CPRD were confirmed upon record review.[43,44] Validation results of this study have been

described previously,[45] and the Read codes used to identify cases are listed in Table S1.

Nested sibling case–control analysis

We conducted a sibling case–control analysis of maternal pregnancy exposures in ASD cases compared to non-ASD siblings of the same mother. This analysis controlled for genetic, time-invariant, and unmeasured confounders (eg, socioeconomic status, mother's education, and race/ethnicity) as well as maternal predisposition to depression. From the cohort study, we identified all ASD cases who had one or more siblings. The sibling was eligible as a control if he/she was the same sex as the ASD case, had no diagnosis of ASD at any time, and had at least 3 years of follow-up after birth and if the mother had at least 12 months of recorded history before the sibling's delivery date.

Covariates

We assessed the presence of various covariates at the cohort entry date (cohort study) and at the child's delivery date (sibling analysis). Covariates were identified from literature review as well as by comparing characteristics between the exposed and nonexposed cohorts. We considered characteristics that changed the main effect estimate by more than 10% to be potential confounders. We evaluated the following covariates in the mothers: age, body mass index (BMI: <18.5, 18.5–24.9, 25.0–29.9, ≥30, unknown), smoking status (never, current, former, unknown), alcohol abuse, drug abuse, diabetes, hypertension, hyperlipidemia, anxiety, other psychiatric conditions (bipolar, schizophrenia), and parity. We evaluated duration of the last episode of treated depression prior to cohort entry, calculated as continuous use of any antidepressant until either cohort entry or a gap of at least 180 days between prescriptions, categorized as <12, 12–35.9, and 36+ months, or unknown duration (those who had the first depression diagnosis recorded at the start of their record and had duration of <36 months). We also evaluated the number of different antidepressants prescribed during the last episode of treated depression. Finally, we evaluated sex, birth order, and year of birth in the children.

Statistical analyses

We estimated the prevalence of ASD with 95% CIs for each cohort, calculated as the number of ASD cases divided by the number of pregnancies that resulted in live-born children who survived to age 3 years. We estimated the prevalence of ASD overall and stratified by the timing of exposure during pregnancy (trimester) and antidepressant class. The RR and 95% CI of ASD in the offspring of women with treated depression and untreated depression and women who used antidepressants for other indications, compared to unexposed, were estimated using generalized estimating equations via PROC GENMOD in SAS (SAS Institute, Cary NC, USA) to adjust for the inclusion of women with more than one pregnancy. We also calculated RRs adjusted for maternal BMI, smoking status, parity, anxiety, or other psychiatric disorders. To assess effect modification, we conducted analyses stratified by parity, maternal duration of depression history, number of different types of antidepressants prescribed in the last episode of depression, and presence or absence of anxiety/other psychiatric disorders. We conducted three sensitivity analyses restricted to 1) women with at least 3 years of recorded history prior to the baby's delivery date, 2) children with at least 5 years of follow-up, and 3) ASD cases with additional Read codes that supported the presence of

ASD (eg, specialist referrals and visits, treatment, or codes indicating developmental delay, speech delay, or behavioral problems) to assess the potential for case misclassification.

For the sibling analysis, we used conditional logistic regression to estimate ORs with 95% CIs, adjusted for child's birth year, child's birth order, and maternal age at delivery. All analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, USA).

The protocol for this study was reviewed and approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency (MHRA) database research (protocol number 15_256), and the protocol was made available to the journal reviewers. This study is based in part on data from the CPRD obtained under license from the UK Medicines and Healthcare Products Regulatory Agency. These data are provided by patients and collected by the National Health Service (NHS) as part of their care and support. The interpretation and conclusions contained in this study are those of the author's alone.

Results

We identified 40,387 eligible exposed mother–baby pairs, of whom 12,994 women had untreated depression, 25,778 had treated depression, and 1,615 received antidepressants for indications other than depression (32.4% for anxiety or other psychiatric disorders, 26.0% for pain, 13.9% for migraine, 11.8% for insomnia, 11.8% for smoking cessation, and 4.1% for neuralgia or fibromyalgia). To these, we matched 154,107 unexposed mother–baby pairs. Exposed women were more likely than unexposed to be current smokers and to have anxiety/other psychiatric diagnoses at cohort entry (Table 1). The mean length of recorded history in the mothers was long (>10 years) and similar for each cohort. The length of follow-up in the babies was also long (>8 years) and similar for the exposed and unexposed cohorts.

We identified 2,154 ASD cases (Table 1). The majority of cases (84.8%) were male, and 50.7% were first born. The peak age at first ASD diagnosis was 3 years, and more than half were diagnosed before age 6 years (median 5.8 years). The prevalence of ASD, per 1,000 pregnancies, was 9.7 (95% CI 9.3–10.2) among children of unexposed women, 15.1 (95% CI 13.1–17.3) for untreated depression, 17.3 (95% CI 15.8–19.0) for treated depression, and 7.4 (95% CI 4.0–12.6) for those who received antidepressants for other indications. Compared to children of unexposed women, the adjusted RRs were 1.49 (95% CI 1.27–1.75) and 1.70 (95% CI 1.51–1.92) for children whose mothers had untreated and treated depression, respectively, and 0.73 (95% CI 0.41–1.29)

Table 1 Characteristics of mothers and offspring, by exposure

	Unexposed N=154,107	Exposed N=40,387	Exposure type		
			Untreated depression N=12,994	Treated depression N=25,778	Other indications for antidepressant use N=1,615
Maternal characteristics at cohort entry					
Year of cohort entry					
<1995	11,995 (7.8)	3,051 (7.6)	1,293 (10.0)	1,663 (6.5)	95 (5.9)
1995–1999	29,623 (19.2)	7,677 (19.0)	2,773 (21.3)	4,637 (18.0)	267 (16.5)
2000–2004	53,212 (34.5)	14,007 (34.7)	4,355 (33.5)	9,139 (35.5)	513 (31.8)
2005–2009	52,027 (33.8)	13,636 (33.8)	5,080 (31.4)	8,944 (34.7)	612 (38.9)
2010–2011	7,250 (4.7)	2,016 (5.0)	493 (2.8)	1,395 (5.4)	128 (7.9)
Age at cohort entry (years)					
13–19	9,757 (6.3)	2,341 (5.8)	662 (5.1)	1,563 (6.1)	116 (7.2)
20–24	31,904 (20.7)	8,841 (21.9)	3,008 (23.2)	5,486 (21.3)	347 (21.5)
25–29	44,146 (28.7)	11,201 (27.7)	3,793 (29.2)	6,964 (27.0)	444 (27.5)
30–34	43,218 (28.0)	11,072 (27.4)	3,469 (26.7)	7,161 (27.8)	442 (27.4)
35–39	21,256 (13.8)	5,796 (14.4)	1,743 (13.4)	3,833 (14.9)	220 (13.6)
40–45	3,826 (2.5)	1,136 (2.8)	319 (2.5)	771 (3.0)	46 (2.9)
BMI					
<18.5	4,815 (3.1)	1,721 (4.3)	553 (4.3)	1,097 (4.3)	71 (4.4)
18.5–24.9	58,676 (38.1)	16,687 (41.3)	5,525 (42.5)	10,494 (40.7)	668 (41.4)
25–29.9	23,216 (15.1)	7,597 (18.8)	2,541 (19.6)	4,769 (18.5)	287 (17.8)
≥30	12,955 (8.4)	5,919 (14.7)	1,888 (14.5)	3,839 (14.9)	192 (11.9)
Unknown	54,445 (35.3)	8,463 (21.0)	2,487 (19.1)	5,579 (21.6)	297 (24.6)
Smoking status					
Nonsmoker	67,525 (43.8)	13,995 (34.7)	4,733 (36.4)	8,666 (33.6)	596 (36.9)
Smoker	27,848 (18.1)	15,618 (38.7)	5,126 (39.5)	9,951 (38.6)	541 (33.5)
Ex-smoker	16,261 (10.6)	5,837 (14.5)	1,886 (14.5)	3,721 (14.4)	230 (14.2)
Unknown	42,473 (27.6)	4,937 (12.2)	1,249 (9.6)	3,440 (13.3)	248 (15.4)
Parity					
0	79,179 (51.4)	15,190 (37.6)	4,792 (36.9)	9,629 (37.4)	769 (47.6)
1	47,913 (31.1)	13,877 (34.4)	4,629 (35.6)	8,768 (34.0)	480 (29.7)
≥2	18,699 (12.1)	9,088 (22.5)	2,828 (21.8)	5,967 (21.2)	293 (18.1)
Unknown	8,316 (5.4)	2,232 (5.5)	745 (5.7)	1,414 (5.5)	73 (4.5)
Comorbidities					
Anxiety	6,125 (4.0)	12,735 (31.5)	4,149 (31.9)	8,101 (31.4)	485 (30.0)
Other psychiatric diagnoses	529 (0.3)	2,260 (5.6)	664 (5.1)	1,514 (5.9)	82 (5.1)
Alcohol abuse	1,987 (1.3)	1,595 (4.0)	470 (3.6)	1,093 (4.2)	32 (2.0)
Drug abuse	419 (0.3)	1,130 (2.8)	309 (2.4)	797 (3.1)	24 (1.5)
Hypertension	1,424 (0.9)	575 (1.4)	161 (1.2)	389 (1.5)	25 (1.6)
Diabetes	622 (0.4)	295 (0.7)	76 (0.6)	205 (0.8)	14 (0.9)
Hyperlipidemia	323 (0.2)	160 (0.4)	42 (0.3)	114 (0.4)	4 (0.3)
Cardiovascular disease	1,218 (0.8)	539 (1.3)	156 (1.2)	351 (1.4)	32 (2.0)
Thyroid disease	2,072 (1.3)	972 (2.4)	267 (2.1)	679 (2.6)	26 (1.6)
ASD (in mother)	6 (0.0)	5 (0.0)	1 (0.0)	4 (0.0)	0 (0.0)
ADHD (in mother)	64 (0.0)	33 (0.1)	9 (0.1)	24 (0.1)	0 (0.0)

(*Continued*)

Table 1 (*Continued*)

	Unexposed N=154,107	Exposed N=40,387	Exposure type		
			Untreated depression N=12,994	Treated depression N=25,778	Other indications for antidepressant use N=1,615
Characteristics of offspring					
Child sex					
Female	69,667 (45.2)	18,308 (45.3)	5,898 (45.4)	11,682 (45.3)	728 (45.1)
Male	84,440 (54.8)	22,079 (54.8)	7,096 (54.6)	14,096 (54.7)	887 (54.9)
Years of follow-up					
Mean ± SD	8.7±4.6	8.7±4.5	9.1±4.7	8.5±4.4	8.2±4.4
Median	7.6	7.6	8.0	7.5	7.0
IQR	4.9–11.5	4.9–11.4	5.1–12.0	4.9–11.2	4.6–10.8
Characteristics of ASD cases (N=2,154)					
ASD cases (n)	1,500	654	196	446	12
Child sex					
Female	228 (15.2)	116 (17.7)	30 (15.3)	83 (18.6)	3 (25.0)
Male	1,272 (84.8)	538 (82.3)	166 (84.7)	363 (81.4)	9 (75.0)
Age at ASD diagnosis (years)					
Mean ± SD	6.5±3.4	6.9±3.6	7.5±4.0	6.5±3.4	8.6±4.8
Median	5.6	6.2	6.6	5.9	7.9
IQR	3.8–8.7	3.9–9.2	3.5–10.2	3.6–8.6	4.8–11.3
Birth order					
1	812 (54.1)	280 (42.8)	81 (41.3)	191 (42.8)	8 (66.7)
2	447 (29.8)	204 (31.2)	65 (33.2)	137 (30.7)	2 (16.7)
3+	147 (9.8)	130 (19.9)	37 (18.9)	91 (20.4)	2 (16.7)
Unknown	94 (6.3)	40 (6.1)	13 (6.6)	27 (6.1)	0 (0.0)

Note: Data are presented as n (%) throughout, unless otherwise indicated (mean, median, IQR).
Abbreviations: ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

for children of mothers who received antidepressants for other indications (Table 2).

When we evaluated the timing of antidepressant use (Table 3), there was a small increased risk for women with depression who received antidepressants during the preconception period only (RR =1.42, 95% CI 1.14–1.76), compared to unexposed, whereas the risk was higher among children of women with depression who were treated during one or more trimesters of pregnancy (RR =1.82, 95% CI 1.60–2.06). The RR was elevated for antidepressant use in all trimesters of pregnancy. When we evaluated exposure by antidepressant class (Table 3), the risks were elevated among those who were exposed to SSRIs only (1.68, 95% CI 1.46–1.92), TCAs only (1.95, 95% CI 1.58–2.40), and for users of multiple classes (1.78, 95% CI 1.29–2.45), compared to children of unexposed women. The RRs were null for children of women who received antidepressants for indications other than depression, regardless of the timing of use during pregnancy (Table 3) and antidepressant class (Table 3).

We conducted three analyses to evaluate effect modification by the severity of depression (Table 4). The risk of ASD increased with longer duration of depression before cohort entry for both treated and untreated depression, although the rates were slightly higher among children of women with treated depression. We also stratified the estimates by the number of different antidepressants prescribed before cohort entry: compared to children of unexposed women, the risk of ASD was elevated among children of women who were prescribed two or more different types of antidepressants before cohort entry, regardless of having treated or untreated depression during pregnancy. Finally, among children of women with treated or untreated depression, the risk of ASD was elevated regardless of the presence of anxiety/other psychiatric disorders; however, the risks were higher among depressed women with comorbid anxiety/psychological disorder. In contrast, among children of unexposed women and women who used antidepressants for other indications, the risk of ASD was only elevated among those whose mothers had comorbid anxiety/psychological disorder.

The results were similar to the main analysis when we stratified by parity (no prior births, ≥1 prior birth) and in all three sensitivity analyses, where we restricted the population

Table 2 Prevalence of ASD by exposure during a year before delivery date

Exposure	ASD cases N=2,154	Pregnancies N=194,494	Prevalence per 1,000 pregnancies (95% CI)	Crude RR (95% CI)	Adjusted RR[a] (95% CI)
Unexposed	1,500	154,107	9.7 (9.3–10.2)	1.00 (reference)	1.00 (reference)
Untreated depression	196	12,994	15.1 (13.1–17.3)	1.55 (1.34–1.80)	1.49 (1.27–1.75)
Treated depression	446	25,778	17.3 (15.8–19.0)	1.78 (1.60–1.98)	1.70 (1.51–1.92)
Other indications for antidepressant use	12	1,615	7.4 (4.0–12.6)	0.76 (0.43–1.35)	0.73 (0.41–1.29)

Notes: [a]Adjusted for child sex, maternal BMI, smoking status, parity, anxiety, and other psychiatric disorders.
Abbreviations: ASD, autism spectrum disorder; BMI, body mass index.

to 1) children of women who had at least 3 years of recorded history in which to assess exposure, 2) children who had at least 5 years of follow-up in which to assess the impact of follow-up time requirements, and 3) cases with other supporting evidence to assess case misclassification.

Nested sibling case–control analysis

There were 601 same-sex siblings who did not have an ASD diagnosis matched to 531 ASD cases (Table S2). After adjusting for child's birth year, birth order, and maternal age at delivery, the risk of ASD in offspring of mothers with untreated depression was 1.18 (95% CI 0.64–2.20) and 1.53 (95% CI 0.89–2.62) for treated depression, compared to unexposed.

Discussion

The results of our study suggest that women with depression during pregnancy have an increased risk of having a child with ASD compared to unexposed women. The risk was slightly higher among women with treated depression (RR =1.70) compared to untreated depression (RR =1.49); however, the finding that the risk of ASD was not elevated in women who were prescribed antidepressants for other indications (RR =0.73) provides evidence that antidepressants are not themselves associated with the increased risk. Rather, the results of our study suggest that the slight increase in risk with antidepressant use reflects differences in the underlying severity of depression.

Numerous published studies have reported an increased risk of ASD in offspring associated with prenatal antidepressant use, although the magnitude of effects varied widely.[20–32] In studies that accounted for potential confounding by indication, the observed increase in risk with the use of antidepressants was attenuated when results were adjusted for maternal affective disorders.[23–26,28,32,33] Hviid et al[23] reported that adjustment for psychiatric diagnoses

contributed the biggest change in effect (crude incidence rate ratio [IRR] =1.62, 95% CI 1.23–2.13 vs fully adjusted IRR =1.20, 95% CI 0.90–1.61). Clements et al[27] reported an independent effect of maternal major depressive disorder of 1.74 (95% CI 1.35–2.23), inclusion of which in the model attenuated the effect of antidepressant use during pregnancy from 1.49 (95% CI 1.01–2.18) to 1.10 (95% CI 0.70–1.70). In three studies that conducted analyses restricted to women with a history of psychiatric disorders, antidepressant use during pregnancy was not associated with a material increase in ASD risk.[22,26,28] Two recent studies estimated that the risk of having a child with ASD was around 1.4 among women who used antidepressants before (but not during) pregnancy, while the risk among women exposed during pregnancy was around 1.60 to 1.75.[31,32] These are similar to our estimates among women with untreated (1.49) and treated depression (1.70). Finally, if antidepressant use does increase the risk of ASD, the elevation should be present among women who were prescribed antidepressants for other indications; however, in our study, there was no increased risk of having an offspring with ASD among these women. Overall, the results of these studies suggest that the observed increase in risk is associated with depression, not its treatment.

The results of our various stratified analyses suggest that there are differences in risk by the severity of depression. By definition, the untreated depression cohort is likely to have less severe depression than those in the treated depression cohort; thus, the observed difference in risk may reflect differences in depression severity. In addition, the risk of ASD among women who received SSRIs only (RR =1.68), which in the UK are often prescribed as first-line treatment, was slightly lower than that of women who were prescribed TCAs only (RR =1.95), which are often prescribed as second-line therapy.[46] Finally, the risk of having a child with ASD was higher for women who were prescribed two or more differ-

Table 3 Prevalence of ASD by exposure, stratified by timing of antidepressant use and antidepressant class

	ASD cases	Pregnancies	Prevalence per 1,000 pregnancies (95% CI)	Crude RR (95% CI)	Adjusted RR[a] (95% CI)
By timing of antidepressant use					
Unexposed	1,500	154,107	9.7 (9.3–10.2)	1.00 (reference)	1.00 (reference)
Untreated depression	196	12,994	15.1 (13.1–17.3)	1.55 (1.34–1.80)	1.51 (1.29–1.77)
Treated depression					
Preconception only	91	6,455	14.1 (11.4–17.2)	1.45 (1.17–1.79)	1.42 (1.14–1.76)
During pregnancy	355	18,968	18.7 (16.8–2.07)	1.89 (1.68–2.11)	1.82 (1.60–2.06)
First trimester only	193	10,694	18.1 (15.6–20.7)	1.85 (1.60–2.15)	1.79 (1.53–2.10)
Second trimester only	6	417	14.4 (5.8–29.9)	1.48 (0.66–3.30)	1.44 (0.64–3.21)
Third trimester only	25	1,073	23.3 (15.4–33.9)	2.40 (1.61–3.42)	2.37 (1.59–3.53)
Entire pregnancy (T1–T3)	80	3,927	20.4 (16.3–25.2)	2.09 (1.67–2.62)	2.00 (1.58–2.08)
Multiple trimesters	51	3,212	15.9 (12.0–20.7)	1.63 (1.23–2.16)	1.56 (1.18–2.08)
Other indications for antidepressant use					
Preconception only	3	385	7.8 (2.0–21.2)	0.80 (0.26–2.49)	0.80 (0.26–2.49)
During pregnancy	9	1,230	7.3 (3.6–13.4)	0.75 (0.39–1.45)	0.71 (0.37–1.37)
First trimester only	4	805	5.0 (1.6–12.0)	0.51 (0.19–1.36)	0.49 (0.18–1.30)
Second trimester only	0	50	b	b	b
Third trimester only	1	69	14.5 (0.7–71.5)	1.49 (0.21–10.58)	1.39 (0.20–9.87)
Entire pregnancy (T1–T3)	3	126	23.8 (6.1–64.8)	2.45 (0.79–7.59)	2.06 (0.66–6.41)
Multiple trimesters	1	180	5.6 (0.3–27.4)	0.57 (0.08–4.05)	0.56 (0.08–4.01)
By antidepressant class					
Unexposed	1,500	154,107	9.7 (9.3–10.2)	1.00 (reference)	1.00 (reference)
Untreated depression	196	12,994	15.1 (13.1–17.3)	1.55 (1.34–1.80)	1.50 (1.28–1.75)
Treated depression					
SSRI only	292	17,362	16.8 (14.8–18.8)	1.73 (1.52–1.96)	1.68 (1.46–1.92)
SNRI only	13	1,246	10.4 (5.8–17.4)	1.07 (0.62–1.85)	1.03 (0.60–1.78)
TCA only	98	4,856	20.2 (16.5–24.5)	2.07 (1.69–2.54)	1.95 (1.58–2.40)
Other antidepressants only	3	115	26.1 (6.6–71.0)	2.68 (0.86–8.32)	2.38 (0.77–7.41)
Multiple classes	40	2,199	18.2 (13.2–24.5)	1.87 (1.37–2.56)	1.78 (1.29–2.45)
SSRI + TCA	21	1,258	16.7 (10.6–25.1)	1.71 (1.11–2.64)	1.66 (1.07–2.56)
SSRI + SNRI	13	621	20.9 (11.6–3.5)	2.15 (1.25–3.71)	1.99 (1.15–3.45)
Other combinations	6	320	18.8 (7.6–39.0)	1.93 (0.86–4.29)	1.86 (0.83–1.76)
Other indications for antidepressant use					
SSRI only	6	719	8.3 (3.4–17.4)	0.86 (0.38–1.93)	0.79 (0.35–1.76)
SNRI only	0	83	b	b	b
TCA only	6	761	7.9 (3.2–16.4)	0.81 (0.36–1.81)	0.78 (0.35–1.75)
Other antidepressants only	0	2	b	b	b
Multiple classes	0	50	b	b	b

Notes: [a]Adjusted for child sex, maternal BMI, smoking status, parity, anxiety, and other psychiatric disorders. [b]Too few cases to calculate a stable estimate.
Abbreviations: ASD, autism spectrum disorder; BMI, body mass index; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

ent types of antidepressants before cohort entry as well as among women with anxiety or other psychiatric disorders, regardless of antidepressant exposure during pregnancy. This interpretation is supported by the results of other published studies that used specialist care records to ascertain depression status.[24,25,29] Finally, three studies reported higher risks with SSRI exposure in the second and third trimester of pregnancy.[25,29,32] In our analysis, the risk estimates were slightly higher for women with depression who were prescribed antidepressants during the third trimester or for the entire pregnancy than for women with depression who were prescribed antidepressants during first trimester only. It is possible that higher risk estimates that persist into late pregnancy reflect effects of depression severity, as women

Table 4 Prevalence of ASD by exposure, stratified by the duration of the last episode of depression before cohort entry, number of antidepressants prescribed during the last episode of depression before cohort entry, and the presence of anxiety and/or other psychiatric disorders

	ASD cases	Pregnancies	Prevalence per 1,000 pregnancies (95% CI)	Crude RR (95% CI)	Adjusted RR[a] (95% CI)
Duration of the last episode of depression					
Unexposed	1,500	154,107	9.7 (9.3–10.2)	1.00 (reference)	1.00 (reference)
Untreated depression					
<12 months	123	8,557	14.4 (12.0–17.1)	1.48 (1.23–1.77)	1.45 (1.20–1.75)
12–35.9 months	61	3,683	16.6 (12.8–21.1)	1.93 (1.59–2.33)	1.68 (1.29–2.18)
≥36 months	10	641	15.6 (7.9–27.8)	1.60 (0.86–2.99)	1.52 (0.81–2.84)
Unknown	2	113	17.7 (2.9–58.5)	1.82 (0.45–7.28)	1.51 (0.38–6.04)
Treated depression					
<12 months	260	16,433	15.8 (14.0–17.8)	1.63 (1.43–1.85)	1.59 (1.38–1.83)
12–35.9 months	115	6,134	18.8 (15.6–24.2)	1.70 (1.32–2.20)	1.88 (1.54–2.30)
≥36 months	66	3,045	21.7 (16.9–27.4)	2.23 (1.74–2.85)	2.11 (1.63–2.74)
Unknown	5	166	30.1 (11.0–66.8)	3.09 (1.29–7.49)	2.90 (1.21–6.99)
Other indications for antidepressant use	12	1,615	7.4 (4.0–12.6)	0.76 (0.43–1.35)	0.74 (0.42–1.30)
Number of different antidepressants prescribed during the last episode of depression					
Unexposed	1,500	154,107	9.7 (9.3–10.2)	1.00 (reference)	1.00 (reference)
Untreated depression					
1	142	10,269	13.8 (11.7–16.3)	1.42 (1.20–1.69)	1.39 (1.16–1.67)
≥2	52	2,628	19.8 (14.9–25.8)	2.03 (1.54–2.68)	1.94 (1.46–2.57)
Unknown	2	97	20.6 (3.5–68.1)	b	b
Treated depression					
1	293	18,161	16.1 (14.4–18.1)	1.66 (1.46–1.88)	1.62 (1.42–1.85)
≥2	146	7,463	19.6 (16.6–22.9)	2.01 (1.70–2.38)	1.91 (1.59–2.29)
Unknown	7	147	47.6 (20.8–94.2)	b	b
Other indications for antidepressant use	12	1,615	7.4 (4.0–12.6)	0.76 (0.43–1.35)	0.74 (0.42–1.30)
Anxiety/other psychiatric disorders					
Unexposed					
No anxiety/other psychiatric disorders	1,421	147,939	9.6 (9.1–10.1)	1.00 (reference)	1.00 (reference)
Anxiety/other psychiatric disorders	79	6,168	12.8 (10.2–15.9)	1.33 (1.06–1.67)	1.36 (1.09–1.72)
Untreated depression					
No anxiety/other psychiatric disorders	127	8,655	14.7 (12.2–17.4)	1.53 (1.27–1.83)	1.58 (1.31–1.90)
Anxiety/other psychiatric disorders	69	4,339	15.9 (12.5–20.0)	1.66 (1.30–2.11)	1.74 (1.37–2.23)
Treated depression					
No anxiety/other psychiatric disorders	283	17,282	16.4 (14.6–18.4)	1.70 (1.50–1.94)	1.76 (1.54–2.00)
Anxiety/other psychiatric disorders	163	8,496	19.2 (16.4–22.3)	2.00 (1.70–2.35)	2.08 (1.76–2.46)
Other indications for antidepressant use					
No anxiety/other psychiatric disorders	6	1,127	5.3 (2.2–11.1)	0.55 (0.25–1.24)	0.56 (0.25–1.25)
Anxiety/other psychiatric disorders	6	488	12.3 (5.0–25.6)	1.28 (0.57–2.85)	1.33 (0.59–2.96)

Notes: [a]Adjusted for child sex, maternal BMI, smoking status, parity, anxiety, and other psychiatric disorders. [b]Too little data to calculate a stable estimate.
Abbreviations: ASD, autism spectrum disorder; BMI, body mass index.

with more severe depression may not be able to discontinue antidepressant treatment during pregnancy.

Heritability is known to be a strong risk factor for ASD,[47] and genetic studies suggest that ASD and depression may share specific single-nucleotide polymorphisms;[48] thus, the increase in ASD in offspring of women with depression may reflect genetic predisposition. Sibling study designs offer a way to control for genetics as well as other unmeasured time-invariant factors. Sørensen et al[22] reported that, among 2,765 families in which at least one child had ASD, the risk of ASD in children exposed to antidepressants for any indication during pregnancy was 1.1 (95% CI 0.5–2.3) compared to their unexposed siblings. In their sibling comparison, Sujan et al[31] reported that the risk of ASD in children exposed to antidepressants in the first trimester was 0.83 (95% CI 0.62–1.13) compared to unexposed siblings. Brown et al[32] estimated that the risk of ASD in children exposed to two or more antidepressant prescriptions was 1.60 (95% CI 0.69–3.74) compared to unexposed siblings. In our sibling analysis based on 136 discordant sibling pairs, the risk of having a child with ASD among women with untreated depression (RR =1.18, 95% CI 0.64–2.20) was similar to that of the Sørensen et al's study, whereas the magnitude of effect was slightly higher among women with treated depression (RR =1.53, 95% CI 0.89–2.62), an estimate that was similar to that of the Brown et al's study. These sibling analyses suggest that after controlling for genetics and time-invariant confounders, prenatal antidepressant use does not significantly increase the risk of ASD in offspring, although there may remain a difference in risk by the severity of depression during pregnancy.

Strengths of our population-based study include use of the CPRD, a large, validated, longitudinal primary care database known for highly accurate diagnoses, completeness of drug prescribing information, and mother–baby linkage. All information on diseases and drug exposures was recorded prospectively; therefore, there is no risk of recall bias. We evaluated the effect of all types of commonly prescribed antidepressants, not just SSRIs. We matched the cohorts on year of entry to control for confounding related to changes in prescribing of antidepressants during pregnancy and in ASD diagnostic criteria and screening practices during the study period. ASD diagnoses in the CPRD have been shown to be of high validity,[43–45] and the prevalence of ASD among unexposed women in our study was similar to that reported in other studies.[16,49–52] We found known risk factors to be independently associated with ASD (eg, child sex and parity), providing further confidence in the data quality. We relied on GP-recorded diagnoses of depression and ASD, rather than

being restricted to diagnoses made in secondary or specialty care settings. Therefore, our study represents a range of depression and ASD severity, and it is unlikely that these diagnoses are underreported in these data. The mean length of recorded history in the mothers (~10 years) and follow-up in the babies (~8 years) was long and similar for each cohort; thus, we are unlikely to have misclassified exposure status in the mothers or to have missed ASD cases. We were able to control for genetics, unmeasured time-invariant factors, and maternal predisposition for depression by conducting a sibling analysis. Finally, we carefully controlled for confounding by indication by creating separate cohorts of pregnant women with treated and untreated depression and with other indications for antidepressant use. Although this last cohort of women was small (n=1,615), this was the first time this association has been evaluated in a cohort of pregnant women who used antidepressants for other indications of use.

We did not have complete information on fathers and, therefore, were unable to evaluate the effects of paternal risk factors on this association. We were unable to evaluate the effect of other indications for antidepressant use in the sibling analysis because of small numbers (n=2). Drug information in the CPRD covers written, but not dispensed prescriptions; therefore, we cannot be sure that women used all the prescribed antidepressants. Exposure misclassification may have occurred if a woman stopped using her prescription soon after she found out she was pregnant, particularly in the analysis by the timing of exposure; however, the RRs did not materially change among those with repeated prescriptions. We did not evaluate the effect of antidepressant dose in this study; this should be evaluated in future research on this association. We did not have information on socioeconomic status or race/ethnicity and, therefore, we could not explore these as covariates. However, the population of the UK is predominantly white, and we matched on general practice attended which may have controlled for socioeconomic status to some degree because people who attend the same practices tend to live in the same communities. Finally, there is concern about the potential for detection bias in all studies evaluating this association; that is, children of mothers with depression may be screened more frequently by their GPs. However, it is unlikely that differential case ascertainment by exposure occurred because the length of follow-up in children was long (~8 years) and the age at ASD diagnosis was similar for all cohorts. In addition, only 0.3% of the babies in our study were born after the publication of the first study that suggested an association between prenatal antidepressant use and ASD; thus, changes in screening practices by maternal

exposure status are unlikely to have materially impacted our study results.

Conclusion

The results of our study suggest that, compared to unexposed women, women with depression during pregnancy have an increased risk of having a child with ASD, regardless of antidepressant use. It is reassuring that 97% of woman who used antidepressants during pregnancy in this study did not have a child with ASD. Future research directions include further investigation into severity of depression on this association, evaluation of antidepressant dose, and replication of the analysis in pregnant women who use antidepressants for other indications among a large cohort of women.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Read codes indicating ASDs

	Read code description
ASDs	
E140.00	Infantile autism
E140000	Active infantile autism
E140100	Residual infantile autism
E140.12	Autism[a]
E140.13	Childhood autism
E140000	Active infantile autism
E140z00	Infantile autism NOS
Eu84000	[X]Childhood autism
Eu84011	[X]Autistic disorder[a]
Eu84012	[X]Infantile autism
Eu84100	[X]Atypical autism
Eu84z11	[X]ASD
Asperger's syndrome	
Eu84500	[X]Asperger's syndrome[a]
PDD	
Eu84.00	[X]PDDs
Eu84y00	[X]Other PDDs
Eu84z00	[X]PDD; unspecified

Note: [a]Indicates Read codes most frequently used by GPs to indicate ASD in the CPRD.
Abbreviations: ASD, autism spectrum disorder; CPRD, Clinical Practice Research Datalink; GPs, general practitioners; NOS, not otherwise specified; PDD, pervasive developmental disorder.

Table S2 Sibling analysis: characteristics of ASD cases and same-sex siblings

	ASD cases N=531 (%)	Siblings N=601 (%)	Univariate OR (95% CI)
Child characteristics			
Year of birth			
<1995	24 (4.5)	62 (10.3)	1.0 (reference)
1995–1999	123 (23.2)	133 (22.1)	2.07 (1.37–3.13)
2000–2004	220 (41.4)	181 (30.1)	3.48 (2.25–5.39)
2005–2009	154 (29.0)	185 (30.8)	2.08 (1.29–3.34)
2010–2011	10 (1.9)	40 (6.7)	0.74 (0.38–1.46)
Child sex			
Female	75 (14.1)	82 (13.6)	Matched
Male	456 (85.9)	519 (86.4)	Matched
Birth order			
First born	233 (43.9)	254 (42.3)	1.0 (reference)
Second born	245 (46.1)	253 (42.1)	1.03 (0.86–1.23)
Third born or higher	53 (10.0)	94 (15.6)	0.79 (0.54–1.16)
Maternal characteristics			
Age at delivery (years)			
13–19	18 (3.4)	23 (3.8)	0.98 (0.50–1.93)
20–24	111 (20.9)	149 (24.8)	1.0 (reference)
25–29	184 (34.7)	169 (28.1)	1.54 (1.08–2.18)
30–34	128 (24.1)	165 (27.5)	1.13 (0.73–1.74)
35–39	71 (13.4)	77 (12.8)	1.31 (0.76–2.25)
40–45	19 (3.6)	18 (3.0)	1.64 (0.66–4.07)
BMI			
<18.5	15 (2.8)	20 (3.3)	0.85 (0.34–2.12)
18.5–24.9	156 (29.4)	170 (28.3)	1.0 (reference)
25–29.9	69 (13.0)	85 (14.1)	0.80 (0.47–1.36)
≥30	59 (11.1)	67 (11.2)	0.91 (0.47–1.76)
Unknown	232 (43.7)	259 (43.1)	0.86 (0.58–1.27)
Smoking status			
Nonsmoker	233 (43.9)	266 (44.3)	1.0 (reference)
Smoker	140 (26.4)	129 (21.5)	2.01 (1.16–3.47)
Ex-smoker	50 (9.4)	69 (1.5)	0.98 (0.53–1.82)
Unknown	108 (20.3)	137 (22.8)	0.95 (0.65–1.39)
Depression	137 (25.8)	134 (22.3)	1.56 (1.03–2.36)
Suicidal behaviors	25 (4.7)	28 (4.7)	2.52 (0.65–9.81)
Anxiety	83 (15.6)	101 (16.8)	0.95 (0.53–1.67)
Other psychiatric disorders	7 (1.3)	9 (1.3)	0.92 (0.23–3.71)

Abbreviation: BMI, body mass index.