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Antidepressants in pregnancy: applying causal epidemiological methods to understand service-use outcomes in women and long-term neurodevelopmental outcomes in exposed children

Hein Heuvelman, Neil M Davies, Yoav Ben-Shlomo, Alan Emond, Jonathan Evans, David Gunnell, Rachel Liebling, Richard Morris, Rupert Payne, Claire Storey, Maria Viner and Dheeraj Rai

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Antidepressants in pregnancy: applying causal epidemiological methods to understand service-use outcomes in women and long-term neurodevelopmental outcomes in exposed children

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Disclosure of interests of authors

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Primary conflicts of interest: David Gunnell reports grants/contracts from Bristol BRC, is a member of Policy and Research Committee, Global Advisory Committee and National Suicide Prevention Strategy Advisory Group. Rupert Payne is a member of the MHRA Pharmacovigilance Expert Advisory Group and was a member of HTA Efficient Study Designs-2 panel. Dheeraj Rai is PI on grant – maternal epilepsy, antiepileptic drugs during pregnancy and autism (1R01NS107607), main supervisor for PhD studentship on risk and benefits of antidepressants during pregnancy (building upon the results of the present study), main supervisor for NIHR predoctoral fellowship on methods to study risk benefit of medication use during pregnancy.

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Abstract

Antidepressants in pregnancy: applying causal epidemiological methods to understand service-use outcomes in women and long-term neurodevelopmental outcomes in exposed children

Hein Heuvelman,[1,2] Neil M Davies,[1,3,4] Yoav Ben-Shlomo,[1] Alan Emond,[1] Jonathan Evans,[1,5,6] David Gunnell,[1,5] Rachel Liebling,[7] Richard Morris,[1] Rupert Payne,[1] Claire Storey,[8] Maria Viner[8] and Dheeraj Rai[1,5,6*]

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Background: Antidepressants are commonly prescribed during pregnancy, despite a lack of evidence from randomised trials on the benefits or risks. Some studies have reported associations of antidepressants during pregnancy with adverse offspring neurodevelopment, but whether or not such associations are causal is unclear.

Objectives: To study the associations of antidepressants for depression in pregnancy with outcomes using multiple methods to strengthen causal inference.

Design: This was an observational cohort design using multiple methods to strengthen causal inference, including multivariable regression, propensity score matching, instrumental variable analysis, negative control exposures, comparison across indications and exposure discordant pregnancies analysis.

Setting: This took place in UK general practice.

Participants: Participants were pregnant women with depression.

Interventions: The interventions were initiation of antidepressants in pregnancy compared with no initiation, and continuation of antidepressants in pregnancy compared with discontinuation.

Main outcome measures: The maternal outcome measures were the use of primary care and secondary mental health services during pregnancy, and during four 6-month follow-up periods up to 24 months after pregnancy, and antidepressant prescription status 24 months following pregnancy. The child

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outcome measures were diagnosis of autism, diagnosis of attention deficit hyperactivity disorder and intellectual disability.

Data sources: UK Clinical Practice Research Datalink.

Results: Data on 80,103 pregnancies were used to study maternal primary care outcomes and were linked to 34,274 children with at least 4-year follow-up for neurodevelopmental outcomes. Women who initiated or continued antidepressants during pregnancy were more likely to have contact with primary and secondary health-care services during and after pregnancy and more likely to be prescribed an antidepressant 2 years following the end of pregnancy than women who did not initiate or continue antidepressants during pregnancy (odds $\text{ratio}_{\text{initiation}}$ 2.16, 95% confidence interval 1.95 to 2.39; odds $\text{ratio}_{\text{continuation}}$ 2.40, 95% confidence interval 2.27 to 2.53). There was little evidence for any substantial association with autism (odds $\text{ratio}_{\text{multivariableregression}}$ 1.10, 95% confidence interval 0.90 to 1.35; odds $\text{ratio}_{\text{propensityscore}}$ 1.06, 95% confidence interval 0.84 to 1.32), attention deficit hyperactivity disorder (odds $\text{ratio}_{\text{multivariableregression}}$ 1.02, 95% confidence interval 0.80 to 1.29; odds $\text{ratio}_{\text{propensityscore}}$ 0.97, 95% confidence interval 0.75 to 1.25) or intellectual disability (odds $\text{ratio}_{\text{multivariableregression}}$ 0.81, 95% confidence interval 0.55 to 1.19; odds $\text{ratio}_{\text{propensityscore}}$ 0.89, 95% confidence interval 0.61 to 1.31) in children of women who continued antidepressants compared with those who discontinued antidepressants. There was inconsistent evidence of an association between initiation of antidepressants in pregnancy and diagnosis of autism in offspring (odds $\text{ratio}_{\text{multivariableregression}}$ 1.23, 95% confidence interval 0.85 to 1.78; odds $\text{ratio}_{\text{propensityscore}}$ 1.64, 95% confidence interval 1.01 to 2.66) but not attention deficit hyperactivity disorder or intellectual disability; however, but results were imprecise owing to smaller numbers.

Limitations: Several causal-inference analyses lacked precision owing to limited numbers. In addition, adherence to the prescribed treatment was not measured.

Conclusions: Women prescribed antidepressants during pregnancy had greater service use during and after pregnancy than those not prescribed antidepressants. The evidence against any substantial association with autism, attention deficit hyperactivity disorder or intellectual disability in the children of women who continued compared with those who discontinued antidepressants in pregnancy is reassuring. Potential association of initiation of antidepressants during pregnancy with offspring autism needs further investigation.

Future work: Further research on larger samples could increase the robustness and precision of these findings. These methods applied could be a template for future pharmaco-epidemiological investigation of other pregnancy-related prescribing safety concerns.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/AQTF4490).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

A&E	accident and emergency
ADHD	attention deficit hyperactivity disorder
CAG	Clinical Advisory Group
CART	classification and regression tree
CDC	US Centers for Disease Control and Prevention
CI	confidence interval
CPRD	Clinical Practice Research Datalink
GP	general practitioner
HES	Hospital Episode Statistics
ICD-10	*International Classification of Diseases*, 10th Edition
IMD	Index of Multiple Deprivation
IRR	incidence risk ratio
IV	instrumental variable
N	number of observations
N/A	not applicable
NHS	National Health Service
NIHR	National Institute for Health Research
OLS	ordinary least squares
ONS	Office for National Statistics
OR	odds ratio
PAG	patient advisory group
PPI	patient and public involvement
PSM	propensity score matching
RCT	randomised controlled trial
SD	standard deviation
SERT	serotonin transporter
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
UK	United Kingdom
US	United States of America
UTS	up to standard GP practice

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Plain language summary

About one in seven women experience depression during pregnancy. Left untreated, this may harm them and their unborn babies. However, the decision to take antidepressants during pregnancy is difficult because women often worry about the risks to their unborn baby. Research findings have been inconsistent, so women often do not have clear information to enable them to make informed decisions.

We studied women's and children's outcomes after starting (compared with not starting) or continuing (compared with stopping) antidepressants in pregnancy. We used a large UK primary care database and several novel methods of analysis.

We tracked 80,103 pregnancies of women with depression for up to 2 years after pregnancy. We also tracked 34,274 children from these pregnancies for at least 4 years to check for developmental outcomes.

Women prescribed antidepressants were more likely than women not prescribed antidepressants to use general practice and mental health services during and after pregnancy, and to be prescribed antidepressants 2 years after pregnancy. This suggests that antidepressants were being prescribed to women with greater clinical need.

Women who continued antidepressants in pregnancy had no higher likelihood than those who discontinued antidepressants of autism, attention deficit hyperactivity disorder or intellectual disability in their children. This should reassure women making the decision to continue taking their medications in pregnancy.

Women who started antidepressants in pregnancy may possibly have had a slightly higher likelihood of autism in their children than those who did not start them. These findings were not seen in all analyses and were based on smaller numbers; therefore, they should be viewed with caution. Importantly, over 98 in every 100 children of women who initiated or continued antidepressants in pregnancy did not receive an autism diagnosis.

The findings may help women and clinicians make informed decisions on treatment with antidepressants in pregnancy.

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Scientific summary

Background

Depression is common in women of childbearing age and up to one in seven women experience depression during pregnancy. Untreated depression may have serious consequences, such as distress, self-neglect and suicidal behaviour, in affected women and birth complications in their babies. Many women with depression may, therefore, encounter a situation in which they need to decide whether to start or continue an antidepressant during their pregnancy; however, the potential for resulting harm to the neurodevelopment of their offspring is a common concern. In the absence of randomised controlled trials, the information available to guide these decisions is based on observational data, which are subject to confounding. Given that maternal depression may itself lead to adverse outcomes, isolating any effect of antidepressants from the underlying depression is particularly difficult: a problem known as confounding by indication. In the absence of randomised trials, studies designed to emulate such trials and using methods to account for confounding may help triangulate results and strengthen causal inference.

Objectives

This research aimed to simulate two scenarios that could be tested in pregnant women with depression in a hypothetical target randomised controlled trial asking the following research questions:

- Does the initiation of antidepressants for depression during pregnancy affect maternal service use outcomes and childhood neurodevelopmental outcomes?
- Does the continuation of antidepressant use during pregnancy for depression affect maternal service use outcomes and childhood neurodevelopmental outcomes?

The data were interrogated using several methods of causal inference, and assessed in relation to dose response, timing of exposure and type of antidepressants according to class and their serotonin-receptor affinity.

Methods

Design: This was an observational cohort design, with use of multiple methods to strengthen causal inference.

Setting and participants: This took place in UK general practice. Participants were UK primary care patients, specifically pregnant women with depression.

Data sources: This study used data from the Clinical Practice Research Datalink (CPRD), a large ongoing database of anonymised primary care medical records in the UK. The CPRD's pregnancy register was used to identify the dates and stages of pregnancy, and the CPRD mother–baby link allowed for the linkage of the records of pregnant women with their live born offspring. For consenting CPRD practices in England, the primary care records were linked to Hospital Episode Statistics, which include registers for inpatient admissions, outpatient care and accident and emergency (A&E) attendance in England, and with mortality data from the Office for National Statistics and Census small-area socioeconomic data.

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Eligible patients: The data extract covered dates between 1 January 1995 and 31 December 2017. Within this time frame, we identified 344,720 pregnancies in the pregnancy register for which there was evidence of depressive symptoms, or prescription of an antidepressant up to 1 year before or during pregnancy. From this sample, we constructed two cohorts: (1) the pregnant women's cohort, which contained all pregnancies for which women could be followed up for at least 2 years beyond the pregnancy end date, regardless of the pregnancy outcome or ability to link to the child; (2) the mother and child cohort, which consisted of pregnancies followed up at least until delivery that could be linked with the patient records of the children arising from these pregnancies.

The pregnant women's cohort: The exclusion criteria were (1) records for which the general practice was not yet up to standard, as defined by CPRD (n = 61,704); (2) where the patient had not yet registered with her current general practice 1 year prior to conception (n = 93,638); (3) records suggesting that the woman had transferred out of the general practice while still pregnant (n = 15,627); (4) records with < 2 years' follow-up beyond the pregnancy end date (n = 18,569); (5) records that showed overlap with a preceding or successive pregnancy episode (i.e. likely recording errors, n = 23,691); (6) any successive pregnancy that started < 4 years after a prior pregnancy had ended to minimise the possibility that women were again pregnant or trying to conceive during follow-up (n = 32,930). A further 18,458 patients who had been prescribed antidepressants for indications other than depression were excluded from these analyses but were used in separate analyses comparing outcomes of antidepressant use for depression with indications other than depression. The analytic cohort included 80,103 pregnancies in 76,687 women to study women's primary care service use outcomes. Of these pregnancies, 45,358 were eligible for record linkage to study secondary care service outcomes. Among these, data on inpatient admission were available for pregnancies that had started on or after 1 April 1997 (n = 43,662); outpatient treatment data were available for pregnancies starting on or after 1 April 2003 (n = 35,674); and A&E attendance data were available for pregnancies starting on or after 1 April 2007 (n = 25,697).

The mother and child cohort: Exclusion criteria were exclusions (1), (2) and (3) described above, (4) pregnancies that showed overlap with a preceding or successive pregnancy (n = 26,357), (5) pregnancies not recorded to have resulted in a live birth (n = 72,565), (6) live deliveries that could not be linked with offspring patient records (n = 15,298), (7) pregnancies that were recorded to have lasted < 22 gestational weeks (n = 542), and (8) any offspring who transferred out of their general practice (n = 10,404) or died (n = 5) before the age of 4 years. Given that the CPRD pregnancy register includes only the first child in case of multiple deliveries, we identified an additional 546 children in the mother–baby link data set, matching on the mother's patient identification number and exact date of delivery. Setting aside mothers who had been prescribed antidepressants for indications other than depression (n = 8485) and children followed up for less than 4 years because of being born after 2013 (n = 6367), there were 34,274 children in the offspring cohort.

Treatment groups: Within each cohort, women were allocated to one of the following treatment groups: (1) women with depressive symptoms who were (i) initiated with a prescription of antidepressants during pregnancy or (ii) not initiated with antidepressant treatment during pregnancy; and (2) women already prescribed antidepressants for the treatment of depressive symptoms who (i) continued being prescribed antidepressants in pregnancy or (ii) discontinued antidepressant treatment by the start of pregnancy, as defined in the CPRD pregnancy register.

The start of follow-up was defined as the day of estimated conception, as recorded in the CPRD pregnancy register, for women who received no treatment or discontinued or continued an existing prescription, and as the date of first prescription for women who initiated an antidepressant in pregnancy. Any difference in the length of follow-up between treatment groups was accounted for in analysis.

Outcomes

Women's outcomes included general practitioner (GP) consultations (for any reason, for depression and for self-harm) and secondary care referrals made by the GP for depression or self-harm. For those with linked data, outcomes included inpatient admission for a mental health problem, outpatient attendance for a mental health problem, A&E department attendance, and all-cause and cause specific mortality. All health-care service use outcomes were assessed during pregnancy and during each of four consecutive 6-month follow-up periods after the pregnancy end date: 1–6 months, 7–12 months, 13–18 months and 19–24 months.

Child outcomes included a diagnosis of (1) autism spectrum disorder, (2) attention deficit hyperactivity disorder (ADHD) and (3) intellectual disability recorded in the GP records based on Read codes.

Analysis: In the analysis, multiple methods for confounding control were used, including multivariable regression methods, propensity score matching to account for measured confounding factors, instrumental variable analysis using prescriber preference as an instrument to account for unmeasured confounding, negative control exposures for child outcomes (discontinuation of antidepressant before pregnancy where no gestational exposure occurred), comparison of risks of outcomes across indications for antidepressants other than depression and analysis of exposure discordant pregnancies to account for confounders shared between pregnancies.

Results

Initiation versus no initiation of antidepressants for depression in pregnancy: In the women's cohort, there were 18,978 pregnancies in which women had evidence of depression during the pregnancy or in the preceding 12 months. Antidepressants were initiated in 6177 of these pregnancies. In the mother and child cohort, there were 8478 pregnancies in which women had evidence of depression and, of these, antidepressants were initiated in 2649 pregnancies.

Multivariable regression and propensity score-matched estimates suggested that women who had initiated an antidepressant consulted more frequently than women who received no antidepressants with their GPs, for any reason or specifically for depressive symptoms, during or up to 2 years after pregnancy. These women were also more likely to be still prescribed an antidepressant 2 years after the pregnancy end date [odds ratio $(OR)_{multivariableregression}$ 2.16, 95% confidence interval (CI) 1.95 to 2.39; $OR_{propensityscore}$ 2.06, 95% CI 1.82 to 2.34].

There was some evidence that offspring of mothers who initiated antidepressants had higher odds of being diagnosed with autism in propensity score-matched analyses (OR 1.64, 95% CI 1.01 to 2.66) although the CIs for this association in multivariable regression analysis crossed the null [OR 1.23 (0.85–1.78)]. There was no strong evidence for differences in odds of offspring ADHD ($OR_{multivariableregression}$ 1.48, 95% CI 0.98 to 2.24; $OR_{propensityscore}$ 1.45, 95% CI 0.87 to 2.42) or intellectual disability ($OR_{multivariableregression}$ 1.16, 95% CI 0.63 to 2.14; $OR_{propensityscore}$ 0.75, 95% CI 0.31 to 1.78) with initiation of an antidepressant during pregnancy although CIs were wide.

Continuation versus discontinuation of antidepressants: In the pregnant women's cohort, there were 61,125 pregnancies in which women had a prior prescription of antidepressants for depression and of these 37,278 women continued the antidepressant into their pregnancy while 23,847 discontinued by the start of pregnancy. In the mother and child cohort, there were 25,796 pregnancies in which women had a prior prescription of antidepressants for depression and of these 15,295 women continued the antidepressant into their pregnancy while 10,501 discontinued by the start of pregnancy.

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There was consistent evidence across the main (multivariable regression and propensity score regression) and additional analyses (treatment-discordant pregnancies analysis) that women who continued antidepressants during pregnancy were more likely to have contact with health-care services at various times during and after pregnancy. These include the number of GP consultations (including consultations for depression, and self-harm), GP referrals for depression, and outpatient contacts and inpatient stays for mental health problems. Women who continued antidepressants in pregnancy were also more likely to continue to be prescribed an antidepressant 2 years following the end of pregnancy ($OR_{multivariableregression}$ 2.40, 95% CI 2.27 to 2.53; $OR_{propensityscore}$ 2.37, 95% CI 2.24 to 2.51).

There was little evidence in our regression and propensity score analyses that continuation of antidepressants into pregnancy was associated with a higher risk in the offspring of autism ($OR_{multivariableregression}$ 1.10, 95% CI 0.90 to 1.35; $OR_{propensityscore}$ 1.06, 95% CI 0.84 to 1.32), ADHD ($OR_{multivariableregression}$ 1.02, 95% CI 0.80 to 1.29; $OR_{propensityscore}$ 0.97, 95% CI 0.75 to 1.25) or intellectual disability ($OR_{multivariableregression}$ 0.81, 95% CI 0.55 to 1.19; $OR_{propensityscore}$ 0.89, 95% CI 0.61 to 1.31) as compared with discontinuing them before pregnancy. Similar results were observed in supplementary analyses including instrumental variable analyses and treatment discordant pregnancies, although these analyses were imprecise due to smaller numbers.

Results of analyses using other approaches

Instrumental variable analyses: Using prescriber preference as an instrument, we found little evidence of associations of initiation or continuation of antidepressants and any of the neurodevelopmental outcomes, although statistical power was limited.

Depression versus other indications: A higher risk of being prescribed antidepressants 2 years after pregnancy was observed when antidepressants had been initiated/continued for depressive symptoms compared with no initiation/discontinuation of antidepressants. The opposite pattern was observed (i.e., a lower risk of being prescribed antidepressants 2 years after pregnancy) when antidepressants had been initiated/continued for indications other than depression compared with no initiation/discontinuation.

Negative control analyses: There was little evidence of an association between prescription of an antidepressant for depression before pregnancy versus no prescriptions; or prescription of antidepressants during pregnancy for depression versus no prescriptions and any of the neurodevelopmental outcomes.

Timing of antidepressants: There was no consistent difference between estimates for offspring neurodevelopmental outcomes in relation to timing of initiation of antidepressants during pregnancy.

Dose response: There was some evidence for a dose response association between antidepressants prescribed to the mother in pregnancy and offspring odds of autism [ORs with 95% CIs for low, medium, and high dose respectively as compared with no antidepressant prescription: 1.19 (0.96–1.46); 1.67 (1.09–2.55); 1.75 (1.27–2.40)], although the CIs around the estimates overlapped. There was no clear evidence for dose–response association with offspring ADHD or intellectual disability.

Type of antidepressant: There was evidence of greater adjusted odds of autism among children whose mothers had been prescribed selective serotonin reuptake inhibitor (OR 1.26, 95% CI 1.04–1.53) or tricyclic antidepressants (OR 1.58, 95% CI 1.12–2.24) during pregnancy as compared with no antidepressant prescriptions. There was little evidence of similar associations for offspring ADHD or intellectual disability.

Antidepressants grouped by serotonin receptor affinity: The point estimates of offspring odds of all neurodevelopmental outcomes were lower for higher-affinity antidepressants than those for lower-affinity

antidepressants (which may often be prescribed for more severe depression) although the CIs for all estimates overlapped.

Individual antidepressants: There were variations in the estimates for neurodevelopmental outcomes in relation to individual medications but due to smaller numbers contributing to the analyses, these results should be interpreted with caution.

Conclusions

This comprehensive study of pregnant women with depression in a representative sample of UK primary care patients found that women who were initiated or continued antidepressants during pregnancy had greater service use at baseline and continued to need support with additional clinical care during pregnancy and in the 2 years following pregnancy. This was not the case for women prescribed these medications for conditions other than depression.

There was consistent evidence against any substantial risk of autism, ADHD or intellectual disability in children of women who continued versus those who discontinued antidepressants during pregnancy. Whether to continue or stop antidepressants in pregnancy is the most common clinical dilemma regarding antidepressant prescribing in pregnancy and these results should reassure women and clinicians.

There was weak and inconsistent evidence of potential associations of initiation of antidepressants during pregnancy with offspring autism which were imprecise due to smaller numbers. Further research on larger samples could help understand the robustness and causal meaning of these findings.

Limitations

Despite the large initial sample, there was limited statistical power in analyses applying several causal inference approaches and further studies in CPRD and similar samples using the approaches applied could provide further clarity and precision to our findings. There were no standard outcome measures of depression available, so we were unable to study improvements in symptoms of depression as an outcome. Finally, outcomes other than those investigated in this study may be important to women and clinicians in their decision-making process and could be investigated in future studies.

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Chapter 1 Introduction

Depression is a common mental health condition and a leading cause of disability worldwide.[1] Prescribing of antidepressant medications for depression and other common mental health problems has markedly increased in recent decades. For example, within the National Health Service (NHS), the number of prescriptions of antidepressants almost doubled in one decade, from 36 million prescriptions in 2008 to 70.9 million prescriptions in 2018.[2] This increase in the number of prescriptions for antidepressants appears to be largely explained by a longer duration of prescriptions,[3] which reflects the chronic course of depression.

Depression is particularly common in women of childbearing age, and antidepressants are commonly prescribed in this patient group.[4] Women receiving antidepressants who are planning pregnancy or those who discover they are pregnant while on antidepressants are, therefore, often faced with a decision about whether to continue or discontinue their antidepressant medication during the pregnancy. Furthermore, pregnancy itself may be a trigger for the onset or worsening of depression, and up to one in seven women suffer from depression during their pregnancy.[5–7] Untreated depression may have serious consequences, such as self-neglect and suicidal behaviour, in affected women and birth complications in their babies.[5,8] Therefore, initiation of antidepressant medications may be considered in the treatment of depression in pregnant women after considering the risks and benefits.[9]

A study of a representative sample of UK primary care patients reported that 8.6% of women who had deliveries between 2004 and 2010 were prescribed antidepressants in the year before their pregnancy.[10] During pregnancy, 3.7% of these women were prescribed an antidepressant, but this number sharply increased to 12.9% in the year following the pregnancy.[10] These prescribing patterns reflect the advice to minimise fetal exposure to medications, but the rise in prescribing in the year following pregnancy may also suggest that many women are re-prescribed antidepressants after they have given birth, for either ongoing or worsened depressive features or because of a new onset of postnatal depression.[11]

Weighing the potential benefits and harms of antidepressant use during pregnancy is challenging. A recent network meta-analysis of randomised controlled trials (RCTs) involving 21 commonly used antidepressants concluded that all antidepressants were more efficacious than placebo in the treatment of depression in adults.[12] However, pregnancy was an exclusion criterion in such RCTs; therefore, prescribing decisions in pregnancy have been reliant on observational data. Recent systematic reviews have highlighted the poverty of studies on the benefits of antidepressants during pregnancy or harms of discontinuing them.[13]

The National Institute for Health and Care Excellence guidance on antenatal and postnatal mental health (CG192)[9] advised that psychotropic use during pregnancy should be informed by the careful individualised weighing of benefits and risks, but acknowledged that data on long-term developmental outcomes are still scarce. In January 2016, the US Centers for Disease Control and Prevention (CDC) also called for further research on the safety of antidepressants during pregnancy, following the most recent data from a convenience sample of 5.8 million privately insured women in the USA of reproductive age showing over 15% filled claims of antidepressants. The CDC highlighted that such work would be important to provide accurate evidence and guidance for women of childbearing age given that many pregnancies are unplanned and first trimester exposure, therefore, is unavoidable. The US Preventative Services Task Force Recommendation Statement also published in 2016 recommended screening for depression in pregnant women but highlighted the lack of data on the benefits and harms of treatment during pregnancy. A comprehensive systematic review, carried out by the US Agency for Healthcare Research and Quality, concluded that 'Evidence about the comparative benefits and harms of pharmacologic treatment of depression in pregnant and postpartum women was largely inadequate to allow informed decisions about treatment'.[14]

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For example, only a few previous studies have specifically investigated the outcomes of continuing or discontinuing antidepressants during pregnancy in relation to worsening or relapse of depression. These studies include a study of 201 women in the USA, which reported over a fivefold risk of relapse of major depression in those who discontinued antidepressants.[15] Another US study of 367 women with mild to moderate depression reported that, compared with non-users, women who discontinued antidepressants in pregnancy had a sixfold risk of a relapse of depression in the second half of pregnancy.[16] However, this latter study also reported a fivefold risk of relapse of depression in women who continued antidepressants without dosage modification [odds ratio (OR) 4.59, 95% confidence interval (CI) 1.44 to 14.64], although the findings for women who continued antidepressants with dosage modification were imprecise (OR 0.58, 95% CI 0.06 to 5.52).[16] Two large studies based on analysis of secondary data (n = 778 and n = 28,493) found little evidence of a risk of relapse of depression following discontinuation of antidepressants,[17,18] although these studies acknowledged the limitations of using routinely collected data for effectiveness research. To date, only one RCT has been attempted to study this topic (the 'Stop or Go' trial in the Netherlands).[19] 'Stop or Go' was a pragmatic, multicentre, randomised non-inferiority trial that aimed to recruit 200 pregnant women with a gestational age of less than 16 weeks who were receiving selective serotonin reuptake inhibitor (SSRI) antidepressants without clinically relevant depressive symptoms.[19] The intervention group received preventative cognitive therapy-guided gradual discontinuation of antidepressants and the control group continued their antidepressant. A brief report of the results of this trial has been recently published,[20] which highlighted that only 44 (of 200 planned) participants were recruited. Women in both groups had similar rates of a relapse of depression,[20] although the trial was clearly underpowered to detect a meaningful difference.

Alongside the potential for benefits of antidepressants to pregnant women, there has been increasing discussion about the potential effects of antidepressants on fetal development. Most antidepressants do not appear to be associated with major congenital malformations,[21,22] but there is evidence of an increased risk of persistent pulmonary hypertension of the newborn with some antidepressants, a rare but serious condition.[23] Apart from immediate birth outcomes, there has also been increasing interest in potential longer-term neurodevelopmental effects of antidepressant exposure during pregnancy.

All antidepressants cross the placental barrier and are available to the developing fetus,[24] and their mechanism of action commonly involves an increase of the availability of serotonin in the synaptic cleft.[25] The serotonergic system is critical for fetal neurodevelopment and emerges early in embryogenesis.[26] Animal studies have reported that exposure to antidepressants in utero can lead to long-term impairments in cognitive, social and behavioural development that is attributed to disruptions in the serotonergic system.[26–31] It is, therefore, biologically plausible that similar effects on fetal neurodevelopment may occur in humans.

However, whether or not long-term development of the exposed offspring is affected as a result of in utero exposure to antidepressant medications is difficult to assess because maternal depression may independently affect offspring neurodevelopment. It is, therefore, difficult to determine whether antidepressants or depression in pregnancy are the cause of any observed adverse outcomes. This is known as confounding by indication[32] and can be an obstacle to clinical guidance and decision-making. If antidepressant use during pregnancy was the cause of any adverse offspring outcomes, pregnant women would need to be made aware of this to make informed decisions; however, if these outcomes are a result of the underlying depression, the benefits of taking them and, therefore, treating the depression would outweigh the risks.

A number of studies have now been carried out to investigate potential long-term neurodevelopmental outcomes in offspring exposed to antidepressants in pregnancy – the majority studying autism spectrum disorder (henceforth autism),[33–49] but also include attention deficit hyperactivity disorder (ADHD)[49–53] and intellectual disability.[54] Many of the studies on autism reported unadjusted associations between antidepressant use during pregnancy and autism. However, all of these studies reported concern about

confounding by indication and one major concern was the under ascertainment of depression owing to reliance on secondary-care records. The results of studies on risk of ADHD[53] and intellectual disability[54] have suggested that the association of antidepressant exposure with these conditions is unlikely to be causal.

Questions about medication effectiveness and safety are best answered using well-designed RCTs. However, RCTs in the area of medication use during pregnancy have not been carried out and pregnancy is one of the common exclusion criteria for controlled trials of investigational medicinal products owing to ethics concerns.[55] Furthermore, the feasibility of carrying out RCTs in pregnancy is a major issue because assessing potential long-terms risks to exposed offspring will require randomising very large numbers of pregnant women, and successful long-term follow-up may be unlikely. Clinical guidance on this issue is, therefore, likely to continue to rely on observational data. However, it is important that efforts are made to minimise the potential for confounding in results of such studies.

In the absence of RCTs, an efficient approach to studying outcomes related to antidepressants prescribed in pregnancy is to use routinely collected observational data to emulate the hypothetical RCT that would have been carried out and use methods that may minimise confounding bias and strengthen causal inference.[56] This approach also addresses constraints in time and cost given that routinely collected health-care data allow us to study large representative patient populations over long periods of time.

The aim of this research, funded by the Efficient study designs committee of the NIHR Health Technology Assessment Programme, was to address some of the gaps in the literature described above.

This research aimed to simulate two scenarios that could be tested among pregnant women with depression in a hypothetical target RCT asking the following research questions:

- Does initiation of antidepressants for depression during pregnancy affect maternal service use outcomes and childhood neurodevelopmental outcomes?
- Does continuation of antidepressant use during pregnancy for depression affect maternal service use outcomes and childhood neurodevelopmental outcomes?

To assess the robustness of the results, multiple methods for confounding control were used, including multivariable regression methods, propensity score matching to account for measured confounding factors, instrumental variable (IV) analysis using prescriber preference as an instrument to account for unmeasured confounding, negative control exposures for child outcomes (discontinuation of antidepressant before pregnancy where no gestational exposure occurred), comparison of risks of outcomes across indications for antidepressants other than depression, and analysis of exposure discordant pregnancies to account for confounders shared between pregnancies.

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Chapter 2 Overview of the methods used in this project

This chapter provides an overview of the data and the methods used in this project. Further details on individual causal approaches are also provided in later chapters.

Design: observational cohorts emulating target randomised controlled trials

This study was an observational cohort study using data from the Clinical Practice Research Datalink (CPRD),[57] and used multiple methods to strengthen causal inference. In discussion with our patient advisory group (PAG), and to inform decisions faced by pregnant women and clinicians, we identified two distinct clinical trial scenarios that would need to be emulated in our observational data. First, we examined the effects of initiating an antidepressant among women with depression not already prescribed antidepressant medications before they became pregnant. Second, we examined the effects of continuing antidepressants into pregnancy among those who were already prescribed antidepressant medications before they became pregnant. The protocol components of each of these hypothetical trials and our approach to emulating these in the observational data are described in *Chapters 3* and *4*, respectively. By making the target trial explicit in the selection of the study cohort and approach to statistical analysis, we can evaluate how well causal analysis of the observational data set emulates the target trial and, therefore, whether or not any observed associations are likely to represent the causal effects that would have been produced by an experimental study.

Study data: the Clinical Practice Research Datalink

This study used data from the CPRD, which is a large, ongoing database of anonymised primary care medical records for patients registered with a general practice in the UK. By 2015, the CPRD included data for over 11.3 million patients from 674 general practices in the UK, of whom 4.4 million patients were alive and registered, representing approximately 7% of the UK population.[57] Patients included in the CPRD are broadly representative of the UK population in terms of age, sex and ethnicity.[57]

Identification of pregnancies and linkage of women to offspring

A validated set of algorithms that identify pregnancies within the CPRD is now integrated within the CPRD as a pregnancy register.[58] This register enables the identification of the dates, stages and outcomes of pregnancies within the CPRD.[58] The CPRD has also developed a probabilistic mother–baby link, which allows the patient identifier numbers of mothers and the patient identifier numbers of their live-born offspring to be linked, enabling the construction of an intergenerational cohort.[59]

Linkage of Clinical Practice Research Datalink data with other resources

For consenting CPRD practices in England, which represent approximately 60% of patients in our data, it was possible to link the anonymised primary care records with other data sources. These sources include the Hospital Episode Statistics (HES), which has separate registers for inpatient admissions, outpatient care and accident and emergency (A&E) attendance in England. Linkage with the Office for National Statistics (ONS) mortality data and the Census small-area socioeconomic data was also available for this same subset.

The use of CPRD data for this project was approved by the CPRD's Independent Scientific Advisory Committee (reference 17_225).

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Study cohort selection

The CPRD data extract for this project covered dates between 1 January 1995 and 31 December 2017. Within this time frame, there were 344,720 pregnancies in the pregnancy register for which there was evidence of depressive symptoms or prescription of an antidepressant up to 1 year before or during pregnancy (see *Report Supplementary Materials 1* and *2* for Read codes and product code lists). This was the eligible sample for our cohort construction, as described below.

We constructed two cohorts: (1) the pregnant women's cohort contained all pregnancies for which women could be followed up for at least 2 years beyond their pregnancy end date, regardless of the pregnancy outcome or availability of linkage with the child in the CPRD mother–baby link; and (2) the mother and child cohort contained pregnancies that could be linked with the offspring patient records. A detailed description of the construction of each cohort is provided in the following sections.

Pregnant women's cohort

Figure 1 shows the derivation of the pregnant women's cohort used for the main analysis.

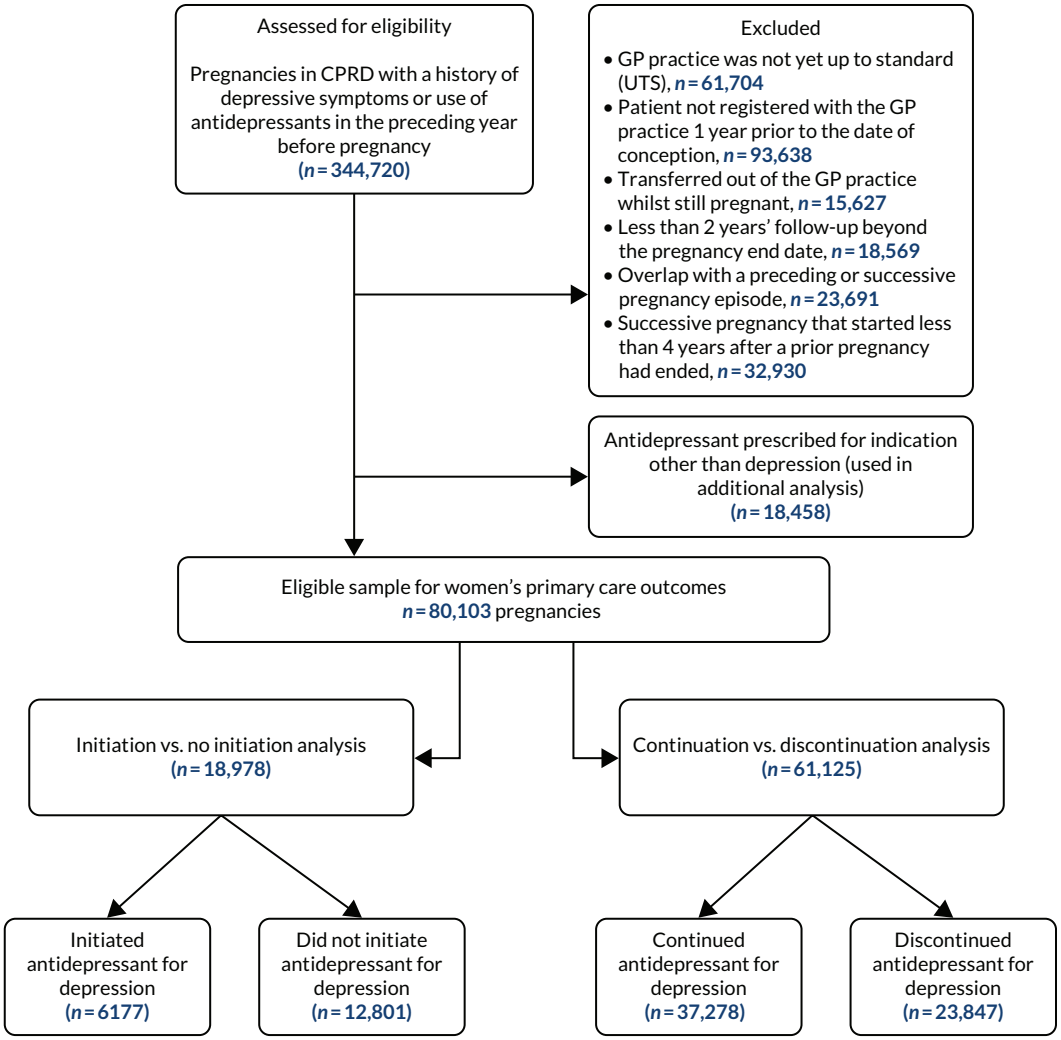

FIGURE 1 Derivation of the pregnant women's cohort.

From the eligible sample of 344,720 pregnancies, we excluded:

- records where the general practice was not yet up to standard (UTS) (*n* = 61,704). CPRD defines practices as being 'up to standard' if they have provided data on a consistent basis
- records where the patient had not yet registered with her current general practice 1 year prior to the date of conception, as recorded in the pregnancy register (*n* = 93,638)
- records suggesting that the woman had transferred out of the general practice while pregnant (*n* = 15,627)
- records with less than 2 years' follow-up beyond the pregnancy end date (*n* = 18,569)
- records that showed overlap with a preceding or successive pregnancy episode (*n* = 23,691)
- records of any successive pregnancy episode that started less than 4 years after a prior episode had ended to minimise biased results arising owing to the possibility of women being pregnant again or trying to conceive during follow-up (*n* = 32,930).

We set aside pregnancies for which antidepressants had been prescribed for indications other than depression (*n* = 18,458; these were used in additional analyses described in *Variation by indication: depression compared with other indication for antidepressant prescribing*); therefore, 80,103 pregnancies were included to study women's primary care service use outcomes. Of these pregnancies, 45,358 were eligible for record linkage to study secondary care service outcomes. Among these, data on inpatient admission were available for pregnancies that had started on or after 1 April 1997 (*n* = 43,662); outpatient treatment data were available for pregnancies starting on or after 1 April 2003 (*n* = 35,674); and A&E attendance data were available for pregnancies starting on or after 1 April 2007 (*n* = 25,697).

Mother and child cohort

Figure 2 shows the derivation of the mother and child cohort.

From the eligible sample of 344,720 pregnancies, we excluded:

- records where the general practice was not yet UTS, as defined by CPRD (*n* = 61,704)
- records where the patient had not yet registered with her current general practice 1 year prior to conception (*n* = 93,638)
- records where the patient had transferred out of the general practice while still pregnant (*n* = 15,627)
- records that showed overlap with a preceding or successive pregnancy (*n* = 26,357)
- pregnancies not recorded to have resulted in a live birth (*n* = 72,565)
- live deliveries that could not be linked with offspring patient records (*n* = 15,298)
- pregnancies that were recorded to have lasted less than 22 gestational weeks (*n* = 542)
- any offspring who transferred out of their general practice (*n* = 10,404) or died (*n* = 5) before the age of 4 years.

Given that the CPRD pregnancy register includes only the first child in cases of multiple deliveries, we identified an additional 546 children with at least 4 years' follow-up in the mother–baby link data set, by matching the mother's patient identification number and exact date of delivery. Setting aside mothers who were likely to have been prescribed antidepressants for indications other than depression (*n* = 8485) and children followed up for less than 4 years owing to being born after 2013 (*n* = 6367), we were able to include 34,274 children in the offspring cohort (mean age at end of follow-up 10.04 years, range 4–22 years).

Definition of treatment groups

As noted above, the treatment groups were based on two clinical scenarios that may be encountered by pregnant women with depression:

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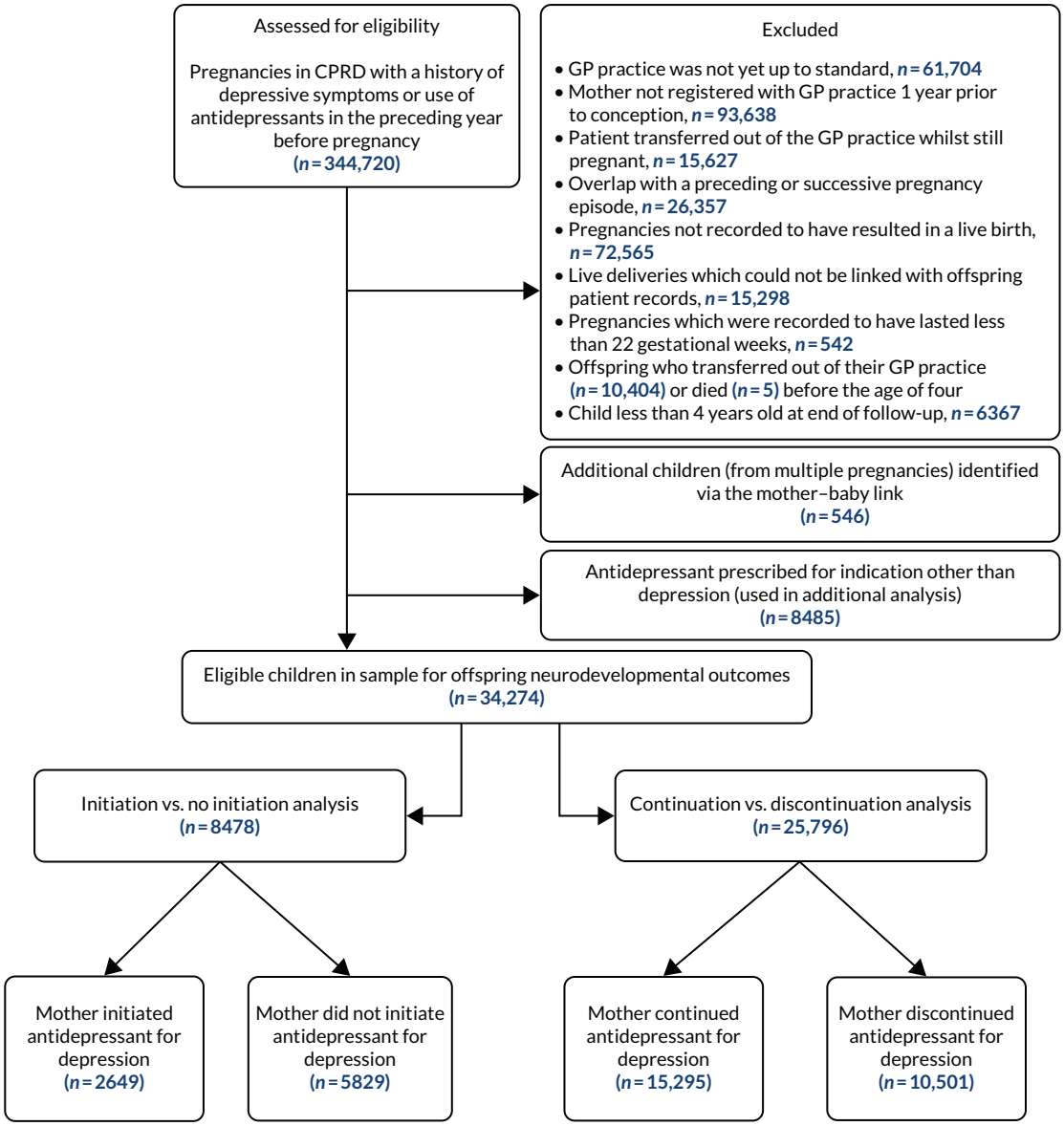

FIGURE 2 Derivation of the mother and child cohort.

- Women who have depression during pregnancy but were not receiving prior treatment may either be initiated with a prescription of antidepressants or not be prescribed antidepressant treatment.
- Women currently prescribed antidepressants for the treatment of depressive symptoms may choose to continue taking these medications in pregnancy or to discontinue them before pregnancy.

To identify each pregnancy as belonging to one of four treatment groups, we extracted information on prescription start dates, daily recommended dose and number of doses prescribed from women's medical records to identify periods of continuous prescribing before or during pregnancy (see *Report Supplementary Material 3*). Using these prescribing periods, we identified (1) women who initiated an antidepressant in pregnancy; (2) women who did not initiate an antidepressant in pregnancy; (3) women who continued an existing prescription into pregnancy; and (4) women who discontinued an antidepressant prescription prior to conceiving. We chose a 2-month grace period preceding the date of conception to take account of the longer pharmacological half-life of some antidepressants, which could still be active in pregnancy if taken shortly before conceiving. Therefore, women who discontinued or initiated antidepressants were required not to have been prescribed during this 2-month grace period. The rules used to define the treatment groups are detailed in *Figure 3*.

Prescribed antidepressants during:			
12 to 2 months pre-conception	*2 to 0 months pre-conception*	*Pregnancy*	**Treatment allocation**
No	No	No	*Not prescribed*
No	No	Yes	*Initiated*
Yes	No	Yes	*Initiated*
Yes	No	No	*Discontinued*
Yes	Yes	Yes	*Continued*
Yes	Yes	No	*Continued*
No	Yes	Yes	*Continued*
No	Yes	No	*Continued*

FIGURE 3 Allocation of treatment groups.

Women's service use outcomes

We examined women's use of health-care services during pregnancy and during each of the four consecutive 6-month follow-up periods after the pregnancy end date: 1–6 months, 7–12 months, 13–18 months and 19–24 months. The start of follow-up was defined as the day of estimated conception, as recorded in the CPRD pregnancy register, for women who received no treatment or discontinued or continued an existing prescription, and as the date of first prescription for women who initiated an antidepressant during pregnancy. Any resulting differential length of follow-up between treatment groups was adjusted for in our statistical models.

General practitioner consultations

During pregnancy and in each of the four consecutive 6-month follow-up periods, we counted the number of days on which women had consulted with their general practice. General practitioner (GP) consultations were required to have been face to face or by telephone and the staff member was required to be a doctor, nurse (including community psychiatric nurse) or psychologist. *Report Supplementary Material 4* contains the operational definitions used in deriving this outcome. Following the same definitions, we counted the number of days on which women consulted with their general practice specifically for further episodes of depression or self-harm (including suicide attempts) during pregnancy and follow-up periods. Symptoms of depression and self-harm were identified in the consultation records using validated Read code lists (see *Report Supplementary Materials 1* and *5*) where the consultation type equalled 'symptom', 'examination', 'diagnosis', 'administration' or 'presenting complaint'.

Referrals made by the general practitioner

We constructed a set of binary variables to indicate whether women had been referred by their GP to secondary services for depression or self-harm/suicide attempts during pregnancy or in each of the four consecutive 6-month follow-up periods. Referrals were defined as the presence of a referral record with a medical code for depression or self-harm/suicide attempt, where the NHS referral specialty classification equalled 'mental handicap', 'mental illness', 'child and adolescent psychiatry', 'forensic psychiatry', 'psychotherapy', 'old age psychiatry', 'clinical psychology', 'learning disabilities', 'adult psychiatry' or 'community psychiatric nurse', or where the Family Health Services Authority referral classification equalled 'psychiatry'.

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Inpatient admissions

Using linked HES data, we constructed a set of binary variables to indicate whether women had been admitted as an inpatient for a mental health problem [*International Classification of Diseases*, 10th Edition (ICD-10): F00–F99] or for intentional self-harm/suicide attempt or self-harm of undetermined intent (ICD-10: X60–X84 and Y10–Y34) during pregnancy or in each of four consecutive 6-month follow-up periods. These inpatient admissions were defined by a record where the main specialisation of the consultant equalled 'accidents and emergency', 'learning disability', 'adult mental illness', 'forensic psychiatry' or 'psychotherapy'; where their treatment specialisation equalled 'accidents and emergency', 'clinical psychology', 'learning disability', 'forensic psychiatry', 'psychotherapy', 'eating disorders', 'liaison psychiatry', 'perinatal psychiatry', 'mental health recovery and rehabilitation service' or 'mental health dual diagnosis service'; and where the method of admission equalled 'A&E or dental casualty department', 'request for immediate admission by GP', 'consultant clinic', 'admission via mental health crisis resolution team' or 'other means'.

Outpatient treatment

Using linked HES data, we constructed a set of binary variables to indicate whether women had used outpatient services for a mental health problem during pregnancy or in each of four consecutive 6-month follow-up periods. Outpatient contacts were defined by outpatient records where the treatment specialty of the consultant equalled 'adult mental illness', 'child and adolescent psychiatry', 'forensic psychiatry' or 'psychotherapy'.

Accident and emergency department attendance

Using linked HES data, we counted the number of instances women had presented to A&E services during pregnancy or in each of four consecutive 6-month follow-up periods. We considered only first A&E attendances (excluding any planned or unplanned follow-up for a prior attendance) and excluded attendances for assault, sports injuries or firework injuries, or where the patient had died on arrival to the A&E unit.

All-cause and cause-specific mortality

We used linked ONS mortality data to identify women who had died at any time after the end of the study pregnancy and specifically within the study window, that is within the 2-year period immediately following the pregnancy end date. In the pregnant women's cohort, only 14 women had died within the 2-year period immediately following the pregnancy end date. We, therefore, did not carry out further analysis on mortality as an outcome.

Prescription of an antidepressant at 2-year follow-up

We determined whether mothers were still or again being prescribed antidepressants at the end of follow-up, that is 2 years after the pregnancy end date. Based on the assumption that antidepressants are generally prescribed where there is greater clinical need, we proxied the mother's recovery from depression by not receiving antidepressants at the end of follow-up. We, therefore, examined all periods of continuous prescribing around this time and considered mothers to have recovered if (1) the end of follow-up did not coincide with a start or estimated end date of a prescription period; and (2) the end of follow-up did not fall within a period of continuous prescribing.

Offspring neurodevelopmental outcomes

Autism spectrum disorder

We examined the primary care clinical and referral records of linked offspring for the presence of autism spectrum disorder (referred to hereafter as autism) using a validated Read code list (see *Report Supplementary Material 6*). Offspring were considered positive on outcome if they had a primary

care record that indicated autism, autism spectrum disorder, autistic disorder, Asperger syndrome, atypical autism, childhood autism, infantile autism, autistic psychopathy or pervasive developmental disorder, and if they had a record of autism when they were at least 4 years of age. A recent study[60] validated the CPRD diagnosis, as recorded in the CPRD, against the clinical records for a subsample and reported a positive predictive value of 91.4%. Given that the HES data were available for only a subsample, and registered diagnoses are recorded in less than 5% of all outpatient attendances (during which most autism-related consultations would happen), we did not use linked data to supplement the autism diagnoses.[61]

Intellectual disability

Following the same approach, we examined the primary care records of linked offspring for presence of intellectual disability that had been diagnosed when the child was at least 4 years of age. Children were considered positive on outcome if their primary care records indicated Read codes related to intellectual disability (see *Report Supplementary Material 7* for the list of Read codes). These codes were similar to those used by previous studies of intellectual disability within CPRD,[62,63] although we did not include codes for autism (i.e. someone with a code of autism would be counted as having an intellectual disability only if there were additional codes related to intellectual disability in their medical record). Similar to autism, linked data were not used to supplement these diagnoses because these data were available for only a subset and the HES outpatient registers had less than 5% recording of diagnostic data.[61]

Attention deficit hyperactivity disorder

Primary care diagnoses of ADHD were identified by the presence of medical codes pertaining to ADHD or therapy records that indicated that the child had been prescribed ADHD medication when they were at least 4 years of age. Children were considered positive on outcome if they had a recorded Read code related to ADHD (see *Report Supplementary Material 8*) or if they had been prescribed any of the following ADHD medications: methylphenidate, dexamphetamine, atomoxetine, dextroamphetamine, amphetamine with dexamphetamine, or lisdexamphetamine (see *Report Supplementary Material 9*). Similar methods have been used to identify ADHD in previous CPRD studies.[64] As above, linked data were not used to supplement these diagnoses because these data were available for only a subset and the HES outpatient registers had incomplete recording of diagnostic data.[61]

Covariates

To account for potential confounders of the treatment–outcome association, we included additional covariates in our statistical models or used them in matching procedures. Covariates extracted from primary care records were:

1. maternal age – defined as the age in years recorded on the pregnancy register
2. the number of days on which the woman consulted with her GP in the year prior to conception – a proxy for illness severity and health-care seeking behaviour
3. Charlson Comorbidity Index score – a continuous measure for presence of comorbid physical health conditions[65] from a previously published code list[66]
4. psychiatric history of any of the following by the start of pregnancy – psychosis, anxiety, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain (see *Report Supplementary Materials 10–17* for Read code lists)
5. prescription of medications for physical health problems (any medications listed within BNF sections 1.1–1.9, 2.1–2.13, 3.1–3.11, 5.1–5.5, 6.1–6.7, 7.2–7.4, 8.1–8.3, 10.1–10.3, 13.5.3, 13.6.2 and 13.6.3)[67]
6. prescription of central nervous system agents (any medication listed within BNF sections 4.1, 4.2 and 4.4–4.10)
7. prescription of nutritional supplements in the year before or during pregnancy (defined as any supplements listed within BNF sections 9.1–9.12)

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8. smoking status at the start of pregnancy – never smoked, current or ex-smoker or status unknown (details of Read codes and categorisation provided in *Report Supplementary Material 18*)
9. history of alcohol use by the start of pregnancy (see *Report Supplementary Material 19*)
10. administrative region of the general practice – The North or Yorkshire and the Humber, Midlands or East of England, the South excluding London, London, Northern Ireland, Scotland or Wales
11. calendar year – 1995–97, 1998–2000, 2001–03, 2004–06, 2007–09, 2010–12 or 2013–17
12. any recorded severity of prior depression – mild, severe or severity not recorded (see *Report Supplementary Material 20*; code lists were rated by two psychiatrists, DR and JE, to derive groups)
13. concurrent use of multiple antidepressants during the study period – a proxy for illness severity
14. switching from one antidepressant to another – a proxy for illness severity.

Using linked HES data, we extracted:

15. a variable indicating past inpatient admission where a mental health problem was mentioned as a primary or secondary diagnosis – a proxy for illness severity.

From linked Census data we extracted:

16. the ranked Index of Multiple Deprivation (IMD) quintile of the patient's postcode area – a proxy for socioeconomic status.

The above two variables extracted from linked records were available for only the subsample of cases with linked data; therefore, they were included in within-multivariable regression and the generation of propensity scores in supplementary analyses only.

Methods to account for confounding

Multivariable regression

We used multivariable regression to estimate the maternal and child outcomes associated with initiating (described further in *Chapter 3*) or continuing (described further in *Chapter 4*) an antidepressant into pregnancy. For each outcome, we first estimated crude associations and then controlled statistically for the range of potential confounders described in *Covariates*. Further detail on the selection and specification of multivariable regression models is provided in *Chapters 3* and *4*.

Propensity score-matched regression

Alongside conventional multivariable regression, we carried out all analyses in subsets of the data for which we matched treatment groups on propensity scores for initiation and continuation of antidepressants during pregnancy. Propensity score matching (PSM) is a commonly used method in pharmaco-epidemiology that allows the identification of pairs of observations that are similar in all measured characteristics, except for treatment status.[68] It, therefore, aims to achieve balanced treatment groups, allowing for a like-with-like comparison that would be achieved by randomisation in RCTs. It has been argued that PSM may provide a more effective approach to minimising confounding bias than traditional multivariable regression methods because it can incorporate large numbers of potential covariates that may overwhelm traditional regression models.[69] However, the main constraint of PSM is that the groups can be matched only on characteristics that are measured, so confounding by unmeasured characteristics is still possible.[32] Furthermore, in analyses using PSM, individuals who cannot be matched for being too dissimilar are excluded from the analysis, which can affect statistical power because of reduced numbers.

In this study, we estimated propensity scores using classification and regression tree (CART) models[69] separately for our two comparisons to match mothers who initiated antidepressants with mothers who received no treatment (see *Chapter 3*) and to match mothers who continued antidepressants into

pregnancy with mothers who discontinued antidepressants before pregnancy (see *Chapter 4*). Further details are provided in the respective chapters.

Instrumental variable analysis

Instrumental variable regression is a statistical technique that can allow the estimation of causal effects in the presence of unmeasured confounding.[70] This is where unobserved characteristics of patients influence their likelihood of being prescribed antidepressants and at the same time influence risk of outcome, resulting in a confounded treatment effect. The rationale for IV analysis, in this particular context, is that the clinical decision to prescribe an antidepressant in pregnancy can be viewed as being influenced by three factors: first, whether or not the GP deems it safe to prescribe antidepressants to a pregnant patient given potential concerns about teratogenicity; second, the characteristics of the patients themselves, for instance their clinical characteristics, including severity of depression during pregnancy; and, third, the propensity of the physician to prescribe antidepressants. Using a well-specified IV, we can, therefore, distinguish between variability in treatment decisions owing patient characteristics (which may confound the treatment effect) and variability in treatment decisions as a result of whether or not GPs are willing to prescribe antidepressants in pregnancy (which is not determined by the characteristics of their current patient). For this reason, IV analysis can overcome unmeasured treatment-outcome confounding and, therefore, identify the causal effect of treatment on outcome. Broadly following methods proposed in earlier work,[71] we aimed to capture as an IV the GPs previous prescribing practice of antidepressants in a pregnant patient given potential concerns around risks. Given that a GP's views on medication safety cannot be directly observed, we proxied this by the number of times that they had issued an antidepressant in prior consultations with other pregnant patients. The validity of the result then depends on the extent to which the following assumptions are tenable: first, the instrument associates with the treatment (relevance assumption); second, the IV should influence only the outcome through the treatment variable (the exclusion restriction); and third, the IV does not share a common cause with the outcome (i.e. there are no confounders of the instrument outcome relationship) (the independence assumption).[70] If these IV assumptions are met, IV analysis can estimate the causal effect of treatment on an outcome.

We used IV analysis separately for women who initiated an antidepressant or continued with an existing prescription into pregnancy. Further details are provided in *Chapter 5*.

Matched treatment-discordance designs

Another approach to account for unmeasured confounding is the matched treatment-discordance design. This design is also commonly referred to as a sibling design when the matching is based on siblings to study outcomes in offspring of treatment or exposure discordant pregnancies.[72,73] We use the term treatment-discordance design because we have used this approach to study women's outcomes across pregnancies, as well as outcomes for the offspring across pregnancies.

In this design, we consider consecutive pregnancies to the same woman that differed in terms of treatment status. For example, a woman may have not taken antidepressants in the first pregnancy but initiated an antidepressant in a second pregnancy, or she may have discontinued antidepressants in the first pregnancy but then continued antidepressants in a second pregnancy. These being pregnancies to the same women, any observed or unobserved characteristics that remain stable between pregnancies cannot confound the treatment–outcome association when they are analysed as matched pairs. For this reason, matched treatment-discordance designs are robust against both observed and unobserved confounders that are constant between pregnancies. Further detail on the selection and specification of statistical models used for these analyses is provided in *Chapter 6*.

Negative control analysis

We examined the risk of offspring neurodevelopmental outcomes where antidepressants were prescribed before but not during the pregnancy.[74] If prescription of antidepressants before the gestational period is associated with increased risk of an adverse outcome, it is unlikely that these

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associations are because of the effect of in utero exposure to the medication and would, therefore, suggest confounding by other characteristics. Further details of the method and results of these analyses are presented in *Chapter 7*.

Variation by indication: depression compared with other indication for antidepressant prescribing

To explore potential confounding by the indication, where the severity of depressive symptoms during pregnancy may influence both the likelihood of treatment and the risk of adverse outcome, we compared associations where antidepressants had been issued for depression with associations where antidepressants were likely to have been issued for other indications. A stronger association of antidepressants prescribed for depression is suggestive of confounding by the indication. Methods and results pertaining to these analyses are described in *Chapter 8*.

Additional analyses

In addition to analyses performed specifically to minimise confounding bias described above, we performed a range of additional analyses, as described in the following sections.

Association by timing of initiation in pregnancy

To identify potentially sensitive periods in fetal development, we compared risk of offspring neurodevelopmental problems where antidepressants were initiated in the first trimester with where they were issued in the second or third trimester. Further detail of the methods and the results of these analyses are presented in *Chapter 9*.

Dose response of associations

To assess dose–response relationships of antidepressant use with offspring neurodevelopmental disorders, we categorised the dose of antidepressants prescribed to each woman into low, moderate and high. It should be noted that, although such associations may highlight any dose–response relationships, they remain vulnerable to the possibility of confounding by the severity of the indication. Further detail of the methods and results for these analyses are presented in *Chapter 9*.

Associations for type of antidepressants

We examined associations with offspring neurodevelopmental outcomes where women had been prescribed SSRIs, tricyclic antidepressants (TCAs) or other types of antidepressants during pregnancy. Where women were issued different types of antidepressants during the same pregnancy, pregnancies counted independently to each risk estimate (e.g. women who were prescribed a SSRI and TCA were considered in the analysis of either drug type). Further detail and results for these analyses are presented in *Chapter 9*.

Associations by serotonin transporter receptor affinity

We examined the risk of offspring neurodevelopmental outcomes in relation to the serotonin transporter (SERT) affinity of antidepressant medications.[46,50] For these analyses, we compared women who were prescribed antidepressants in pregnancy with women who were not prescribed antidepressants in pregnancy. Further detail and results for these analyses are presented in *Chapter 9*.

Associations for specific antidepressant medications

Where we had sufficient numbers to enable statistical analyses, we report the associations of specific medications with neurodevelopmental outcomes. Where women were prescribed different medications within the same pregnancy, we counted them independently towards the risk estimates for all medications prescribed and then limited our analyses to women prescribed only a single medication within the same pregnancy as a sensitivity analysis. Further detail and results for these analyses are presented in *Chapter 9*.

Patient and public involvement

This project benefited from valuable patient and public involvement (PPI) from the very outset at the application for funding stage. We received important feedback on the study plan and design at the funding application stage from leaders of two perinatal mental health charities – Mothers for Mothers (Bristol, UK) (Mrs Maria Viner) and Bluebell Care (Bristol, UK) (Mrs Ruth Jackson). Following the project award, Mrs Maria Viner co-led the PPI strategy for this project along with Mrs Claire Storey who has significant experience of PPI in research. A bespoke PAG comprising women who have had lived experience of perinatal depression and had faced decision-making regarding medications during pregnancy was set up and three meetings were held where our PPI co-leads facilitated a discussion around important issues in relation to this project. Our co-leads purposefully recruited women known to the charity who were well and not currently in the decision-making process around medication use during pregnancy to ensure their well-being. The co-leads took particular care to ensure that the members of the PAG were supported during and after each group meeting in case any distressing issues arose.

At the start of the project, we discussed the research plan with the PAG and the challenges of decision-making regarding risks and benefits of medications during pregnancy, the portrayal of recent studies in the popular press and the media. In the next two meetings, we presented our progress and findings to the group and discussed their meaning and potential implications, as well as ideas for dissemination. The group will help support dissemination of the findings of this report upon publication.

Alongside the PAG, we also set up a Clinical Advisory Group (CAG) of multidisciplinary clinicians, which fed back on the aims of the project. The CAG meetings were later carried out within the meetings of the Health Integration Team for improving perinatal mental health, 'IMPROVE', based in Bristol. This unique local collaboration of service users, commissioners, service providers and researchers in the field funded by the Bristol Health Partners (www.bristolhealthpartners.org.uk/health-integration-teams/improving-perinatal-mental-health-hit/) (accessed 1 March 2021), where we received feedback on our methods and results.

These groups will continue to support the dissemination of our work to ensure that it reaches a wider audience.

Deviations from the protocol

The following deviations to the protocol were made:

- we used the GP records within the CPRD to ascertain diagnoses of childhood neurodevelopmental conditions and did not supplement these diagnoses with HES records. This was because the HES outpatient register had less than 5% of diagnoses in outpatient appointments recorded
- following feedback from the patient and CAGs and the discussions within the team in relation to a potential measure of 'recovery' from depression, we defined an additional outcome measure of women still being prescribed an antidepressant 2 years following the pregnancy as described in *Prescription of an antidepressant at 2-year follow-up*
- we frequently encountered violations of non-proportionality of hazards; therefore, we did not use survival analysis in our traditional regression models and instead used logistic regression with cluster robust variance for the analysis of binary outcomes and negative binomial regression with cluster robust variance for count outcomes, while accounting for differential time at risk in all analyses by including the natural logarithm of a time-at-risk variable in our models, constraining its regression coefficient to one.

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Chapter 3 Emulating the antidepressant initiation trial

This chapter describes our emulation of the target trial for initiation compared with no initiation of an antidepressant during pregnancy. Our aim was to examine the outcomes of initiating an antidepressant for depression during pregnancy compared with not initiating an antidepressant for depression during pregnancy. *Figure 4* provides the specification of the target RCT and how we aimed to emulate it in observational CPRD data.

Protocol component of the target trial	Description	Emulation in observational data
(a) Eligibility criteria	Women with current depressive symptoms trying to become pregnant, who have not taken antidepressants in the last year.	Between 01.01.1995 and 31.12.2017, we identified all women within the CPRD Pregnancy Register whose primary care records indicated Read codes for depression up to a year before or during pregnancy but did not indicate product codes for antidepressants in the year prior to conception. Women who had been prescribed antidepressants in the year prior to conception were excluded from these analyses.
(b) Treatment strategies	Initiating versus not initiating an antidepressant after becoming pregnant.	Among the women identified under (a) we compared the group whose primary care records indicated antidepressant prescriptions between conception and the pregnancy end date with the group who had not been prescribed antidepressants during this period.

FIGURE 4 Specification of the target initiation trial.

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Methods

Study cohorts

Depending on the outcome under investigation, we used the pregnant women's cohort or the mother and child cohort for analysis, as described *Chapter 2*, *Study cohort selection*, to use the largest available sample size relevant to each outcome.

Statistical analysis

First, we compared the characteristics of women in each arm of our target trial to assess differences in covariate distributions.

Logistic regression models with cluster-robust variances were used to estimate the relative odds associated with initiating an antidepressant in pregnancy for each of the following binary outcomes:

- whether or not women consulted with their GP for depression or self-harm during pregnancy and in each of the four consecutive 6-month follow-up periods
- whether or not women had been referred by their GPs to specialist services during pregnancy and each of the four consecutive 6-month follow-up periods
- whether or not they had been admitted as an inpatient or outpatient to specialist mental health services during pregnancy and each of the four consecutive 6-month follow-up periods
- whether or not they were still or again on antidepressants 2 years after the pregnancy end date
- whether or not children resulting from the study pregnancies had been diagnosed with autism, ADHD or intellectual disability.

We used negative binomial regression models with cluster-robust variances to estimate incidence rate ratios for the following count outcomes:

- the number of days on which the mother had consulted with her GP during pregnancy and further follow-up periods
- the number of days on which the mother had consulted with her GP specifically for depression during pregnancy and further follow-up periods
- the number of times the mother had attended A&E services during pregnancy and further follow-up periods.

To account for differential length of follow-up between treatment groups, for instance because of differences in time of initiation or length of pregnancy, we included the natural logarithm of a time-at-risk variable in our models, constraining its regression coefficient to one.

Multivariable regression

Using the models described above, we estimated crude associations between initiating an antidepressant during pregnancy and the range of outcomes described above. We then statistically adjusted our estimates for all potential confounders described in *Chapter 2*, *Covariates*. We did not, however, adjust for concurrent use of multiple antidepressants or switching between medications because these variables cannot be used to proxy illness severity for mothers who received no treatment during the study period. All analyses were conducted in Stata® 15.1/MP (Stata Corp LP, College Station, TX, USA).

Propensity score-matched regression

Using a CART model[69] with 15,000 iterations in RStudio version 1.0.153 (The R Foundation for Statistical Computing, Vienna, Austria), we estimated a continuous score capturing women's propensity to initiate an antidepressant in pregnancy based on their other measured characteristics. By contrast with propensity score estimation by parametric methods (where a single model is chosen to predict the data), a CART model uses a multitude of potential models, including interaction terms, and optimises

its prediction across these. For this reason, CART models are well suited to predictive data modelling problems, such as propensity score estimation, because they do not depend on subjective decisions regarding the specification of the predictive model. Using the estimated propensity scores, we matched pregnancies during which women initiated antidepressants with pregnancies during which they received no treatment during the study period. Matches were carried out in a 1 : 1 ratio, without replacement and not allowing the propensity scores of matched pairs to differ by more than 0.2 standard deviations (SDs). We evaluated the quality of the matching algorithm by comparing standardised mean differences in covariate distributions before and after matching (*Figures 5* and *6*; see *Report Supplementary Materials 21–23* for PSM analyses carried out in cohort subsets for which linked data were also included) and then exported the matched data sets to Stata 15.1/MP for statistical analysis. In these analyses, no further statistical adjustments for covariates were made because the groups were sufficiently balanced on the propensity score.

Results

Descriptive statistics of initiators versus non-initiators of antidepressants

Table 1 describes the characteristics of the study population of the women's cohort by treatment status. There were 18,978 pregnancies in which women had evidence of depression during the pregnancy or within the preceding 12 months and, of these, antidepressants were initiated in 6177 pregnancies. Women who initiated an antidepressant during pregnancy were, on average, 0.3 years older and had seen the GP more frequently in the year prior to pregnancy than women who were not initiated on an antidepressant. At the start of pregnancy, women who were thereafter initiated on an antidepressant were more likely to have a history of physical comorbidities and, except for psychosis and bipolar affective disorder, were more likely to have a history of other psychiatric illness. They were also more likely to have been prescribed medications other than antidepressants in the year prior to or during pregnancy, to be current or ex-smokers, and to have a record of severe depression in their medical histories when they became pregnant. The treatment groups also differed in terms of area of residence within the UK and calendar year of the pregnancy.

Table 2 describes the characteristics of the study population of the mother and child cohort by treatment status in terms of women with depression who were initiated on an antidepressant during pregnancy compared with women who were not initiated on an antidepressant and had the child's record linked with a minimum follow-up period of 4 years. There were 8478 pregnancies in which women had evidence of depression and, of these pregnancies, antidepressants were initiated in 2649. The characteristics of women initiating in this cohort were largely similar to those described in *Table 1* for the women's cohort, barring that there was no age difference between women in the treatment groups observed.

Table 3 provides descriptive statistics for the outcomes evaluated (number and percentages for categorical outcomes and the average number of events with SD for count outcomes) in the regression and propensity score analysis. We used the maximum data available for each outcome under investigation; given that linked data were available for only a subset of women, these analyses included a smaller number of women.

All neurodevelopmental conditions were relatively rare and were observed in less than 2% of the sample in either group. The prevalence of autism (1.85%) and ADHD (1.7%) was slightly greater in children of women who initiated antidepressants for depression in the main sample than in children of women who had depression but were not initiated on antidepressants (1.58% for autism and 1.01% for ADHD).

Results of multivariable regression and propensity score-matched analysis

To control for differences in measured characteristics between treatment groups, we examined associations between treatment status and the various outcomes while adjusting statistically for covariates and matching on the propensity to initiate antidepressants (*Tables 4–6*).

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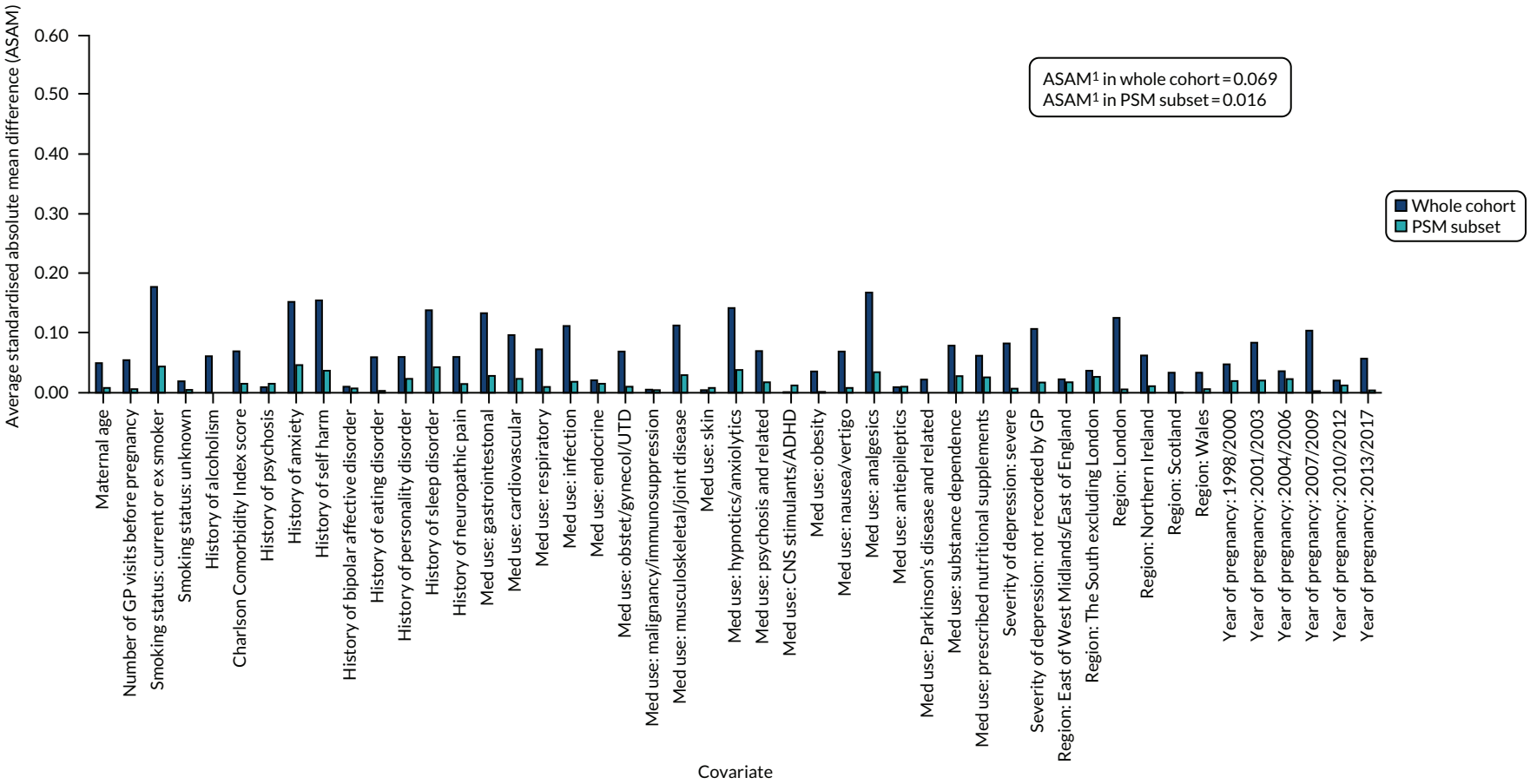

FIGURE 5 Standardised absolute mean differences in covariate distributions between initiators and non-initiators of antidepressants in the women's cohort before (blue) and after (orange) matching on propensity scores. Note: (1) ASAM = the Average Standardised Absolute Mean difference for all covariates.

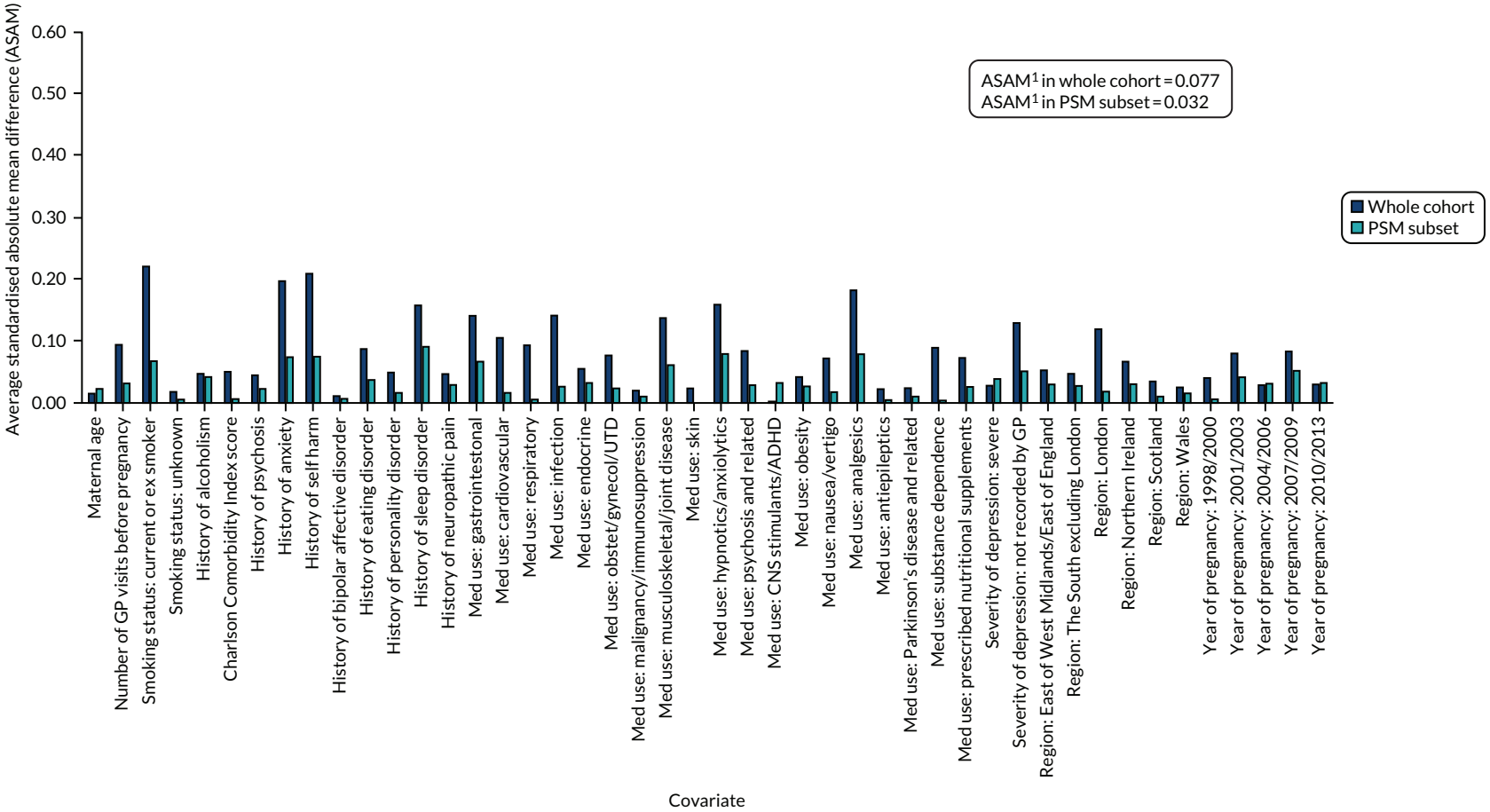

FIGURE 6 Standardised absolute mean differences in covariate distributions between initiators and non-initiators of antidepressants in the offspring cohort, before (blue) and after (orange) matching on propensity scores. Note: (1) ASAM = the Average Standardised Absolute Mean difference for all covariates.

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TABLE 1 Descriptive statistics for women's cohort: not prescribed vs. initiated an antidepressant for depression in pregnancy

Variable	Not prescribed (*N* = 12,801)	Initiated (*N* = 6177)	*p*-value
Maternal age (years), mean (SD)	28.00 (6.89)	28.33 (6.66)	0.002
Number of GP visits in the year prior to pregnancy, mean (SD)	5.89 (6.15)	6.25 (6.69)	< 0.001
Charlson Comorbidity Index score, *n* (%)			
0	9158 (71.54)	4205 (68.08)	< 0.001
1	2877 (22.47)	1530 (24.77)	
≥ 2	766 (5.98)	442 (7.16)	
Psychiatric history at the start of pregnancy, *n* (%)			
Alcohol dependence	86 (0.67)	86 (1.39)	< 0.001
Psychosis	54 (0.42)	30 (0.49)	0.535
Anxiety	2912 (22.75)	1836 (29.72)	< 0.001
Self-harm	1266 (9.89)	958 (15.51)	< 0.001
Bipolar affective disorder	57 (0.45)	32 (0.52)	0.492
Eating disorder	258 (2.02)	188 (3.04)	< 0.001
Personality disorder	79 (0.62)	80 (1.30)	< 0.001
Sleep disorder	915 (7.15)	716 (11.59)	< 0.001
Neuropathic pain disorder	469 (3.66)	307 (4.97)	< 0.001
Use of other medications, *n* (%)			
Medications for physical health problems	10,412 (81.34)	5277 (85.43)	< 0.001
Central nervous system agents	4103 (32.05)	2583 (41.82)	< 0.001
Prescribed nutritional supplements	1993 (15.57)	1109 (17.95)	< 0.001
Smoking status at the start of pregnancy, *n* (%)			
Never smoked	4887 (38.18)	1860 (30.11)	< 0.001
Current or ex-smoker	7830 (61.17)	4285 (69.37)	
Unknown	84 (0.66)	32 (0.52)	
Recorded severity of past depression, *n* (%)			
Mild	9777 (76.38)	4348 (70.39)	< 0.001
Severe	387 (3.02)	337 (5.46)	
Unknown	2637 (20.60)	1492 (24.15)	
Region of the general practice, *n* (%)			
North East/North West/ Yorkshire and the Humber	2265 (17.69)	1127 (18.25)	< 0.001
East Midlands/West Midlands/East of England	2696 (21.06)	1359 (22.00)	

TABLE 1 Descriptive statistics for women's cohort: not prescribed vs. initiated an antidepressant for depression in pregnancy (*continued*)

Variable	Not prescribed (*N* = 12,801)	Initiated (*N* = 6177)	*p*-value
South West/South Central/ South East	3695 (28.86)	1681 (27.21)	
London	1271 (9.93)	418 (6.77)	
Northern Ireland	349 (2.73)	244 (3.95)	
Scotland	1155 (9.02)	620 (10.04)	
Wales	1370 (10.70)	728 (11.79)	
Year of pregnancy, *n* (%)			
1995–97	663 (5.18)	290 (4.69)	< 0.001
1998–2000	831 (6.49)	480 (7.77)	
2001–03	1487 (11.62)	901 (14.59)	
2004–06	2318 (18.11)	1035 (16.76)	
2007–09	2725 (21.29)	1071 (17.34)	
2010–12	2420 (18.90)	1119 (18.12)	
2013–17	2357 (18.41)	1281 (20.74)	

p-values for comparisons of categorical variables were obtained using Pearson's chi-square test. *p*-values for comparisons of continuous variables were obtained using Student's *t*-test.

TABLE 2 Descriptive statistics for the mother and child cohort: not prescribed vs. initiated an antidepressant for depression in pregnancy

	Not prescribed (*N* = 5829)	Initiated (*N* = 2649)	*p*-value
Maternal age (years), mean (SD)	28.62 (6.41)	28.54 (6.12)	0.555
Number of GP visits in year prior to pregnancy, mean (SD)	5.85 (5.85)	6.49 (6.80)	< 0.001
Charlson Comorbidity Index score, *n* (%)			
0	4131 (70.87)	1803 (68.06)	0.028
1	1345 (23.07)	678 (25.59)	
≥ 2	353 (6.06)	168 (6.34)	
Psychiatric history at the start of pregnancy, *n* (%)			
Alcohol dependence	38 (0.65)	30 (1.13)	0.021
Psychosis	15 (0.26)	16 (0.60)	0.014
Anxiety	1368 (23.47)	868 (32.77)	< 0.001
Self-harm	558 (9.57)	463 (17.48)	< 0.001
Bipolar affective disorder	22 (0.38)	13 (0.49)	0.451
Eating disorder	125 (2.14)	101 (3.81)	< 0.001

continued

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TABLE 2 Descriptive statistics for the mother and child cohort: not prescribed vs. initiated an antidepressant for depression in pregnancy (*continued*)

	Not prescribed (*N* = 5829)	Initiated (*N* = 2649)	*p*-value
Personality disorder	39 (0.67)	32 (1.21)	0.012
Sleep disorder	431 (7.39)	335 (12.65)	< 0.001
Neuropathic pain disorder	222 (3.81)	126 (4.76)	0.041
Use of other medications, *n* (%)			
Medications for physical health problems	4776 (81.94)	2289 (86.41)	< 0.001
Central nervous system agents	1826 (31.33)	1113 (42.02)	< 0.001
Prescribed nutritional supplements	854 (14.65)	457 (17.25)	0.002
Smoking status at the start of pregnancy, *n* (%)			
Never smoked	2331 (39.99)	782 (29.52)	< 0.001
Current or ex-smoker	3468 (59.50)	1850 (69.84)	
Unknown	30 (0.51)	17 (0.64)	
Recorded severity of past depression, *n* (%)			
Mild	4526 (77.65)	2003 (75.61)	< 0.001
Severe	165 (2.83)	156 (5.89)	
Unknown	1138 (19.52)	490 (18.50)	
Region of the general practice, *n* (%)			
North East/North West/ Yorkshire and the Humber	1160 (19.90)	510 (19.25)	< 0.001
East Midlands/West Midlands/East of England	1305 (22.39)	654 (24.69)	
South West/South Central/ South East	1759 (30.18)	743 (28.05)	
London	443 (7.60)	134 (5.06)	
Northern Ireland	146 (2.50)	99 (3.74)	
Scotland	537 (9.21)	273 (10.31)	
Wales	479 (8.22)	236 (8.91)	
Year of pregnancy, *n* (%)			
1995–97	114 (1.96)	37 (1.40)	< 0.001
1998–2000	252 (4.32)	137 (5.17)	
2001–03	816 (14.00)	452 (17.06)	
2004–06	1351 (23.18)	579 (21.86)	
2007–09	1519 (26.06)	604 (22.80)	
2010–12	1777 (30.49)	840 (31.71)	

p-values for comparisons of categorical variables were obtained using Pearson's chi-square test. *p*-values for comparisons of continuous variables were obtained using Student's *t*-test.

TABLE 3 Cohort outcomes by treatment status: not prescribed vs. initiated an antidepressant for depression in pregnancy

	Cohort used for multivariable regression analyses		Subset used for propensity score-matched regression analyses	
	Not prescribed	Initiated	Not prescribed	Initiated
Women's cohort	*N* = 12,801	*N* = 6177	*N* = 5679	*N* = 5679
Number of GP consultations, mean (SD)				
During pregnancy	0.92 (0.93)	1.29 (1.96)	0.91 (0.93)	1.27 (1.90)
0–6 months after pregnancy	0.60 (0.64)	0.67 (0.71)	0.60 (0.66)	0.64 (0.68)
6–12 months after pregnancy	0.44 (0.57)	0.51 (0.64)	0.45 (0.59)	0.49 (0.61)
12–18 months after pregnancy	0.43 (0.58)	0.47 (0.62)	0.43 (0.59)	0.46 (0.59)
18–24 months after pregnancy	0.40 (0.55)	0.45 (0.60)	0.41 (0.57)	0.43 (0.58)
Number of GP consultations for depression, mean (SD)				
During pregnancy	0.05 (0.17)	0.11 (0.59)	0.05 (0.17)	0.11 (0.61)
0–6 months after pregnancy	0.03 (0.11)	0.06 (0.16)	0.03 (0.11)	0.06 (0.15)
6–12 months after pregnancy	0.02 (0.09)	0.04 (0.12)	0.02 (0.09)	0.04 (0.12)
12–18 months after pregnancy	0.02 (0.09)	0.03 (0.10)	0.02 (0.08)	0.03 (0.10)
18–24 months after pregnancy	0.02 (0.08)	0.03 (0.10)	0.02 (0.08)	0.03 (0.10)
Consulted with GP for self-harm, *n* (%)				
During pregnancy	9 (0.07)	9 (0.15)	5 (0.09)	7 (0.12)
0–6 months after pregnancy	11 (0.09)	11 (0.18)	5 (0.09)	9 (0.16)
6–12 months after pregnancy	9 (0.07)	13 (0.21)	3 (0.05)	10 (0.18)
12–18 months after pregnancy	9 (0.07)	6 (0.10)	3 (0.05)	5 (0.09)
18–24 months after pregnancy	10 (0.08)	1 (0.02)	5 (0.09)	0 (0.00)
Referred by GP for depression, *n* (%)				
During pregnancy	140 (1.09)	36 (0.58)	74 (1.30)	33 (0.58)
0–6 months after pregnancy	59 (0.46)	34 (0.55)	24 (0.42)	28 (0.49)
6–12 months after pregnancy	42 (0.33)	25 (0.40)	21 (0.37)	24 (0.42)
12–18 months after pregnancy	29 (0.23)	29 (0.47)	12 (0.21)	27 (0.48)
18–24 months after pregnancy	22 (0.17)	15 (0.24)	11 (0.19)	13 (0.23)
Still or again on antidepressants at end of follow-up, *n* (%)	985 (7.69)	941 (15.23)	459 (8.09)	844 (14.86)

continued

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TABLE 3 Cohort outcomes by treatment status: not prescribed vs. initiated an antidepressant for depression in pregnancy (*continued*)

	Cohort used for multivariable regression analyses		Subset used for propensity score-matched regression analyses	
	Not prescribed	Initiated	Not prescribed	Initiated
Women's cohort with linked HES inpatient data	*N* = 7390	*N* = 3482	*N* = 3063	*N* = 3063
Admitted as an inpatient for a mental health issue, *n* (%)				
During pregnancy	7 (0.09)	7 (0.20)	3 (0.10)	3 (0.10)
0–6 months after pregnancy	12 (0.16)	16 (0.46)	7 (0.23)	10 (0.33)
6–12 months after pregnancy	12 (0.16)	19 (0.55)	6 (0.20)	14 (0.46)
12–18 months after pregnancy	7 (0.09)	13 (0.37)	3 (0.10)	8 (0.26)
18–24 months after pregnancy	11 (0.15)	9 (0.26)	3 (0.10)	6 (0.20)
Women's cohort with linked HES outpatient data	*N* = 6173	*N* = 2736	*N* = 2378	*N* = 2378
Treated as outpatient for mental health issue, *n* (%)				
During pregnancy	107 (1.73)	75 (2.74)	39 (1.64)	60 (2.52)
0–6 months after pregnancy	101 (1.64)	89 (3.25)	40 (1.68)	65 (2.73)
6–12 months after pregnancy	87 (1.41)	70 (2.56)	36 (1.51)	47 (1.98)
12–18 months after pregnancy	63 (1.02)	67 (2.45)	25 (1.05)	49 (2.06)
18–24 months after pregnancy	50 (0.81)	46 (1.68)	27 (1.14)	33 (1.39)
Women's cohort with linked HES A&E data	*N* = 4381	*N* = 1883	*N* = 1536	*N* = 1536
Number of A&E attendances, mean (SD)				
During pregnancy	0.08 (0.30)	0.10 (0.31)	0.09 (0.23)	0.09 (0.30)
0–6 months after pregnancy	0.04 (0.11)	0.04 (0.12)	0.04 (0.12)	0.04 (0.10)
6–12 months after pregnancy	0.03 (0.10)	0.04 (0.12)	0.04 (0.11)	0.04 (0.10)
12–18 months after pregnancy	0.03 (0.09)	0.04 (0.11)	0.03 (0.12)	0.04 (0.10)
18–24 months after pregnancy	0.03 (0.09)	0.04 (0.11)	0.03 (0.11)	0.04 (0.11)
Offspring cohort	*N* = 5829	*N* = 2649	*N* = 2245	*N* = 2245
Child diagnosed with autism, *n* (%)	92 (1.58)	49 (1.85)	27 (1.20)	44 (1.96)
Child diagnosed with ADHD, *n* (%)	59 (1.01)	45 (1.70)	25 (1.11)	36 (1.60)
Child diagnosed with intellectual disability, *n* (%)	26 (0.45)	15 (0.57)	12 (0.53)	9 (0.40)

Table 4 presents results relating to women's use of primary care services during pregnancy and within each of the four additional 6-month follow-up periods. Crude regression estimates suggested that women who had initiated an antidepressant consulted more frequently with their GPs, for any reason or specifically for depressive symptoms, during or up to 2 years after pregnancy than women who received no antidepressants. These women were also more likely to be prescribed an antidepressant medication at the end of the 2-year follow-up period. These associations remained after statistical adjustment for measured differences between treatment groups and in propensity score-matched analysis.

Differences between treatment groups in odds of consulting with the GP for episodes of self-harm were imprecise owing to a small number of observations (see *Table 4*). Where estimates were sufficiently powered, we observed greater odds of GP consultations for self-harm between 6 and 12 months after the pregnancy end date associated with initiating an antidepressant in multivariable regression analyses (OR 2.81, 95% CI 1.15 to 6.85). The apparently protective effect of initiating an antidepressant in terms of consulting for self-harm between 18 and 24 months after pregnancy (OR 0.11, 95% CI 0.01 to 0.92) was based on less than three treated individuals who experienced the outcome and is, therefore, likely to be unreliable.

With regard to GP referrals to secondary care services for depression during pregnancy, there was weak evidence that these were less likely among women who had initiated antidepressants compared with women who did not initiate antidepressants in pregnancy when the data were examined using multivariable regression analyses (OR 0.72, 95% CI 0.49 to 1.06) and comparably stronger evidence when using propensity score-matched regression analyses (OR 0.59, 95% CI 0.38 to 0.90). Conversely, we observed evidence for a twofold increased odds of referral to secondary services between 12 and 18 months after the pregnancy end date among women who had initiated antidepressants using both multivariable and propensity score-matched regression models.

Examining differences in continued need for antidepressants at the end of follow-up, we observed that women who had been initiated on an antidepressant in pregnancy were twofold more likely than women who had not been prescribed in the year before or during the study pregnancy to be prescribed an antidepressant 2 years after the pregnancy end date in regression (OR 2.16, 96% CI 1.95 to 2.39) and propensity score analyses.

The results of the analyses presented in *Table 4* were very similar when repeated in the subset of the data with record linkages available to enable additional control for deciles of IMD as a covariate (see *Report Supplementary Material 24*).

The results pertaining to women's use of secondary care services are presented in *Table 5*. These were broadly consistent with results for primary care outcomes in suggesting that odds of in-patient admission or out-patient treatment for a mental health problem were greater among women who had initiated antidepressants. However, low statistical power resulted in wide confidence intervals (CIs) around some estimates. While crude regression analyses suggested that A&E attendances were more common among women who had initiated antidepressants, these associations did not persist on statistical adjustment for potential confounders and/or matching on propensity scores.

Associations between initiation of an antidepressant and diagnoses related to neurodevelopmental problems in offspring are reported in *Table 6*. While we observed little evidence of associations in crude and multivariable regression analyses, there was some evidence for increased odds of offspring autism with initiation of an antidepressant in propensity score-matched analyses (OR 1.64, 95% CI 1.01, 2.66). There was evidence of increased odds of offspring ADHD with initiation of antidepressants in crude regression analyses, although this association attenuated on statistical adjustment for potential confounders and in propensity score-matched regression analyses, albeit with wide CIs. We observed little evidence for a difference in odds of offspring intellectual disability with initiation of an antidepressant during pregnancy.

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TABLE 4 Association between initiation of an antidepressant in pregnancy and women's primary care outcomes

	Multivariable regression				Propensity score-matched regression	
	Crude[a]	*p*-value	Fully adjusted[b]	*p*-value	IRR (95% CI)	*p*-value
Number of GP consultations[c]						
During pregnancy	1.26 (1.22 to 1.30)	< 0.001	1.23 (1.19 to 1.26)	< 0.001	1.26 (1.21 to 1.31)	< 0.001
0–6 months after pregnancy	1.11 (1.08 to 1.15)	< 0.001	1.07 (1.04 to 1.11)	< 0.001	1.07 (1.03 to 1.12)	< 0.001
6–12 months after pregnancy	1.15 (1.10 to 1.19)	< 0.001	1.10 (1.06 to 1.15)	< 0.001	1.09 (1.04 to 1.14)	< 0.001
12–18 months after pregnancy	1.11 (1.06 to 1.15)	< 0.001	1.07 (1.03 to 1.12)	0.001	1.06 (1.01 to 1.11)	0.025
18–24 months after pregnancy	1.12 (1.07 to 1.16)	< 0.001	1.09 (1.04 to 1.14)	< 0.001	1.07 (1.02 to 1.12)	0.011
Number of GP consultations for depression[c]						
During pregnancy	1.65 (1.52 to 1.80)	< 0.001	1.67 (1.53 to 1.82)	< 0.001	1.66 (1.50 to 1.83)	< 0.001
0–6 months after pregnancy	1.97 (1.80 to 2.15)	< 0.001	1.94 (1.76 to 2.13)	< 0.001	1.89 (1.68 to 2.11)	< 0.001
6–12 months after pregnancy	1.65 (1.49 to 1.83)	< 0.001	1.57 (1.41 to 1.75)	< 0.001	1.59 (1.40 to 1.81)	< 0.001
12–18 months after pregnancy	1.64 (1.47 to 1.84)	< 0.001	1.58 (1.41 to 1.77)	< 0.001	1.72 (1.49 to 1.97)	< 0.001
18–24 months after pregnancy	1.54 (1.36 to 1.74)	< 0.001	1.47 (1.29 to 1.67)	< 0.001	1.48 (1.27 to 1.73)	< 0.001
Consulted with GP for self-harm[d]						
During pregnancy	2.11 (0.81 to 5.53)	0.127	1.92 (0.75 to 4.91)	0.174	1.32 (0.40 to 4.36)	0.651
0–6 months after pregnancy	2.07 (0.90 to 4.79)	0.087	1.64 (0.70 to 3.82)	0.252	1.80 (0.60 to 5.38)	0.292
6–12 months after pregnancy	3.00 (1.28 to 7.02)	0.011	2.81 (1.15 to 6.85)	0.023	3.34 (0.92 to 12.13)	0.067
12–18 months after pregnancy	1.38 (0.49 to 3.88)	0.540	1.36 (0.49 to 3.79)	0.557	1.67 (0.40 to 6.98)	0.484
18–24 months after pregnancy	0.21 (0.03 to 1.62)	0.133	0.11 (0.01 to 0.92)	0.042	N/A	N/A
Referred by GP to secondary services for depression[d]						
During pregnancy	0.74 (0.51 to 1.08)	0.124	0.72 (0.49 to 1.06)	0.092	0.59 (0.38 to 0.90)	0.015
0–6 months after pregnancy	1.20 (0.78 to 1.82)	0.409	1.10 (0.71 to 1.70)	0.671	1.17 (0.68 to 2.02)	0.579

TABLE 4 Association between initiation of an antidepressant in pregnancy and women's primary care outcomes (*continued*)

	Multivariable regression				Propensity score-matched regression	
	Crude[a]	*p*-value	Fully adjusted[b]	*p*-value	IRR (95% CI)	*p*-value
6–12 months after pregnancy	1.23 (0.75 to 2.03)	0.405	1.15 (0.69 to 1.93)	0.597	1.14 (0.64 to 2.06)	0.655
12–18 months after pregnancy	2.08 (1.24 to 3.48)	0.005	2.04 (1.21 to 3.44)	0.008	2.26 (1.14 to 4.46)	0.019
18–24 months after pregnancy	1.41 (0.73 to 2.73)	0.301	1.24 (0.59 to 2.58)	0.571	1.18 (0.53 to 2.64)	0.684
Prescription status at end of follow-up[d]						
Prescribed an antidepressant	2.29 (2.08 to 2.53)	< 0.001	2.16 (1.95 to 2.39)	< 0.001	2.06 (1.82 to 2.34)	< 0.001

N/A, not applicable.
[a]Unadjusted association. Incidence risk ratios or ORs with 95% CIs.
[b]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, and region of the general practice.
[c]Incidence risk ratio (95% CI).
[d]OR (95% CI).

Notes
Multivariable regression estimates based on *n* = 6177 initiators and *n* = 12,801 non-initiators. Propensity score-matched regression estimates based on *n* = 5679 initiators and *n* = 5679 non-initiators.

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TABLE 5 Association between initiation of an antidepressant in pregnancy and women's secondary care outcomes

	Multivariable regression				Propensity score-matched regression	
	Crude[a]	*p*-value	Fully adjusted[b]	*p*-value	OR (95% CI)	*p*-value
Admitted as inpatient for a mental health issue[c]						
During pregnancy	2.36 (0.76 to 7.39)	0.139	1.66 (0.46 to 5.94)	0.436	1.54 (0.36 to 6.55)	0.562
0–6 months after pregnancy	2.84 (1.34 to 6.01)	0.006	2.22 (0.99 to 4.95)	0.052	1.43 (0.54 to 3.76)	0.470
6–12 months after pregnancy	3.37 (1.64 to 6.96)	0.001	2.81 (1.28 to 6.15)	0.010	2.34 (0.90 to 6.09)	0.082
12–18 months after pregnancy	3.95 (1.58 to 9.92)	0.003	3.43 (1.18 to 9.97)	0.024	2.67 (0.71 to 10.07)	0.147
18–24 months after pregnancy	1.73 (0.72 to 4.20)	0.219	1.28 (0.49 to 3.39)	0.614	2.00 (0.50 to 8.01)	0.327
Treated as out-patient for a mental health issue[c]						
During pregnancy	1.94 (1.43 to 2.65)	< 0.001	1.91 (1.37 to 2.67)	< 0.001	1.97 (1.32 to 2.95)	0.001
0–6 months after pregnancy	2.02 (1.51 to 2.70)	< 0.001	1.92 (1.40 to 2.64)	< 0.001	1.64 (1.10 to 2.44)	0.015
6–12 months after pregnancy	1.84 (1.34 to 2.52)	< 0.001	1.63 (1.15 to 2.31)	0.006	1.31 (0.85 to 2.03)	0.225
12–18 months after pregnancy	2.43 (1.72 to 3.44)	< 0.001	2.32 (1.59 to 3.38)	< 0.001	1.98 (1.22 to 3.22)	0.006
18–24 months after pregnancy	2.09 (1.40 to 3.13)	< 0.001	1.79 (1.13 to 2.85)	0.014	1.22 (0.73 to 2.04)	0.437
Number of A&E attendances[d]						
During pregnancy	1.26 (1.10 to 1.43)	0.001	1.11 (0.98 to 1.27)	0.113	0.98 (0.83 to 1.15)	0.785
0–6 months after pregnancy	1.18 (1.02 to 1.37)	0.027	1.05 (0.91 to 1.21)	0.511	1.02 (0.84 to 1.25)	0.826
6–12 months after pregnancy	1.23 (1.05 to 1.44)	0.012	1.04 (0.90 to 1.22)	0.575	0.95 (0.77 to 1.16)	0.592
12–18 months after pregnancy	1.30 (1.11 to 1.51)	0.001	1.20 (1.03 to 1.41)	0.022	1.05 (0.84 to 1.32)	0.638
18–24 months after pregnancy	1.44 (1.23 to 1.68)	< 0.001	1.34 (1.14 to 1.58)	< 0.001	1.09 (0.88 to 1.34)	0.446

[a]Unadjusted association.
[b]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the general practice, in-patient admission for a mental health problem prior to the study pregnancy, and IMD quintile.
[c]OR (95% CI).
[d]Incidence risk ratio (95% CI).

Notes
Multivariable regression estimates for in-patient admissions based on 3482 initiators and 7390 non-initiators; for outpatient contacts based on 2736 initiators and 6173 non-initiators; for A&E attendances based on 1883 initiators and 4381 non-initiators. Propensity score-matched regression estimates for in-patient admissions based on 3063 initiators and 3063 non-initiators; for outpatient contacts based on 2378 initiators and 2378 non-initiators; for A&E attendances based on 1536 initiators and 1536 non-initiators.

Repeating the analysis presented in *Table 6* on a smaller subset with availability of linked data to enable further adjustment for deciles of IMD led to similar point estimates in multivariable regression for all neurodevelopmental outcomes. The point estimates were attenuated for autism, and inflated for ADHD in the propensity score analysis, albeit with wide CIs due to smaller numbers (see *Report Supplementary Material 25*).

TABLE 6 Association between initiation of an antidepressant in pregnancy and offspring neurodevelopmental outcomes

Offspring neurodevelopmental outcome	Multivariable regression				Propensity score-matched regression[b]	
	Crude[a,b]	*p*-value	Fully adjusted[b,c]	*p*-value		
Autism	1.18 (0.83 to 1.67)	0.366	1.23 (0.85 to 1.78)	0.272	1.64 (1.01 to 2.66)	0.044
ADHD	1.69 (1.14 to 2.50)	0.008	1.48 (0.98 to 2.24)	0.064	1.45 (0.87 to 2.42)	0.158
Intellectual disability	1.27 (0.67 to 2.40)	0.461	1.16 (0.63 to 2.14)	0.634	0.75 (0.31 to 1.78)	0.513

[a]Unadjusted association.
[b]ORs with 95% CIs.
[c]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the general practice.

Notes
Multivariable regression estimates based on *n* = 2649 initiators and *n* = 5829 non-initiators. (5) Propensity score-matched regression estimates based on *n* = 2245 initiators and *n* = 2245 non-initiators.

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Chapter 4 Emulating the antidepressant continuation trial

This chapter describes our emulation of the target trial for examining the risks and potential benefits associated with continuing an antidepressant into pregnancy compared with discontinuing it prior to pregnancy. The specification of the target RCT for this question is provided in *Figure 7*.

Methods

Study cohorts

As described in the previous chapter, depending on the outcome under investigation we used the pregnant women's cohort and the mother and child cohort for analysis. Each of these made optimal use of the available data, as described in *Chapter 2*, *Study cohort selection*.

Statistical analysis

We first compared the characteristics of women in each arm of our target trial, that is women who continued an antidepressant into pregnancy with women who discontinued prior to becoming pregnant, to assess differences in covariate distributions.

Logistic regression models with cluster-robust variance estimators were used to estimate the relative odds of the following outcomes: GP consultations for self-harm, GP referrals to specialist services, admission as an inpatient or outpatient to specialist mental health services, prescription status 2 years after the pregnancy end date, and diagnoses relating to autism, ADHD or intellectual disability in offspring from the age of 4 years.

We used negative binomial regression models with cluster-robust variance estimators to estimate incidence rate ratios for the number of days on which the mother had consulted with her GP, consulted with her GP specifically for depression and attended A&E services during pregnancy and further follow-up periods. To account differential length of follow-up between treatment groups, we included the natural logarithm of a time-at-risk variable in our models, constraining its regression coefficient to one.

Multivariable regression

We estimated crude associations between continuing an antidepressant into pregnancy and the various outcomes described earlier in this report, and then statistically adjusted our estimates for potential confounders (see *Chapter 2*, *Covariates*). All statistical analyses were conducted in Stata 15.1/MP.

Propensity score-matched regression

Using a CART model with 15,000 iterations,[69] we estimated a continuous score capturing women's propensity to continue an antidepressant in pregnancy based on their other measured characteristics. Using the estimated propensity scores, we then matched pregnancies where women continued antidepressants with pregnancies where women discontinued prior to conception. Matches were carried out in a 1 : 1 ratio, without replacement, with a calliper of 0.2 SDs. We evaluated covariate imbalance between treatment groups before and after matching (*Figures 8* and *9*; see *Report Supplementary Materials 26–28* for PSM analyses carried out in cohort subsets in which linked data were also included) and then exported the matched data sets to Stata 15.1/MP for further analysis. No further statistical adjustment for covariates were made as the groups were sufficiently balanced on the propensity score.

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Protocol component	Description	Emulation in observational data
(a) Eligibility criteria	Women trying to become pregnant, who have taken antidepressants in the last year, or are currently taking antidepressants, for the treatment of depressive symptoms.	Between 01.01.1995 and 31.12.2017, we identified all pregnant women within CPRD whose primary care records indicated product codes for antidepressants up to a year prior to conception, as well as Read codes for depression at any time prior to conception. Women had not been prescribed antidepressants in the year prior to conception were excluded from these analyses.
(b) Treatment strategies	Continuing an antidepressant into pregnancy versus discontinuing it prior to becoming pregnant.	Among the women identified under (a), we compared the group whose primary care records indicated antidepressant prescriptions between conception and the pregnancy end date with the group who had not been prescribed antidepressants during this period. We chose a grace period of two months to account for the longer pharmacological half-life of some antidepressants, which could still be active in pregnancy if taken shortly before conception. Anyone prescribed during the grace period was therefore defined as having continued antidepressants into pregnancy.

FIGURE 7 Specification of the target continuation trial.

Results

Descriptive statistics of continuers versus discontinuers of antidepressants

Table 7 describes the characteristics of the study population of the women's cohort by treatment status. There were 61,125 pregnancies in which women had a prior prescription of antidepressants for depression; of these 37,278 women continued the antidepressant into their pregnancy and 23,847 discontinued the antidepressant at least 2 months before the start of pregnancy. Women who continued antidepressants into pregnancy were, on average, 1.2 years older when they became

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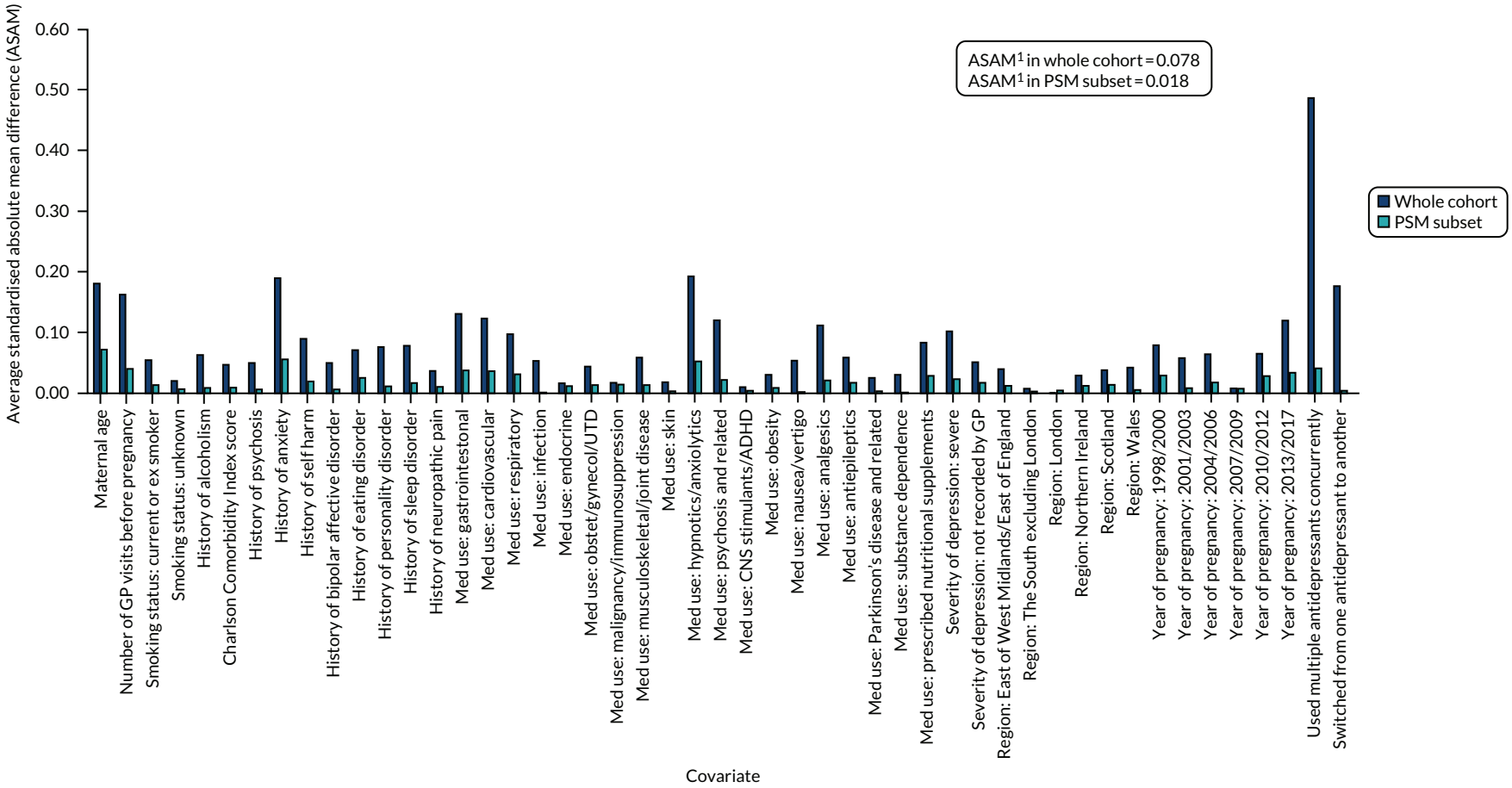

FIGURE 8 Standardised absolute mean differences in covariate distributions between continuers and discontinuers in the women's cohort, before (blue) and after (orange) matching on propensity scores. Note: (1) ASAM = the Average Standardised Absolute Mean difference for all covariates.

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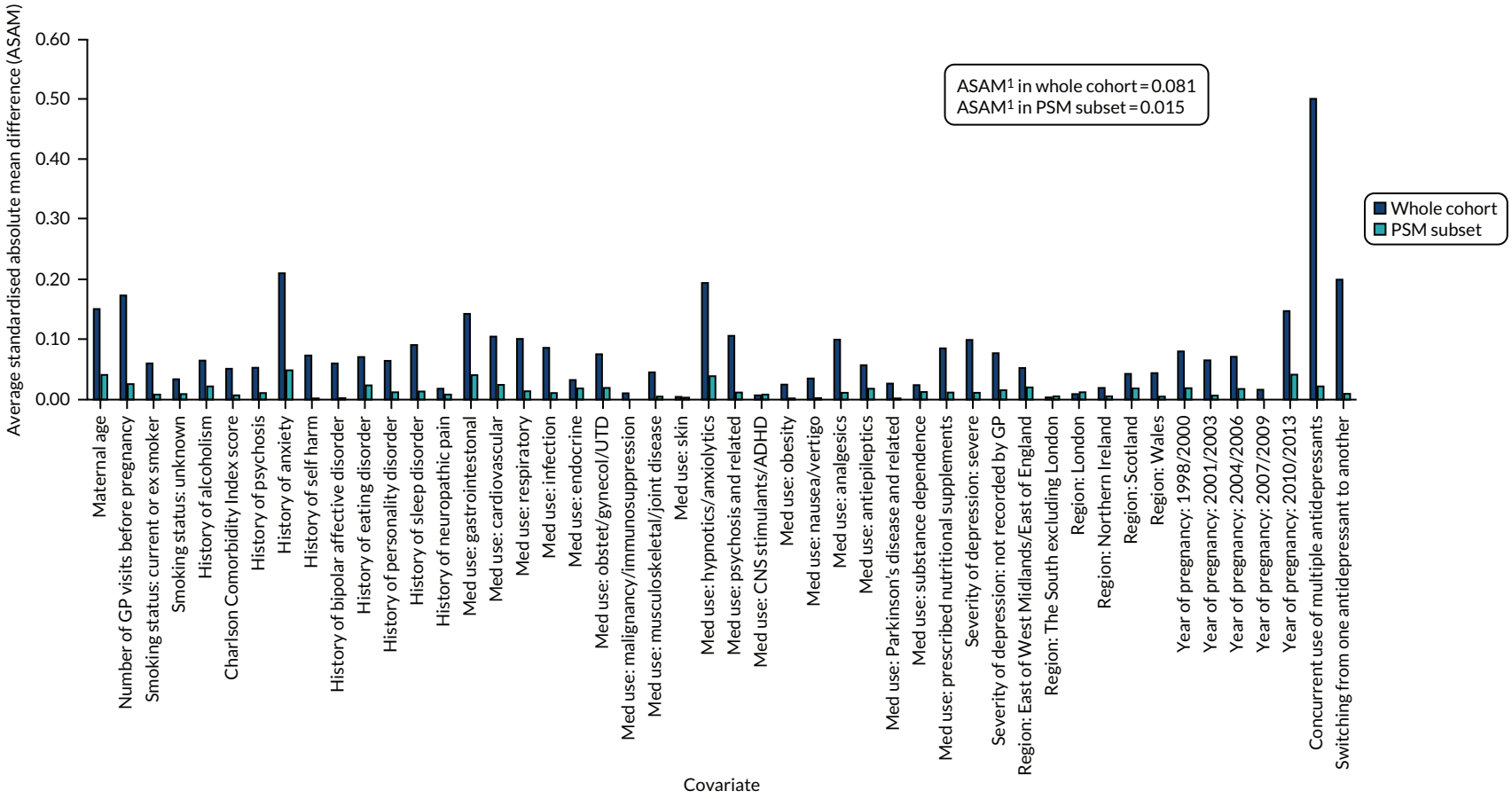

FIGURE 9 Standardised absolute mean differences in covariate distributions between continuers and discontinuers in the mother and child cohort, before (blue) and after (orange) matching on propensity scores. Note: (1) ASAM = the Average Standardised Absolute Mean difference for all covariates.

TABLE 7 Descriptive statistics for women's cohort: discontinued vs. continued

Variable	Discontinued (*N* = 23,847)	Continued (*N* = 37,278)	*p*-value
Maternal age (years), mean (SD)	29.05 (6.30)	30.24 (6.60)	< 0.001
Number of GP visits in year prior to pregnancy, mean (SD)	6.57 (6.54)	7.86 (7.90)	< 0.001
Charlson Comorbidity Index score, *n* (%)			
0	16,651 (69.82)	25,190 (67.57)	< 0.001
1	5640 (23.65)	9427 (25.29)	
≥ 2	1556 (6.52)	2661 (7.14)	
Psychiatric history at the start of pregnancy, *n* (%)			
Alcohol dependence	311 (1.30)	836 (2.24)	< 0.001
Psychosis	84 (0.35)	298 (0.80)	< 0.001
Anxiety	8399 (35.22)	16,651 (44.67)	< 0.001
Self-harm	3324 (13.94)	6462 (17.33)	< 0.001
Bipolar affective disorder	111 (0.47)	354 (0.95)	< 0.001
Eating disorder	698 (2.93)	1634 (4.38)	< 0.001
Personality disorder	254 (1.07)	812 (2.18)	< 0.001
Sleep disorder	2812 (11.79)	5426 (14.56)	< 0.001
Neuropathic pain disorder	1401 (5.87)	2538 (6.81)	< 0.001
Use of other medications, *n* (%)			
Medications for physical health problems	20,446 (85.74)	32,748 (87.85)	< 0.001
Central nervous system agents	10,162 (42.61)	19,273 (51.70)	< 0.001
Prescribed nutritional supplements	2973 (12.47)	5772 (15.48)	< 0.001
Smoking status at the start of pregnancy, *n* (%)			
Never smoked	7867 (32.99)	11,401 (30.58)	< 0.001
Current or ex-smoker	15,868 (66.54)	25,747 (69.07)	
Unknown	112 (0.47)	130 (0.35)	
Recorded severity of past depression, *n* (%)			
Mild	15,927 (66.79)	26,099 (70.01)	< 0.001
Severe	1025 (4.30)	2039 (5.47)	
Unknown	6895 (28.91)	9140 (24.52)	
Region of the general practice, *n* (%)			
North East/North West/Yorkshire and the Humber	4416 (18.52)	6387 (17.13)	< 0.001
East Midlands/West Midlands/East of England	4990 (20.93)	7215 (19.35)	
South West/South Central/South East	6610 (27.72)	10,203 (27.37)	
London	1535 (6.44)	2401 (6.44)	
Northern Ireland	1025 (4.30)	1840 (4.94)	
Scotland	2463 (10.33)	4306 (11.55)	
Wales	2808 (11.78)	4926 (13.21)	

continued

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TABLE 7 Descriptive statistics for women's cohort: discontinued vs. continued (*continued*)

Variable	Discontinued (*N* = 23,847)	Continued (*N* = 37,278)	*p*-value
Year of pregnancy, *n* (%)			
1995–97	1190 (4.99)	1276 (3.42)	
1998–2000	1798 (7.54)	2124 (5.70)	
2001–03	3270 (13.71)	4414 (11.84)	
2004–06	4151 (17.41)	5628 (15.10)	
2007–09	4240 (17.78)	6512 (17.47)	
2010–12	4156 (17.43)	7472 (20.04)	
2013–17	5042 (21.14)	9852 (26.43)	< 0.001
Prescribed multiple antidepressants simultaneously, *n* (%)	3662 (15.36)	14,587 (39.13)	< 0.001
Switched from one antidepressant medication to another, *n* (%)	1346 (5.64)	4183 (11.22)	< 0.001

p-values for comparisons of categorical variables were obtained using Pearson's χ^2 test. *p*-values for comparisons of continuous variables were obtained using Student's *t*-test.

pregnant and had consulted with their GPs on 1.2 more occasions in the year prior to pregnancy than women who had discontinued antidepressants prior to becoming pregnant. On becoming pregnant, women who had continued antidepressants were more likely to have a history of physical health comorbidities and a range of psychiatric comorbidities, to have been prescribed other medications during the study period and to be current or ex-smokers than women who discontinued antidepressants. They were also more likely to have records of both mild and severe depression in their medical histories, to have been prescribed multiple antidepressants at the same time or to have switched from one antidepressant to another during the study period than women who discontinued. There was evidence of a difference between treatment groups in the area of residence within the UK and calendar year of the pregnancy.

Table 8 describes the characteristics of the study population of the mother and child cohort by treatment status used for these analyses (i.e. these refer to women whose pregnancies could be linked to the child's records), with a minimum follow-up of 4 years. There were 25,796 pregnancies in which women had a prior prescription of antidepressants for depression; of these pregnancies, 15,295 women continued the antidepressant into their pregnancy and 10,501 discontinued the antidepressant by the start of pregnancy. The characteristics of women who continued antidepressants into pregnancy compared with those who discontinued in this cohort were similar to those described above for the women's cohort.

Table 9 provides descriptive statistics for the outcomes evaluated (number and percentages for categorical outcomes and the average number of events with SD for count outcomes) in the regression and propensity score analysis. We used the maximum data available for each outcome under investigation and given that linked data were available for only a subset of women those analyses included fewer women. All neurodevelopmental conditions were relatively rare and observed in less than 2% of either group. The prevalence of autism, ADHD and intellectual disability appeared similar in all groups irrespective of whether the women continued or discontinued antidepressants during pregnancy.

TABLE 8 Descriptive statistics for the mother and child cohort: discontinued vs. continued

Variable	Discontinued (*N* = 10,501)	Continued (*N* = 15,295)	*p*-value
Maternal age (years), mean (SD)	29.17 (5.78)	30.06 (5.91)	< 0.001
Number of GP visits in year prior to pregnancy, mean (SD)	6.94 (6.54)	8.30 (7.84)	< 0.001
Charlson Comorbidity Index score, *n* (%)			
0	7257 (69.11)	10,184 (66.58)	< 0.001
1	2577 (24.54)	4029 (26.34)	
≥ 2	667 (6.35)	1082 (7.07)	
Psychiatric history at the start of pregnancy, *n* (%)			
Alcohol dependence	113 (1.08)	306 (2.00)	< 0.001
Psychosis	23 (0.22)	99 (0.65)	< 0.001
Anxiety	3709 (35.32)	7015 (45.86)	< 0.001
Self-harm	1396 (13.29)	2439 (15.95)	< 0.001
Bipolar affective disorder	34 (0.32)	131 (0.86)	< 0.001
Eating disorder	317 (3.02)	687 (4.49)	< 0.001
Personality disorder	103 (0.98)	286 (1.87)	< 0.001
Sleep disorder	1274 (12.13)	2371 (15.50)	< 0.001
Neuropathic pain disorder	635 (6.05)	1001 (6.54)	0.107
Use of other medications, *n* (%)			
Medications for physical health problems	9077 (86.44)	13,531 (88.47)	< 0.001
Central nervous system agents	4469 (42.56)	7816 (51.10)	< 0.001
Prescribed nutritional supplements	1433 (13.65)	2604 (17.03)	< 0.001
Smoking status at the start of pregnancy, *n* (%)			
Never smoked	3585 (34.14)	4829 (31.57)	< 0.001
Current or ex-smoker	6858 (65.31)	10,412 (68.07)	
Unknown	58 (0.55)	54 (0.35)	
Recorded severity of past depression, *n* (%)			
Mild	7354 (70.03)	11,048 (72.23)	< 0.001
Severe	434 (4.13)	917 (6.00)	
Unknown	2713 (25.84)	3330 (21.77)	
Region of the general practice, *n* (%)			
North East/North West/ Yorkshire and the Humber	2121 (20.20)	2899 (18.95)	< 0.001
East Midlands/West Midlands/ East of England	2506 (23.86)	3324 (21.73)	
South West/South Central/ South East	3049 (29.04)	4472 (29.24)	

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TABLE 8 Descriptive statistics for the mother and child cohort: discontinued vs. continued (*continued*)

Variable	Discontinued (*N* = 10,501)	Continued (*N* = 15,295)	*p*-value
London	479 (4.56)	722 (4.72)	
Northern Ireland	480 (4.57)	751 (4.91)	
Scotland	1004 (9.56)	1676 (10.96)	
Wales	862 (8.21)	1451 (9.49)	
Year of pregnancy, *n* (%)			
1995–97	235 (2.24)	194 (1.27)	< 0.001
1998–2000	640 (6.09)	680 (4.45)	
2001–03	1792 (17.07)	2231 (14.59)	
2004–06	2428 (23.12)	3083 (20.16)	
2007–09	2345 (22.33)	3541 (23.15)	
2010–13	3061 (29.15)	5566 (36.39)	
Prescribed multiple antidepressants simultaneously, *n* (%)	1609 (15.32)	6104 (39.91)	< 0.001
Switched from one antidepressant medication to another, *n* (%)	592 (5.64)	1852 (12.11)	< 0.001

p-values for comparisons of categorical variables were obtained using Pearson's χ^2 test. *p*-values for comparisons of continuous variables were obtained using Student's *t*-test.

Results of multivariable and propensity score-matched regression analysis

To control for differences in measured characteristics between treatment groups, we examined associations between treatment status and the various outcomes while adjusting statistically for covariates, and matching on the propensity to initiate antidepressants, as shown in *Tables 10–12*.

For results relating to women's use of primary care services during pregnancy and each of the four additional 6-month follow-up periods, see *Table 10*. Although crude associations suggested that women who had continued antidepressants had consulted with their GPs more frequently for any reason, statistical adjustment for covariates revealed a slight protective effect. However, this finding was not replicated in propensity score-matched regression analyses in which control for potential confounders would have been more efficient. In terms of GP consultations specifically for depression, women who had continued antidepressants consulted more frequently with their GPs than women who had discontinued antidepressants, with consistent associations observed for crude, multivariable and propensity score-matched regression analyses. In general, women who had continued an antidepressant were more likely to have consulted for self-harm or to have been referred to specialist mental health services for depression during pregnancy and in further follow-up periods. Women who had continued antidepressant in pregnancy also had over two-fold odds of still being prescribed antidepressants at 2-year follow-up than women who had discontinued. Repeating these analyses on a subsample with linked data for further adjustment with decile of IMD led to similar results (see *Report Supplementary Material 29*).

In term of outcomes related to secondary care (see *Table 11*), crude associations suggested that women who had continued an antidepressant were more likely than women who had discontinued an antidepressant to have received inpatient or outpatient treatment for a mental health problem during pregnancy or in further follow-up periods. Statistical adjustment for potential confounders and/or matching on propensity scores resulted in weaker associations, but odds generally remained elevated. Crude associations suggested that women who continued antidepressants had attended A&E services

more frequently than those who discontinued antidepressants, although these associations attenuated to the null on statistical adjustment for potential confounders or after matching on the propensity to continue antidepressant treatment.

See *Table 12* for a description of the associations between continuation of an antidepressants and diagnoses of neurodevelopmental disorders in offspring. We observed no differences in odds for autism or for intellectual disability for mothers who continued or discontinued antidepressants during pregnancy. Although we observed lower odds of offspring intellectual disability among women who had continued taking antidepressants, this association attenuated to the null on statistical adjustment for potential confounders and in propensity score-matched regression analyses. Repeating these analyses on the subset of the sample with linked data to further adjust for deciles of IMD led to broadly similar results with wider CIs (see *Report Supplementary Material 30*).

TABLE 9 Cohort outcomes by treatment status: continuation of antidepressants in pregnancy vs. discontinuation of antidepressants in pregnancy

	Cohort used for multivariable regression analyses		Subset used for propensity score-matched regression analyses	
	Discontinued	Continued	Discontinued	Continued
Women's cohort	*N* = 23,847	*N* = 37,278	*N* = 22,650	*N* = 22,650
Number of GP consultations, mean (SD)				
During pregnancy	0.89 (0.92)	1.02 (1.04)	0.89 (0.93)	0.95 (0.96)
0–6 months after pregnancy	0.62 (0.66)	0.68 (0.75)	0.62 (0.67)	0.63 (0.69)
6–12 months after pregnancy	0.47 (0.60)	0.52 (0.68)	0.47 (0.60)	0.49 (0.61)
12–18 months after pregnancy	0.45 (0.59)	0.48 (0.66)	0.45 (0.60)	0.46 (0.60)
18–24 months after pregnancy	0.42 (0.59)	0.45 (0.66)	0.42 (0.60)	0.43 (0.60)
Number of GP consultations for depression, mean (SD)				
During pregnancy	0.01 (0.06)	0.05 (0.16)	0.01 (0.06)	0.04 (0.15)
0–6 months after pregnancy	0.03 (0.11)	0.05 (0.13)	0.03 (0.11)	0.04 (0.12)
6–12 months after pregnancy	0.03 (0.10)	0.03 (0.11)	0.03 (0.10)	0.03 (0.11)
12–18 months after pregnancy	0.02 (0.09)	0.03 (0.10)	0.02 (0.09)	0.03 (0.10)
18–24 months after pregnancy	0.02 (0.09)	0.03 (0.10)	0.02 (0.09)	0.02 (0.09)
Consulted with GP for self-harm, *n* (%)				
During pregnancy	10 (0.04)	37 (0.10)	10 (0.04)	18 (0.08)
0–6 months after pregnancy	15 (0.06)	57 (0.15)	15 (0.07)	34 (0.15)
6–12 months after pregnancy	20 (0.08)	42 (0.11)	19 (0.08)	19 (0.08)
12–18 months after pregnancy	19 (0.08)	59 (0.16)	19 (0.08)	27 (0.12)
18–24 months after pregnancy	11 (0.05)	51 (0.14)	11 (0.05)	21 (0.09)
Referred by GP for depression, *n* (%)				
During pregnancy	29 (0.12)	137 (0.37)	27 (0.12)	80 (0.35)
0–6 months after pregnancy	82 (0.34)	159 (0.43)	76 (0.34)	96 (0.42)
6–12 months after pregnancy	52 (0.22)	136 (0.36)	46 (0.20)	74 (0.33)
12–18 months after pregnancy	55 (0.23)	109 (0.29)	50 (0.22)	63 (0.28)

continued

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TABLE 9 Cohort outcomes by treatment status: continuation of antidepressants in pregnancy vs. discontinuation of antidepressants in pregnancy (*continued*)

	Cohort used for multivariable regression analyses		Subset used for propensity score-matched regression analyses	
	Discontinued	Continued	Discontinued	Continued
18–24 months after pregnancy	40 (0.17)	107 (0.29)	39 (0.17)	65 (0.29)
Still or again on antidepressants at end of follow-up, *n* (%)	2158 (9.05)	8080 (21.67)	2079 (9.18)	4359 (19.25)
Women's cohort with linked HES data	*N* = 13,110	*N* = 19,680	*N* = 12,046	*N* = 12,046
Admitted as in-patient for mental health issue, *n* (%)				
During pregnancy	6 (0.05)	53 (0.27)	5 (0.04)	21 (0.17)
0–6 months after pregnancy	38 (0.29)	101 (0.51)	37 (0.31)	44 (0.37)
6–12 months after pregnancy	28 (0.21)	105 (0.53)	25 (0.21)	48 (0.40)
12–18 months after pregnancy	24 (0.18)	77 (0.39)	22 (0.18)	25 (0.21)
18–24 months after pregnancy	24 (0.18)	87 (0.44)	22 (0.18)	41 (0.34)
Women's cohort with linked HES outpatient data	*N* = 10,388	*N* = 16,377	*N* = 9670	*N* = 9670
Treated as outpatient for mental health issue, *n* (%)				
During pregnancy	100 (0.96)	689 (4.21)	98 (1.01)	275 (2.85)
0–6 months after pregnancy	147 (1.42)	736 (4.49)	144 (1.49)	285 (2.95)
6–12 months after pregnancy	141 (1.36)	614 (3.75)	136 (1.41)	230 (2.38)
12–18 months after pregnancy	136 (1.31)	558 (3.41)	132 (1.37)	223 (2.31)
18–24 months after pregnancy	138 (1.33)	499 (3.05)	134 (1.39)	192 (1.99)
Women's cohort with linked HES A&E data	*N* = 7203	*N* = 12,230	*N* = 6835	*N* = 6835
Number of A&E attendances, mean (SD)				
During pregnancy	0.10 (0.32)	0.10 (0.27)	0.10 (0.32)	0.09 (0.27)
0–6 months after pregnancy	0.04 (0.11)	0.05 (0.13)	0.04 (0.11)	0.04 (0.11)
6–12 months after pregnancy	0.04 (0.11)	0.04 (0.13)	0.04 (0.11)	0.04 (0.10)
12–18 months after pregnancy	0.04 (0.10)	0.04 (0.12)	0.04 (0.11)	0.03 (0.09)
18–24 months after pregnancy	0.03 (0.10)	0.04 (0.12)	0.03 (0.10)	0.03 (0.10)
Offspring cohort, *n* (%)	*N* = 10,501	*N* = 15,295	*N* = 9135	*N* = 9135
Child diagnosed with autism	162 (1.54)	250 (1.63)	146 (1.60)	154 (1.69)
Child diagnosed with ADHD	135 (1.29)	178 (1.16)	119 (1.30)	115 (1.26)
Child diagnosed with intellectual disability	62 (0.59)	65 (0.42)	55 (0.60)	49 (0.54)

TABLE 10 Association between continuation of an antidepressant into pregnancy and women's primary care outcomes

	Multivariable regression				Propensity score-matched regression	
	Crude[a]	*p*-value	Fully adjusted[b]	*p*-value	IRR/OR (95% CI)	*p*-value
Number of GP consultations[c]						
During pregnancy	1.15 (1.13 to 1.17)	< 0.001	1.00 (0.99 to 1.02)	0.807	1.07 (1.05 to 1.09)	< 0.001
0–6 months after pregnancy	1.10 (1.08 to 1.12)	< 0.001	0.96 (0.95 to 0.98)	< 0.001	1.02 (1.00 to 1.05)	0.016
6–12 months after pregnancy	1.11 (1.08 to 1.13)	< 0.001	0.97 (0.95 to 0.99)	0.013	1.03 (1.00 to 1.05)	0.027
12–18 months after pregnancy	1.08 (1.06 to 1.10)	< 0.001	0.95 (0.93 to 0.97)	< 0.001	1.01 (0.99 to 1.04)	0.272
18–24 months after pregnancy	1.06 (1.03 to 1.08)	< 0.001	0.95 (0.93 to 0.97)	< 0.001	1.00 (0.98 to 1.03)	0.815
Number of GP consultations for depression[c]						
During pregnancy	7.45 (6.77 to 8.21)	< 0.001	5.66 (5.13 to 6.25)	< 0.001	6.11 (5.51 to 6.79)	< 0.001
0–6 months after pregnancy	1.43 (1.36 to 1.51)	< 0.001	1.24 (1.17 to 1.31)	< 0.001	1.32 (1.25 to 1.40)	< 0.001
6–12 months after pregnancy	1.26 (1.20 to 1.34)	< 0.001	1.14 (1.07 to 1.21)	< 0.001	1.21 (1.13 to 1.29)	< 0.001
12–18 months after pregnancy	1.30 (1.22 to 1.38)	< 0.001	1.17 (1.10 to 1.25)	< 0.001	1.24 (1.16 to 1.33)	< 0.001
18–24 months after pregnancy	1.20 (1.13 to 1.28)	< 0.001	1.06 (0.99 to 1.14)	0.078	1.13 (1.05 to 1.22)	0.001
Consulted with GP for self-harm[d]						
During pregnancy	2.36 (1.18 to 4.75)	0.016	1.59 (0.76 to 3.29)	0.215	1.79 (0.83 to 3.88)	0.138
0–6 months after pregnancy	2.43 (1.38 to 4.30)	0.002	2.14 (1.19 to 3.85)	0.011	2.27 (1.23 to 4.17)	0.008
6–12 months after pregnancy	1.34 (0.79 to 2.29)	0.277	1.14 (0.66 to 1.95)	0.645	1.00 (0.53 to 1.89)	0.999
12–18 months after pregnancy	1.99 (1.19 to 3.33)	0.009	1.82 (1.05 to 3.18)	0.034	1.42 (0.80 to 2.56)	0.241
18–24 months after pregnancy	2.97 (1.55 to 5.70)	0.001	2.38 (1.25 to 4.53)	0.008	1.91 (0.92 to 3.96)	0.082
Referred by GP to secondary services for depression[d]						
During pregnancy	3.10 (2.08 to 4.64)	< 0.001	2.72 (1.79 to 4.13)	< 0.001	3.04 (1.96 to 4.70)	< 0.001
0–6 months after pregnancy	1.24 (0.95 to 1.62)	0.112	1.16 (0.87 to 1.54)	0.321	1.26 (0.93 to 1.71)	0.128

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TABLE 10 Association between continuation of an antidepressant into pregnancy and women's primary care outcomes (*continued*)

	Multivariable regression				Propensity score-matched regression	
	Crude[a]	*p*-value	Fully adjusted[b]	*p*-value	IRR/OR (95% CI)	*p*-value
6–12 months after pregnancy	1.68 (1.22 to 2.31)	0.002	1.56 (1.12 to 2.18)	0.009	1.61 (1.11 to 2.33)	0.011
12–18 months after pregnancy	1.27 (0.92 to 1.76)	0.151	1.20 (0.84 to 1.72)	0.322	1.26 (0.87 to 1.83)	0.222
18–24 months after pregnancy	1.71 (1.19 to 2.46)	0.003	1.67 (1.13 to 2.47)	0.010	1.67 (1.13 to 2.47)	0.011
Prescription status at end of follow-up[d]						
Prescribed an antidepressant	2.80 (2.66 to 2.94)	< 0.001	2.40 (2.27 to 2.53)	< 0.001	2.37 (2.24 to 2.51)	< 0.001

[a]Unadjusted association.
[b]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the general practice, concurrent use of multiple antidepressants, and switching from one antidepressant to another.
[c]Incidence risk ratios with 95% CIs.
[d]ORs with 95% CIs.

Note
Multivariable regression estimates based on 23,847 continuers and 37,278 discontinuers. Propensity score-matched regression estimates based on 22,650 continuers and 22,650 discontinuers.

TABLE 11 Association between continuation of an antidepressant into pregnancy and maternal secondary care outcomes

	Multivariable regression				Propensity score-matched regression	
	Crude[a]	*p*-value	Fully adjusted[b]	*p*-value	OR/IRR (95% CI)	*p*-value
Admitted as inpatient for a mental health issue[c]						
During pregnancy	5.94 (2.55 to 13.81)	< 0.001	3.52 (1.49 to 8.34)	0.004	4.20 (1.59 to 11.14)	0.004
0–6 months after pregnancy	1.77 (1.22 to 2.58)	0.003	1.31 (0.87 to 1.99)	0.199	1.19 (0.77 to 1.84)	0.437
6–12 months after pregnancy	2.51 (1.65 to 3.80)	< 0.001	1.98 (1.29 to 3.03)	0.002	1.92 (1.19 to 3.12)	0.008
12–18 months after pregnancy	2.14 (1.35 to 3.39)	0.001	1.48 (0.91 to 2.40)	0.111	1.14 (0.64 to 2.02)	0.662
18–24 months after pregnancy	2.42 (1.53 to 3.81)	< 0.001	1.83 (1.14 to 2.93)	0.012	1.87 (1.11 to 3.13)	0.018
Treated as out-patient for a mental health issue[c]						
During pregnancy	4.60 (3.72 to 5.69)	< 0.001	2.92 (2.34 to 3.64)	< 0.001	2.90 (2.30 to 3.66)	< 0.001
0–6 months after pregnancy	3.28 (2.74 to 3.92)	< 0.001	2.08 (1.72 to 2.52)	< 0.001	2.01 (1.64 to 2.46)	< 0.001
6–12 months after pregnancy	2.83 (2.35 to 3.41)	< 0.001	1.84 (1.51 to 2.23)	< 0.001	1.71 (1.38 to 2.12)	< 0.001
12–18 months after pregnancy	2.66 (2.20 to 3.22)	< 0.001	1.81 (1.48 to 2.22)	< 0.001	1.71 (1.37 to 2.12)	< 0.001
18–24 months after pregnancy	2.33 (1.93 to 2.82)	< 0.001	1.59 (1.30 to 1.94)	< 0.001	1.44 (1.15 to 1.80)	0.001
Number of A&E attendances[d]						
During pregnancy	1.07 (1.00 to 1.15)	0.050	1.01 (0.94 to 1.08)	0.752	0.97 (0.90 to 1.06)	0.536
0–6 months after pregnancy	1.12 (1.03 to 1.21)	0.007	1.05 (0.97 to 1.13)	0.213	1.02 (0.93 to 1.11)	0.647
6–12 months after pregnancy	1.09 (1.00 to 1.20)	0.060	1.01 (0.93 to 1.10)	0.777	1.00 (0.91 to 1.11)	0.950

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TABLE 11 Association between continuation of an antidepressant into pregnancy and maternal secondary care outcomes (*continued*)

	Multivariable regression				Propensity score-matched regression	
	Crude[a]	*p*-value	Fully adjusted[b]	*p*-value	OR/IRR (95% CI)	*p*-value
12–18 months after pregnancy	1.05 (0.96 to 1.15)	0.321	0.97 (0.90 to 1.06)	0.554	0.92 (0.84 to 1.02)	0.099
18–24 months after pregnancy	1.10 (1.01 to 1.21)	0.039	0.99 (0.91 to 1.08)	0.873	0.96 (0.87 to 1.07)	0.459

[a]Unadjusted association.

[b]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the general practice, in-patient admission for a mental health problem prior to the study pregnancy, concurrent use of multiple antidepressants, and switching from one antidepressant to another, and IMD quintile.

[c]OR with 95% CI.

[d]Incidence risk ratios with 95% CI.

Notes

Multivariable regression estimates for inpatient admissions based on 19,680 continuers and 13,110 discontinuers; for outpatient contacts based on 16,377 continuers and 10,388 discontinuers; for A&E attendances based on 12,230 continuers and 7203 discontinuers. Propensity score-matched regression estimates for inpatient admissions based on 12,046 continuers and 12,046 discontinuers; for outpatient contacts based on 9670 continuers and 9670 discontinuers; for A&E attendances based on 6835 continuers and 6835 discontinuers.

TABLE 12 Association between continuation of an antidepressant into pregnancy and offspring neurodevelopmental outcomes

	Multivariable regression				Propensity score-matched regression	
	Crude[a]		Fully adjusted[b]			
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Autism	1.06 (0.87 to 1.29)	0.563	1.10 (0.90 to 1.35)	0.354	1.06 (0.84 to 1.32)	0.639
ADHD	0.90 (0.72 to 1.13)	0.380	1.02 (0.80 to 1.29)	0.889	0.97 (0.75 to 1.25)	0.792
Intellectual disability	0.72 (0.51 to 1.02)	0.063	0.81 (0.55 to 1.19)	0.279	0.89 (0.61 to 1.31)	0.555

[a]Unadjusted association.

[b]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the GP practice, concurrent use of multiple antidepressants, and switching from one antidepressant to another.

Notes

Multivariable regression estimates based on 15,295 continuers and 10,501 discontinuers. Propensity score-matched regression estimates based on 9135 continuers and 9135 discontinuers.

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Chapter 5 Instrumental variable analysis

We carried IV analyses to further strengthen causal inference from associations reported in the emulated initiation and continuation trials. IV regression can allow the estimation of causal effects in the presence of unmeasured treatment–outcome confounding. A well-defined IV is associated with the outcome variable only because of the instrument's effect on the treatment variable and has no confounders of the instrument–outcome association. We chose GPs' prescribing behaviour with regard to their prior pregnant patients with depression as an IV, and then used this to instrument the decision to initiate or continue an antidepressant for their current pregnant patient with depression. Conceptually, the IV is intended to capture the willingness of GPs to prescribe antidepressants to pregnant patients given the potential concerns around teratogenicity. For this reason, we carried out these analyses only for the neurodevelopmental outcomes under study in relation to initiation or continuation of antidepressants in pregnancy.

Definition of potential instrumental variables

We defined 10 potential IVs based on the treatment decisions made in an increasing number of prior consultations with other pregnant patients with depression. For instance, the first instrument was defined as the treatment decision made in the last consultation with another pregnant patient, the second instrument as the number of times the GP had prescribed an antidepressant in the last two consultations with other pregnant patients, the third instrument as the number of times an antidepressant was prescribed among the last three pregnant patients, and so on. It is worth noting that instruments based on *n* prior treatment decisions will require GPs to have seen at least *n* prior pregnant patients with depression. IVs based on larger numbers of prior treatment decisions will, therefore, result in smaller numbers of observations being available for IV analysis. For each instrument, we calculated F-statistics for first-stage regressions and checked for associations between the instrument and the potential confounders of the treatment–outcome association using bias plots. We also examined the number of observations with complete IVs for each of the 10 IV definitions. Our aim was to select the instrument that was optimally associated with the treatment variable but minimally associated with potential confounders of the treatment–outcome association, while optimising the number of observations available for IV analysis.

Methods

Identification of the general practitioner

Many women in our sample will have been seen by different GPs during the course of their pregnancies. Therefore, we aimed to identify the GP who, by issuing or not issuing an antidepressant, had determined the woman's the treatment status, and defined the IV on that GP's prior prescribing behaviour. That is, for patients who initiated or continued an antidepressant into pregnancy, we identified the first GP to have prescribed an antidepressant in pregnancy, whereas for patients who received no treatment or discontinued an existing prescription, we identified the GP who had attended the first consultation after the estimated date of conception. Where antidepressants were issued as part of a repeat prescription, we did not consider prescriptions for which there had been no face-to-face or telephone consultation. We made these exclusions because it may be likely that, in these instances, the GPs would have been unaware of their patient being pregnant.

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Treatment variables

We considered two treatment variables. The first treatment variable captured the initiation of an antidepressant during pregnancy compared with receiving no antidepressant treatment, and the second captured the continuation of an antidepressant into pregnancy compared with discontinuing at least 2 months prior to conception, as described in *Chapter 2*, *Definition of treatment groups*.

Outcome variables

Our outcome variables for these analyses included a diagnosis of (1) autism, (2) ADHD or (3) intellectual disability when the child was at least 4 years of age.

Statistical analysis

For all observations with a non-missing value on the IV, we estimated the associations using ordinary least squares (OLS) regression (using a linear probability model for the binary outcomes) to allow for comparison of these estimates with associations estimated using the IV method applying two-stage least squares regression. All associations were estimated using robust standard errors to account for clustering of patients treated by the same GP.

Results

Selection and evaluation of the instrumental variable

We found an IV based on eight prior consultations with other pregnant patients to be optimally associated with the treatment variables, while including an optimal number of observations in IV analyses. For the IV based on eight prior consultations, we checked associations of the instrument with potential confounders of the treatment–outcome association using bias component plots.[75] Results from these analyses suggested weak associations of the instrument with the following covariates: (1) number of GP visits in the year prior to pregnancy; (2) region of residence in the UK; (3) calendar year of the pregnancy; (4) concurrent use of multiple antidepressants; (5) maternal age; and (6) Charlson Comorbidity Index score. We, therefore, adjusted for these characteristics in the analytical models.

Results of standard and instrumental variable analysis

The results of the standard and IV analyses are presented in *Table 13*. Among observations with a non-missing value on the IV, there was no observed association between initiation or continuation of antidepressants and any of the neurodevelopmental outcomes in either the standard or the IV approach, although CIs were wide in all analyses. Using Wu–Hausman *F*-tests, there was little evidence for differences in effect size between OLS regression and IV estimates for these outcomes. This does not provide any evidence that residual confounding can explain our OLS results.

TABLE 13 Instrumental variable analysis: effect of initiating or continuing antidepressants on offspring neurodevelopmental outcomes

	OLSs regression coefficient	*p*-value	Two-stage least squares regression coefficient	*p*-value	Wu–Hausman F-test *p*-value
Effect of initiating an antidepressant					
Offspring autism	0.006 (–0.05 to 0.017)	0.300	0.040 (–0.039 to 0.119)	0.321	0.391
Offspring ADHD	0.002 (–0.006 to 0.010)	0.648	–0.004 (–0.059 to 0.050)	0.873	0.820
Offspring ID	0.003 (–0.003 to 0.009)	0.279	0.007 (–0.031 to 0.044)	0.735	0.865

TABLE 13 Instrumental variable analysis: effect of initiating or continuing antidepressants on offspring neurodevelopmental outcomes (*continued*)

	OLSs regression coefficient	*p*-value	Two-stage least squares regression coefficient	*p*-value	Wu–Hausman F-test *p*-value
Effect of continuing an antidepressant					
Offspring autism	0.006 (–0.001 to 0.013)	0.083	–0.010 (–0.061 to 0.040)	0.690	0.520
Offspring ADHD	0.003 (–0.002 to 0.008)	0.211	0.000 (–0.039 to 0.040)	0.982	0.890
Offspring ID	–0.001 (–0.004 to 0.003)	0.755	–0.005 (–0.035 to 0.025)	0.740	0.768

Comparison of initiators with non-initiators adjusted for calendar year, region within the UK, and number of GP visits in the year prior to conception. Comparison of continuers with discontinuers adjusted for calendar year, region within the UK, number of GP visits in the year prior to conception, maternal age, concurrent use of multiple antidepressants and Charlson's Comorbidity Index scores. (6) Regression estimates based on 760 initiators and 2878 non-initiators, and on 2014 continuers and 4738 discontinuers.

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Chapter 6 Analysis of treatment-discordant pregnancies

The matched treatment-discordance design is another effective approach to strengthening causal inference when using observational data. Where the outcomes relate to siblings born to the same mother in treatment-discordant (or other exposure) pregnancies, this design is also known as a sibling or sibship design and is increasingly used in intergenerational observational studies strengthening causal inference of prenatal factors.[32,73,74] Given that we study both maternal and child outcomes in this study, and the unit for sampling was pregnant women with exposure discordant pregnancies, we refer to this analysis as a treatment-discordance design.

In this design, we consider consecutive pregnancies to the same woman that differed in terms of treatment status, for instance where they had received no antidepressants in the first pregnancy but initiated an antidepressant in the second pregnancy. By examining pregnancies to the same women as matched observations, all characteristics that are constant between pregnancies (e.g. time-stable socioeconomic factors or genetic risk for depression) cease to confound the treatment–outcome association. For this reason, the analysis of treatment-discordant pregnancies can help to reduce bias due to unmeasured time-stable confounders and, therefore, allow stronger causal inference from observational data. If associations observed in the emulated initiation and continuation trials (described in *Chapters 3* and *4*) are replicated in an analysis of treatment-discordant pregnancies, this would, therefore, suggest robustness against shared unmeasured confounding.

Methods

We first identified all women who had contributed more than one pregnancy to the study cohort and who differed in treatment status between pregnancies. Among these matched treatment-discordant pregnancies, only those that also differed in terms of outcome contributed to the analysis. Therefore, an inherent limitation of this approach is that the smaller number of treatment- and outcome-discordant observations can limit statistical power.

Definition of treatment discordance

Treatment discordance was defined as (1) having initiated an antidepressant in one pregnancy and having received no treatment in another pregnancy, or (2) having continued an antidepressant in one pregnancy and having discontinued antidepressants in another. All women contributing at least two pregnancies that were discordant in terms of treatment status were considered in the analysis.

Definition of outcome discordance

Women's use of primary care

To maximise statistical power, we combined all follow-up beyond the pregnancy end date into a single 2-year window. For count outcomes, discordance was considered as the difference in count value between pregnancies. For example, having consulted with a GP on 2 more days in one pregnancy compared with another. Owing to small cell counts, it was only possible to examine primary care outcomes using the discordant-treatment method. We, therefore, report the following count outcomes in our analyses: (1) frequency of GP consultation during and after pregnancy; (2) frequency of GP consultation for depressive symptoms during or after pregnancy; and (3) the binary outcomes of women's antidepressant prescription status 2 years after pregnancy.

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Offspring neurodevelopmental outcomes

We examined discordance in matched offspring in terms of a diagnosis of (1) autism, (2) ADHD or (3) intellectual disability. These analyses were carried out for continuation compared with discontinuation of antidepressants only, as there were insufficient numbers to estimate the results for the initiation compared with no initiation of antidepressant analyses for these outcomes.

Statistical analysis

For binary outcomes, we first estimated associations using standard logistic regression models to assess whether or not the associations observed in *Chapters 3* and *4* of this report were present in this subset of the data. Associations were estimated using robust standard errors, clustering on women's patient identification numbers, as our estimates were based on comparisons of more than one pregnancy in the same women. We then used fixed-effects logistic regression models to estimate the matched treatment–outcome association. We followed a similar approach for count outcomes, first estimating associations using standard negative binomial regression and second using a fixed-effects negative binomial regression model to estimate the matched treatment–outcome association. We statistically adjusted all associations for calendar year and maternal age at delivery.

Results

Table 14 shows the results of the treatment-discordant design, as applied to women's primary care outcomes. It is evident that owing to the smaller cell counts these estimates were less precise in both the standard regression analyses on this subset of data and the fixed-effects analyses, reflecting the matched design. In the service use outcomes relating to antidepressant initiation, women who initiated an antidepressant consulted with their GP more frequently for depressive symptoms than when they received no treatment in another pregnancy. In the service use outcomes relating to antidepressant continuation, women who continued antidepressants in one pregnancy compared with discontinuing in another consulted with their GPs more frequently for any reason as well as for depression specifically and were more likely to be prescribed antidepressants at 2 years of follow-up.

Table 15 shows the results of the treatment-discordant design, as applied to the neurodevelopmental outcomes in offspring of women who continued antidepressants in one pregnancy but not the other. Similar analyses were not possible for discordance in relation to initiation of antidepressants owing to zero cell counts. The results suggest little evidence of an association between continuation of antidepressants and any of the neurodevelopmental outcomes, although the CIs were wide.

TABLE 14 Relative incidence or odds of primary care outcomes among matched treatment-discordant pregnancies to the same women

	Standard negative binomial regression		Fixed-effects negative binomial regression	
	IRR/OR (95% CI)	*p*-value	IRR/OR (95% CI)	*p*-value
Matched pregnancies discordant for initiation				
GP consultations[a]				
During pregnancy	1.03 (0.86 to 1.23)	0.768	1.14 (0.92 to 1.41)	0.225
In 2 years following pregnancy	1.11 (0.88 to 1.39)	0.386	0.97 (0.79 to 1.19)	0.758
GP consultations for depression[a]				
During pregnancy	1.24 (0.77 to 1.98)	0.374	1.17 (0.52 to 2.65)	0.702
In 2 years following pregnancy	1.77 (1.02 to 3.07)	0.042	2.05 (1.13 to 3.72)	0.018

TABLE 14 Relative incidence or odds of primary care outcomes among matched treatment-discordant pregnancies to the same women (*continued*)

	Standard negative binomial regression		Fixed-effects negative binomial regression	
	IRR/OR (95% CI)	*p*-value	IRR/OR (95% CI)	*p*-value
	Standard logistic regression		Fixed-effects logistic regression	
Prescribed at end of follow-up[b]	1.31 (0.38 to 4.58)	0.670	1.13 (0.31 to 4.07)	0.858
Matched pregnancies discordant for continuation[c]				
GP consultations[a]				
During pregnancy	1.12 (1.06 to 1.18)	< 0.001	1.06 (1.00 to 1.12)	0.046
In 2 years following pregnancy	1.09 (1.03 to 1.15)	0.004	1.07 (1.01 to 1.13)	0.023
GP consultations for depression[a]				
During pregnancy	3.20 (2.32 to 4.41)	< 0.001	6.23 (4.01 to 9.66)	< 0.001
In 2 years following pregnancy	1.27 (1.14 to 1.43)	< 0.001	1.24 (1.08 to 1.43)	0.002
	Standard logistic regression		Fixed-effects logistic regression	
Prescribed at end of follow-up[b]	1.81 (1.41 to 2.32)	< 0.001	1.82 (1.41 to 2.36)	< 0.001

[a]Incidence risk ratio (95% CI).
[b]OR (95% CI).
[c]Analyses of initiation based on 89 pregnancies where an antidepressant was initiated and 139 other pregnancies to the same women where no antidepressant treatment was taken. (3) Analyses of continuation based on *n* = 2305 pregnancies where an antidepressant was continued and *n* = 1162 other pregnancies to the same women where antidepressants were discontinued. (4) Associations were statistically adjusted for maternal age and calendar year.

TABLE 15 Relative odds of offspring neurodevelopmental outcomes among matched treatment-discordant pregnancies to the same women

Offspring neurodevelopmental outcome	Standard logistic regression,[a] OR (95% CI)	*p*-value	Fixed-effects logistic regression,[b] OR (95% CI)	*p*-value
Offspring autism	1.13 (0.57 to 2.23)	0.721	1.65 (0.66 to 4.12)	0.288
Offspring ADHD	0.93 (0.49 to 1.76)	0.832	0.89 (0.33 to 2.40)	0.824
Offspring ID	0.57 (0.15 to 2.16)	0.409	0.64 (0.16 to 2.50)	0.522

[a]In analyses employing standard logistic regression, repeated pregnancies to the same women were treated as statistically independent.
[b]In analyses employing fixed effects logistic regression, repeated pregnancies to the same women were treated as matched observations.

Notes
Analyses of continuation based on 37 pregnancies in which an antidepressant was continued and 114 other pregnancies to the same women in which antidepressants were discontinued. Associations were statistically adjusted for maternal age and calendar year.

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Chapter 7 Negative control analyses

When a particular exposure and outcome are being investigated, a negative control approach is one that utilises an additional exposure or outcome that would be liable to the same sources of confounding or bias as the ones under investigation, but for which causal associations cannot be plausibly ascribed.[74,76] For this study, we chose as a negative control the prescription of antidepressants before but not during pregnancy, that is where it is likely that no gestational exposure to antidepressants had occurred. These analyses were, therefore, relevant for outcomes only for which the timing of prescription within pregnancy could have potentially influenced risk (i.e. for offspring neurodevelopmental outcomes). If antidepressants prescribed before but not during the pregnancy period are associated with later risk of neurodevelopmental problems in offspring, these associations are unlikely to be attributable to the effects of the medications but would suggest confounding by other characteristics.

Methods

Definition of the treatment variable and its negative control

As a negative control, we identified all women who had discontinued an antidepressant at least 3 months prior to becoming pregnant, comparing them with a reference group that had not been prescribed antidepressants at all. To contrast the effect of the negative control with that of the actual treatment, we combined women who had initiated or continued an antidepressant in pregnancy and compared them with the same reference group. Any woman who had been prescribed antidepressants solely during the grace period, as described in *Chapter 2*, was not considered for these analyses.

Outcome variables

These analyses were relevant only for outcomes for which the timing of prescription in relation to the pregnancy period could have potentially influenced risk. We, therefore, carried them out only for neurodevelopmental outcomes in offspring where exposure to an antidepressant in utero may be a potentially causal mechanism of any observed association (i.e. autism, ADHD and intellectual disability).

Statistical analysis

We used logistic regression to compare associations with outcomes for the actual treatment variable (prescription during pregnancy) with its negative control (prescription before but not during pregnancy). Associations were estimated using cluster robust variance estimators to recognise the presence of consecutive pregnancies to the same women. We adjusted all associations for the potential confounders described in *Chapter 2*, *Covariates*.

Results

We observed similar ORs for neurodevelopmental outcomes in children of women who were treated with antidepressants during pregnancy and for the negative control (i.e. children of women who were treated with antidepressants before but not during pregnancy) with overlapping CIs, which all included the null (*Table 16*). In these analyses, there was little evidence of an association of a prescription of an antidepressant for depression before or during pregnancy compared with no prescriptions and any of the neurodevelopmental outcomes, although CIs were wide.

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TABLE 16 Exposure to antidepressants and offspring neurodevelopmental outcomes: negative control analysis results

Offspring neurodevelopmental outcome	Actual exposure: prescribed during pregnancy vs. not at all prescribed		Negative control: prescribed before pregnancy vs. not at all prescribed	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Autism	1.15 (0.88 to 1.51)	0.318	1.06 (0.81 to 1.39)	0.665
ADHD	1.27 (0.91 to 1.78)	0.163	1.26 (0.91 to 1.74)	0.166
Intellectual disability	1.07 (0.65 to 1.75)	0.796	1.21 (0.75 to 1.96)	0.434

Analyses of the actual exposure variable were based on 14,563 pregnancies in which an antidepressant had been prescribed up to 2 months before or during pregnancy and 5829 pregnancies in which no antidepressants had been prescribed. Analyses of the negative control exposure variable was based on 10,501 pregnancies in which an antidepressant had been prescribed up to 1 year before pregnancy but had been discontinued at least 2 months prior to conception, and 5829 pregnancies in which no antidepressants had been prescribed. Associations were adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the GP practice, concurrent use of multiple antidepressants, and switching from one antidepressant to another.

Chapter 8 Variation by indication for antidepressant prescription

To investigate potential confounding by the indication, we compared associations where antidepressants had been prescribed for depression with associations where they had been prescribed for other indications. If there were causal associations between antidepressant use during pregnancy and risk of an adverse outcome, we would expect these associations to be similar irrespective of the indication the antidepressant was issued for. A different risk associated with antidepressants prescribed for depression than for other conditions will be suggestive of confounding by indication.

Methods

Pregnancies where antidepressants had not been issued for depression

To identify pregnancies during which antidepressants had been issued for other indications than depression, we selected those where prescription had occurred during the study period, but no current or past depressive symptoms were present in women's medical records. Readers should note that the pregnancies identified here are the same as those set aside as described in *Chapter 2*, *Study cohort selection*.

Treatment variables

As described in *Chapter 2*, *Design: observational cohorts emulating target randomised controlled trials*, and elsewhere in this report, we considered associations with the following treatment variables: (1) initiating an antidepressant during pregnancy compared with receiving no antidepressant treatment during the study period, and (2) continuing an antidepressant into pregnancy compared with discontinuing the antidepressant.

Outcome variables

Women's use of primary and secondary health-care care services

We combined all follow-up beyond the pregnancy end date into a single 2-year window and examined the following outcomes: (1) the number of days on which women had consulted with their GPs; (2) inpatient admission to specialist mental health services; (3) outpatient treatment for a mental health problem; and (4) frequency of A&E attendance. We also examined women's antidepressant prescription status 2 years after the study pregnancy end date. For the purpose of these analyses, we did not consider use of primary or secondary care services in relation to specific indications (e.g. the number of days consulted with the GP for depressive symptoms) as women prescribed antidepressants for other indications than depression would, by definition, not have consulted for depressive symptoms during the study period.

Offspring neurodevelopmental outcomes

Neurodevelopmental outcomes in offspring included a diagnosis of (1) autism, (2) ADHD or (3) intellectual disability.

Statistical analysis

We used logistic regression models to estimate the relative odds of binary outcomes where antidepressants had been prescribed for depression or for other indications. Negative binomial regression models were used to estimate the relative incidence of count outcomes. Associations were estimated using cluster-robust variance estimators to allow for clustering owing to consecutive

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pregnancies to the same women. We statistically adjusted the identified associations for the potential confounders described in *Chapter 2*, *Covariates*. Differential length of follow-up was accounted for in our statistical models.

Results

Table 17 shows the results of women and offspring outcomes by variation by indication for which the antidepressants were initiated compared with no treatment. *Table 18* shows the results of the same analysis for the continuation of antidepressants compared with discontinuation.

In both sets of analyses, a higher risk of being prescribed antidepressants 2 years after pregnancy was observed in women who initiated or continued antidepressants for depressive symptoms than in women who did not initiate or discontinue antidepressants. By contrast, a lower risk of being prescribed antidepressants 2 years after pregnancy was observed in women who initiated or continued antidepressants for indications other than depression than in women who did not initiate or discontinue antidepressants.

There was also evidence of a higher risk of inpatient admission for a mental health problem after pregnancy when antidepressants had been initiated or continued for depressive symptoms, but not when issued for other indications, compared with women who did not initiate or discontinue.

For other associations, there was no strong evidence for confounding by the indication due to overlap in 95% CIs and inconsistencies in the direction of risk differences for different outcomes and comparisons.

TABLE 17 Variation by indication for which the antidepressant was issued: initiation vs. no treatment

	Antidepressants issued for depression		Antidepressants issued for other indication	
	IRR/OR (95% CI)	*p*-value	IRR/OR (95% CI)	*p*-value
Primary care outcomes				
GP consultations[a]				
During pregnancy	1.22 (1.18 to 1.26)	< 0.001	1.05 (0.97 to 1.14)	0.193
After pregnancy	1.08 (1.05 to 1.12)	< 0.001	1.15 (1.06 to 1.24)	0.001
Prescribed at end of follow-up[b]	1.88 (1.71 to 2.08)	< 0.001	0.66 (0.49 to 0.89)	0.007
Secondary care outcomes				
In-patient admission[b]				
During pregnancy	1.86 (0.63 to 5.56)	0.264	2.53 (0.36 to 17.89)	0.353
After pregnancy	2.12 (1.36 to 3.31)	0.001	2.18 (0.78 to 6.07)	0.136
Outpatient treatment[b]				
During pregnancy	1.88 (1.38 to 2.55)	< 0.001	1.14 (0.41 to 3.13)	0.806
After pregnancy	1.90 (1.51 to 2.37)	< 0.001	1.88 (1.07 to 3.29)	0.027
A&E attendance[a]				
During pregnancy	1.15 (1.02 to 1.31)	0.027	1.06 (0.66 to 1.73)	0.803

TABLE 17 Variation by indication for which the antidepressant was issued: initiation vs. no treatment (*continued*)

	Antidepressants issued for depression		Antidepressants issued for other indication	
	IRR/OR (95% CI)	*p*-value	IRR/OR (95% CI)	*p*-value
After pregnancy	1.17 (1.06 to 1.30)	0.002	1.67 (1.27 to 2.21)	< 0.001
Offspring neurodevelopmental outcomes				
Autism[b]	1.27 (0.90 to 1.80)	0.180	0.97 (0.53 to 1.80)	0.933
ADHD[b]	1.45 (0.97 to 2.17)	0.068	1.42 (0.68 to 2.95)	0.355
Intellectual disability[b]	1.31 (0.74 to 2.31)	0.357	2.13 (0.96 to 4.69)	0.061

[a]Incidence risk ratio with 95% CI.
[b]OR with 95% CI.

Notes
Analyses of primary care outcomes based on 7111 pregnancies during which an antidepressant was initiated for depression, 892 pregnancies during which an antidepressant was initiated for other indications and 12,801 pregnancies during which no antidepressants were prescribed. Analyses of secondary care outcomes based on 4014 pregnancies during which an antidepressant was initiated for depression, 490 pregnancies during which an antidepressant was initiated for other indications and 7390 pregnancies during which no antidepressants were prescribed. Analyses of offspring neurodevelopmental outcomes based on 2988 pregnancies during which an antidepressant was initiated for depression, 754 pregnancies during which an antidepressant was initiated for other indications and 5791 pregnancies during which no antidepressant was prescribed. Associations were adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, and region of the GP practice.

TABLE 18 Variation by indication for which the antidepressant was issued: continuation vs. discontinuation

	Antidepressants issued for depression		Antidepressants issued for other indication	
	IRR/OR (95% CI)	*p*-value	IRR/OR (95% CI)	*p*-value
Primary care outcomes				
GP consultations[a]				
During pregnancy	1.01 (0.99 to 1.02)	0.363	0.91 (0.87 to 0.94)	< 0.001
After pregnancy	0.94 (0.93 to 0.96)	< 0.001	1.01 (0.97 to 1.06)	0.609
Prescribed at end of follow-up[b]	2.54 (2.41 to 2.68)	< 0.001	0.82 (0.71 to 0.95)	0.007
Secondary care outcomes				
Inpatient admission[b]				
During pregnancy	3.29 (1.46 to 7.41)	0.004	5.92 (1.83 to 19.11)	0.003
After pregnancy	1.53 (1.21 to 1.93)	< 0.001	1.28 (0.70 to 2.34)	0.417
Outpatient treatment[b]				
During pregnancy	2.99 (2.41 to 3.72)	< 0.001	1.69 (0.98 to 2.91)	0.057
After pregnancy	1.76 (1.55 to 2.01)	< 0.001	1.02 (0.70 to 1.49)	0.920

continued

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TABLE 18 Variation by indication for which the antidepressant was issued: continuation vs. discontinuation (*continued*)

	Antidepressants issued for depression		Antidepressants issued for other indication	
	IRR/OR (95% CI)	*p*-value	IRR/OR (95% CI)	*p*-value
A&E attendance[a]				
During pregnancy	0.97 (0.91 to 1.04)	0.398	1.20 (1.00 to 1.44)	0.047
After pregnancy	0.98 (0.93 to 1.03)	0.447	1.06 (0.92 to 1.22)	0.388
Offspring neurodevelopmental outcomes				
Autism[b]	1.16 (0.95 to 1.41)	0.146	1.09 (0.77 to 1.53)	0.633
ADHD[b]	1.00 (0.80 to 1.25)	0.977	1.32 (0.93 to 1.88)	0.123
Intellectual disability[b]	0.86 (0.59 to 1.25)	0.420	0.82 (0.43 to 1.57)	0.554

[a]Incidence risk ratio (95% CI).
[b]OR (95% CI).

Notes
Analyses of primary care outcomes based on 37,278 pregnancies during which an antidepressant was continued for depression, 2927 pregnancies during which an antidepressant was continued for other indications and 26,658 pregnancies during which antidepressants had been discontinued at least 2 months prior to conception. Analyses of secondary care outcomes based on 19,680 pregnancies during which an antidepressant was continued for depression, 1431 pregnancies during which an antidepressant was continued for other indications and 14,535 pregnancies during which antidepressants had been discontinued at least 2 months prior to conception. Analyses of offspring neurodevelopmental outcomes based on 15,196 pregnancies during which an antidepressant was continued for depression, 2676 pregnancies during which an antidepressant was continued for other indications and 13,692 pregnancies during which antidepressants had been discontinued at least 2 months prior to conception. Associations were adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the GP practice, concurrent use of multiple antidepressants, and switching from one antidepressant to another.

Chapter 9 Additional analyses: timing of initiation, dose response, antidepressant class, serotonin receptor affinity and individual antidepressant drugs

We carried out the following additional analyses to investigate associations between antidepressants prescribed during pregnancy and offspring neurodevelopmental outcomes: (1) associations by timing of initiation within pregnancy; (2) associations for low, moderate and high doses of antidepressants; (3) associations for SSRIs, TCAs or other types of antidepressants; (4) associations for antidepressants with low, moderate and high affinity for the SERT; and (5) associations for individual antidepressant medications. We confined these analyses to offspring neurodevelopmental outcomes where it was plausible that the timing of exposure, dose level, type of antidepressant, SERT affinity or specific medication prescribed may have influenced the size of the associated risks. Except for analyses pertaining to the timing of initiation, we combined groups who had initiated or continued antidepressants and compared these with groups who did not initiate or discontinued antidepressants to comprehensively capture all prescribing during pregnancy.

Associations by timing of initiation of antidepressants in pregnancy

Methods

We limited these analyses to the timing of initiation of antidepressants in pregnancy because we could clearly identify the point at which women were first exposed to antidepressants during pregnancy. We coded a time-specific exposure variable to indicate exposure in the first trimester compared with prescriptions issued in the second or third trimesters (these latter time points had to be combined because of small cell counts). We then used logistic regression models with cluster-robust variances to estimate the relative odds of offspring autism, ADHD and intellectual disability associated with initiating an antidepressant in the first trimester, or in the second or third trimesters, compared with offspring born to women who did not initiate an antidepressant. In addition, to providing crude estimates, we adjusted the ORs for potential confounding variables (see *Chapter 2*, *Covariates*).

Results

Table 19 shows the results of the analysis estimating relative odds of offspring neurodevelopmental disorders by timing of initiation of antidepressants in pregnancy. Overall, associations between antidepressants during pregnancy and offspring odds of autism, ADHD or intellectual disability did not appear to vary with timing of initiation. We observed weak evidence for an association between first trimester initiation of an antidepressant and offspring ADHD, although a similar association was observed for second or third trimester initiation of an antidepressant with wide CIs.

Associations by dose level

Methods

We identified the generic drug category and daily dose in milligrams for each individual prescription of an antidepressant. Using this information, we calculated tertiles of distributions of daily doses in milligrams separately for each of 34 generic drug categories, and then combined this information in a single dose level variable (first tertile defined as low doses, second tertile as moderate doses and third

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TABLE 19 Relative odds of offspring neurodevelopmental disorders by timing of initiation in pregnancy

	Initiated in the first trimester				Initiated in the second or third trimester			
	Crude[a,b]	*p*-value	Adjusted[b,c]	*p*-value	Crude[a,b]	*p*-value	Adjusted[b,c]	*p*-value
Autism	1.29 (0.87 to 1.91)	0.205	1.32 (0.86 to 2.01)	0.202	0.96 (0.55 to 1.70)	0.895	1.05 (0.59 to 1.87)	0.861
ADHD	1.85 (1.20 to 2.85)	0.006	1.51 (0.96 to 2.40)	0.077	1.40 (0.77 to 2.56)	0.275	1.42 (0.76 to 2.65)	0.268
Intellectual disability	1.17 (0.55 to 2.50)	0.688	1.11 (0.55 to 2.27)	0.768	1.46 (0.60 to 3.57)	0.402	1.47 (0.59 to 3.65)	0.410

[a]Unadjusted association.
[b]OR with 95% CI.
[c]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, and region of the GP practice.

Notes
Analyses based on 1728 pregnancies during which an antidepressant was initiated in the first trimester, 921 pregnancies during which an antidepressant was initiated in the second or third trimester and 5829 pregnancies during which no antidepressants were prescribed.

tertile as high doses). In case of pregnancies during which prescriptions had been issued at different dose levels, we used the highest daily dose prescribed. Using logistic regression models with cluster-robust variances, we estimated relative odds of offspring neurodevelopmental disorders associated with being prescribed a low, moderate or high dose of antidepressants during pregnancy, compared with not having been prescribed antidepressants while pregnant. We provide both crude and statistically adjusted estimates.

Results

There was some evidence for a dose–response association between antidepressants prescribed to the mother during pregnancy and offspring odds of autism, although the CIs around estimates for low, moderate and high doses overlapped (*Table 20*). There was no clear evidence for dose–response association with offspring ADHD or intellectual disability.

TABLE 20 Relative odds of offspring neurodevelopmental outcomes for low, moderate and high doses of antidepressants

Offspring neurodevelopmental outcomes	Crude		Adjusted[a]	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Autism				
Not prescribed	1.00		1.00	
Prescribed a low dose	1.05 (0.86 to 1.27)	0.660	1.19 (0.96 to 1.46)	0.106
Prescribed a moderate dose	1.24 (0.86 to 1.79)	0.242	1.67 (1.09 to 2.55)	0.018
Prescribed a high dose	1.42 (1.06 to 1.90)	0.019	1.75 (1.27 to 2.40)	0.001
ADHD				
Not prescribed	1.00		1.00	
Prescribed a low dose	1.00 (0.80 to 1.26)	0.982	1.06 (0.83 to 1.36)	0.630
Prescribed a moderate dose	1.18 (0.77 to 1.81)	0.441	1.21 (0.73 to 1.99)	0.455
Prescribed a high dose	1.03 (0.71 to 1.49)	0.868	1.21 (0.78 to 1.89)	0.399
Intellectual disability				
Not prescribed	1.00		1.00	
Prescribed a low dose	0.77 (0.53 to 1.11)	0.157	0.75 (0.50 to 1.12)	0.159
Prescribed a moderate dose	0.98 (0.49 to 1.94)	0.943	1.11 (0.47 to 2.58)	0.817
Prescribed a high dose	0.96 (0.55 to 1.69)	0.899	1.18 (0.60 to 2.31)	0.640

[a]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the GP practice, concurrent use of multiple antidepressants, and switching from one antidepressant to another.

Notes

Analyses based on 10,158 pregnancies during which a low dose of antidepressants was prescribed, 1712 pregnancies during which a moderate dose of antidepressants was prescribed, 2693 during which a high dose of antidepressants was prescribed and 16,330 pregnancies during which no antidepressants had been prescribed.

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Associations by type of antidepressant

Method

We categorised individual antidepressants prescribed during pregnancy into the following groups: (1) SSRIs included prescriptions for citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline; (2) TCAs included prescriptions for amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, mianserin, nortriptyline and trimipramine; and (3) 'other' antidepressants included agomelatine, duloxetine, isocarboxazid, mirtazapine, moclobemide, nefazodone, trazodone, phenelzine, reboxetine and venlafaxine. In cases where women had been prescribed different types of antidepressants during pregnancy, they counted independently towards analyses for each type (e.g. pregnancies where a SSRI and TCA had been prescribed were considered in analyses of SSRIs as well as in analyses of TCAs). We used logistic regression models with cluster-robust variances to estimate relative odds of offspring neurodevelopmental disorders associated with being prescribed a SSRI, a TCA, or an 'other' antidepressant during pregnancy, compared with not having been prescribed antidepressants while pregnant. We provide both crude and statistically adjusted estimates.

Results

The results of the analyses comparing no antidepressant prescription for depression in pregnancy with prescription of antidepressants grouped into SSRIs, TCAs and other antidepressants are provided in *Table 21*. We observed greater adjusted odds of autism among children whose mothers had been prescribed SSRIs (OR 1.26, 95% CI 1.04 to 1.53) or TCAs (OR 1.58, 95% CI 1.12 to 2.24) during pregnancy, although CIs for other antidepressants were wider, probably reflecting smaller numbers. There was little evidence for association between the type of antidepressant issued during pregnancy and later risk of ADHD or intellectual disability in resulting offspring.

TABLE 21 Relative odds of offspring neurodevelopmental outcomes for SSRIs, TCAs and other types of antidepressants

Neurodevelopmental outcome by prescription status	Crude		Adjusted[a]	
	OR (95% CI)	*p*-value	OR (95% CI)[1]	*p*-value
Autism				
Not prescribed	1.00		1.00	
Prescribed SSRI	1.15 (0.95 to 1.38)	0.145	1.26 (1.04 to 1.53)	0.018
Prescribed TCA	1.32 (0.96 to 1.83)	0.089	1.58 (1.12 to 2.24)	0.009
Prescribed other antidepressant	0.95 (0.55 to 1.63)	0.852	1.25 (0.69 to 2.28)	0.456
ADHD				
Not prescribed	1.00		1.00	
Prescribed SSRI	0.99 (0.79 to 1.23)	0.916	1.09 (0.86 to 1.39)	0.471
Prescribed TCA	1.38 (0.96 to 1.98)	0.083	1.24 (0.83 to 1.85)	0.302
Prescribed other antidepressant	1.07 (0.59 to 1.92)	0.827	1.11 (0.57 to 2.16)	0.768
Intellectual disability				
Not prescribed	1.00		1.00	
Prescribed SSRI	0.78 (0.55 to 1.10)	0.160	0.82 (0.56 to 1.21)	0.328

TABLE 21 Relative odds of offspring neurodevelopmental outcomes for SSRIs, TCAs and other types of antidepressants (*continued*)

Neurodevelopmental outcome by prescription status	Crude		Adjusted[a]	
	OR (95% CI)	*p*-value	OR (95% CI)[1]	*p*-value
Prescribed TCA	1.04 (0.57 to 1.90)	0.906	0.90 (0.46 to 1.77)	0.763
Prescribed other antidepressant	1.18 (0.51 to 2.70)	0.701	1.29 (0.48 to 3.46)	0.616

[a]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the GP practice, concurrent use of multiple antidepressants, and switching from one antidepressant to another.

Notes

Analyses based on 12,093 pregnancies during which a SSRI was prescribed, 2148 pregnancies during which a TCA was prescribed, 947 pregnancies during which other antidepressants were prescribed and 16,330 pregnancies during which no antidepressants had been prescribed.

Associations by serotonin transporter binding affinity of antidepressants

Methods

We identified prescriptions where antidepressants with low, moderate or high SERT affinity had been issued during pregnancy: (1) low-affinity medications included desipramine, nortriptyline, amoxapine, doxepin, trimipramine, trazodone, nefazodone and mirtazapine; (2) moderate-affinity medications included citalopram, imipramine, fluvoxamine, amitriptyline and venlafaxine; and (3) high-affinity medications included escitalopram, fluoxetine, paroxetine, sertraline, duloxetine and clomipramine. These groupings were based on previous work on this topic[46,50] but it is important to note that the empirical evidence behind these remains limited and, therefore, results should be viewed with caution. Where women were prescribed antidepressants with different affinities, they were counted independently in each analysis. We used logistic regression models with cluster-robust variances to estimate relative odds associated with being prescribed a low, moderate or high SERT affinity medication compared with not having been prescribed antidepressants during pregnancy, providing both crude and statistically adjusted estimates.

Results

The point estimates of offspring odds of all neurodevelopmental outcomes were lower for higher-affinity antidepressants than those for lower-affinity antidepressants, although the CIs for all estimates overlapped (*Table 22*). There were increased odds of autism among children whose mothers had been

TABLE 22 Relative odds of offspring neurodevelopmental outcomes for low-, moderate- and high-affinity antidepressants

Neurodevelopmental outcome by prescription status	Crude		Adjusted[a]	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Autism				
Not prescribed	1.00		1.00	
Prescribed low-affinity antidepressant	1.01 (0.56 to 1.80)	0.984	1.46 (0.78 to 2.74)	0.239
Prescribed moderate-affinity antidepressant	1.18 (0.95 to 1.48)	0.140	1.50 (1.16 to 1.94)	0.002
Prescribed high-affinity antidepressant	1.11 (0.90 to 1.37)	0.323	1.18 (0.95 to 1.46)	0.126

continued

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TABLE 22 Relative odds of offspring neurodevelopmental outcomes for low-, moderate- and high-affinity antidepressants (*continued*)

Neurodevelopmental outcome by prescription status	Crude		Adjusted[a]	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
ADHD				
Not prescribed	1.00		1.00	
Prescribed low-affinity antidepressant	1.77 (1.06 to 2.97)	0.030	1.96 (1.06 to 3.64)	0.032
Prescribed moderate-affinity antidepressant	0.88 (0.67 to 1.17)	0.384	1.05 (0.75 to 1.48)	0.772
Prescribed high-affinity antidepressant	1.10 (0.87 to 1.40)	0.422	1.14 (0.88 to 1.47)	0.328
Intellectual disability				
Not prescribed	1.00		1.00	
Prescribed low-affinity antidepressant	1.21 (0.49 to 2.99)	0.678	1.66 (0.54 to 5.15)	0.376
Prescribed moderate-affinity antidepressant	0.61 (0.38 to 0.98)	0.042	0.69 (0.39 to 1.22)	0.203
Prescribed high-affinity antidepressant	0.91 (0.63 to 1.32)	0.607	0.85 (0.57 to 1.28)	0.443

[a]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the GP practice, concurrent use of multiple antidepressants, and switching from one antidepressant to another. (3) Analyses based on n = 8179 pregnancies where a high-affinity antidepressant was prescribed, n = 6377 pregnancies where a moderate-affinity antidepressant was prescribed, n = 767 pregnancies where a low-affinity antidepressant was prescribed, and n = 16,330 pregnancies where no antidepressants had been prescribed.

prescribed moderate-affinity antidepressants (OR 1.50, 95% CI 1.16 to 1.94), and increased odds of ADHD among children whose mothers had been prescribed low-affinity antidepressants (OR 1.96, 95% CI 1.06 to 3.64), compared with children whose mothers had not been prescribed antidepressants during pregnancy. It should be noted that low- or moderate-affinity antidepressants are generally used for the treatment of more severe depression; therefore, these associations may be consistent with residual confounding by the severity of depression.

Associations for individual antidepressant medications

Methods

Analyses of individual medications were limited by small cell counts. We will, therefore, report results only for which we had at least five observations within each cell of bivariate tables of exposure and outcome variables. For example, we required at least five instances in which women had been prescribed citalopram while pregnant with linked offspring who were later diagnosed with autism to report this result. Where women had been prescribed multiple medications during pregnancy, they counted independently towards analyses of each medication. We used logistic regression models with cluster robust variances to estimate associations with specific antidepressant medications, providing both crude and adjusted relative risk and odds estimates.

Results

The results of the associations of individual medications with neurodevelopmental outcomes are presented in *Table 23*. There were some variations in the outcomes in relation to individual medications. The adjusted odds of offspring autism were greater when mothers had been prescribed amitriptyline, citalopram, lofepramine or paroxetine during pregnancy. There was weak evidence that the odds of

offspring ADHD were increased among mothers who had been prescribed amitriptyline or mirtazapine while pregnant, but little evidence for increased odds of intellectual disability with prescription of any individual antidepressant medications during pregnancy. The CIs of all these results are wider owing to smaller numbers contributing to the analyses.

TABLE 23 Relative odds of offspring neurodevelopmental outcomes for individual antidepressant medications

Neurodevelopmental outcome by prescription status	Crude		Adjusted[b]	
	OR (95% CI)[a]	*p*	OR (95% CI)[a]	*p*
Autism				
Not prescribed	1.00		1.00	
Amitriptyline	1.62 (1.08 to 2.44)	0.020	2.02 (1.32 to 3.11)	0.001
Citalopram	1.13 (0.87 to 1.46)	0.354	1.57 (1.17 to 2.11)	0.003
Dosulepin	1.14 (0.56 to 2.32)	0.712	1.53 (0.73 to 3.20)	0.262
Escitalopram	0.94 (0.46 to 1.91)	0.867	0.93 (0.46 to 1.89)	0.845
Fluoxetine	1.14 (0.88 to 1.46)	0.318	1.16 (0.90 to 1.49)	0.239
Lofepramine	1.98 (1.01 to 3.89)	0.046	2.52 (1.23 to 5.17)	0.012
Mirtazapine	0.93 (0.46 to 1.89)	0.843	1.45 (0.67 to 3.14)	0.346
Paroxetine	1.66 (1.09 to 2.50)	0.017	2.04 (1.31 to 3.16)	0.001
Sertraline	0.86 (0.58 to 1.27)	0.453	1.37 (0.88 to 2.14)	0.159
Venlafaxine	1.10 (0.64 to 1.90)	0.726	1.46 (0.78 to 2.73)	0.235
ADHD				
Not prescribed	1.00		1.00	
Amitriptyline	1.46 (0.90 to 2.38)	0.125	1.74 (1.00 to 3.03)	0.050
Citalopram	0.71 (0.50 to 1.00)	0.050	0.93 (0.61 to 1.40)	0.713
Escitalopram	1.24 (0.61 to 2.52)	0.558	1.11 (0.52 to 2.38)	0.783
Fluoxetine	1.13 (0.85 to 1.51)	0.397	1.12 (0.82 to 1.51)	0.480
Lofepramine	2.31 (1.13 to 4.73)	0.022	1.74 (0.82 to 3.67)	0.148
Mirtazapine	1.69 (0.92 to 3.13)	0.094	2.03 (0.99 to 4.16)	0.054
Paroxetine	1.29 (0.76 to 2.19)	0.344	1.06 (0.61 to 1.84)	0.847
Sertraline	0.80 (0.51 to 1.28)	0.356	1.20 (0.71 to 2.04)	0.497
Venlafaxine	1.13 (0.61 to 2.09)	0.688	0.97 (0.48 to 1.96)	0.927
Intellectual disability				
Not prescribed	1.00		1.00	
Amitriptyline	0.89 (0.36 to 2.20)	0.803	1.00 (0.39 to 2.58)	0.999
Citalopram	0.48 (0.26 to 0.88)	0.017	0.59 (0.29 to 1.19)	0.140
Fluoxetine	1.01 (0.66 to 1.56)	0.956	0.93 (0.58 to 1.47)	0.741
Lofepramine	3.17 (1.28 to 7.85)	0.013	1.88 (0.72 to 4.86)	0.195

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TABLE 23 Relative odds of offspring neurodevelopmental outcomes for individual antidepressant medications (*continued*)

Neurodevelopmental outcome by prescription status	Crude		Adjusted[b]	
	OR (95% CI)[a]	*p*	OR (95% CI)[a]	*p*
Paroxetine	1.14 (0.50 to 2.60)	0.764	0.77 (0.32 to 1.85)	0.554
Sertraline	0.44 (0.18 to 1.09)	0.077	0.61 (0.23 to 1.58)	0.304
Venlafaxine	1.14 (0.46 to 2.80)	0.783	0.99 (0.33 to 2.93)	0.984

[a]OR with 95% CI.
[b]Association adjusted for calendar year, maternal age, number of days consulted with GP in year prior to pregnancy, Charlson Comorbidity Index score at conception, past diagnosis of alcohol-related disorders, psychosis, anxiety disorders, self-harm, bipolar affective disorder, eating disorders, personality disorders, sleep disorders and neuropathic pain disorders at conception, use of medications for physical health problems, central nervous system agents, and nutritional supplements during the treatment window, smoking status at conception, any recorded severity of past depressive symptoms, region of the GP practice, concurrent use of multiple antidepressants, and switching from one antidepressant to another.

Note
Analyses based on *n* = 1040 pregnancies where amitriptyline was prescribed, *n* = 4620 where citalopram was prescribed, *n* = 451 where dosulepin was prescribed, *n* = 546 where escitalopram was prescribed, *n* = 4767 where fluoxetine was prescribed, *n* = 296 where lofepramine was prescribed, *n* = 552 where mirtazapine was prescribed, *n* = 982 where paroxetine was prescribed, *n* = 2088 where sertraline was prescribed, *n* = 818 where venlafaxine was prescribed, and *n* = 16,330 pregnancies where no antidepressants had been prescribed.

Chapter 10 Triangulation of results and discussion

Maternal outcomes: triangulation of results for initiating or continuing an antidepressant during pregnancy

Table 24 summarises the evidence from the various analyses on maternal outcomes in relation to initiation compared with no initiation of antidepressants during pregnancy, and *Table 25* provides the summary of evidence of these outcomes for the analyses for continuation compared with discontinuation of antidepressants for depression in pregnancy.

TABLE 24 Summary of evidence from analyses of maternal outcomes for initiation compared with no initiation of antidepressants for depression in pregnancy

	Analytical approach			
Maternal outcome	Multivariable regression	Propensity score-matched regression	Treatment-discordant pregnancies	Variation by indication for antidepressants
GP consultations	Greater frequency among initiators	Greater frequency among initiators	Little evidence for greater frequency (null association)	More frequent when issued for depression
GP consultations for depression	Greater frequency among initiators	Greater frequency among initiators	Greater frequency among initiators	N/A
GP consultations for self-harm	Null association or greater risk among initiators	Null association or greater risk among initiators	N/A: insufficient numbers	N/A
GP referral for depression	Some evidence for fewer referrals in pregnancy but null or increased risk thereafter	Stronger evidence for fewer referrals during pregnancy but null or increased risk thereafter	N/A: insufficient numbers	N/A
Prescription status at end of follow-up	Initiators more likely prescribed at 2 years of follow-up	Initiators more likely prescribed at 2 years follow-up	Null associations	Initiators for depression more likely to be prescribed at 2 years of follow-up, less likely for 'other' indications
Inpatient admission for MH	Little evidence of association or greater risk among initiators	Little evidence of association	N/A: insufficient numbers	Little evidence for difference between prescribing for depression and other indications (overlapping 95% CIs)
Outpatient treatment for MH	Greater risk among initiators	Greater risk among initiators	N/A: insufficient numbers	Little evidence for difference between prescribing for depression and other indications (overlapping 95% CIs)
A&E attendance	Little evidence of association or greater frequency among initiators	Little evidence of association	N/A	Weak evidence for more frequent A&E attendance for 'other' indications

N/A, not applicable.

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TABLE 25 Summary of evidence from analyses of maternal outcomes for continuation compared with discontinuation of antidepressants in pregnancy

	Analytical approach			
Maternal outcome	**Multivariable regression**	**Propensity score-matched regression**	**Treatment-discordant pregnancies**	**Variation by indication for antidepressants**
GP consultations	Lower frequency among those who continued	Little evidence of associations or increased frequency	Greater frequency with continuation in fixed-effects model	Lower frequency in pregnancy when prescribed for other indications, lower frequency after pregnancy when prescribed for depression
GP consultations for depression	Greater frequency among those who continued	Greater frequency among those who continued	Greater frequency with continuation in fixed-effects model	N/A: analysis not appropriate for outcome
GP consultations for self-harm	Null association or greater risk among those who continued	Null association or greater risk among those who continued	Insufficient numbers during pregnancy, greater risk thereafter	N/A: analysis not appropriate for outcome
GP referral for depression	Null association or greater risk among those who continued	Null association or greater risk among those who continued	Insufficient numbers during pregnancy, null association thereafter	N/A: analysis not appropriate for outcome
Prescription status at end of follow-up	Continuers more likely prescribed at 2 years of follow-up	Continuers more likely prescribed at 2 years of follow-up	Continuers more likely prescribed at 2 years of follow-up	Continuers for depression more likely to be prescribed at 2 years of follow-up if depression, less likely for other indications
In-patient admission for MH	Null association or greater risk among continuers	Null association or greater risk among continuers	Insufficient numbers during pregnancy, null association thereafter	Little evidence for confounding by indication (overlapping 95% CIs)
Out-patient treatment for MH	Greater risk among those who continued	Greater risk among those who continued	Weak evidence of greater risk in fixed-effects models	Weak evidence for greater risk if prescribed for depression
A&E attendance	Little evidence for association	Weak evidence for lower attendance at 1 year after pregnancy, otherwise little evidence for associations	Weak evidence of lower attendance during pregnancy in fixed-effects model	More frequent during pregnancy if prescribed for indications other than depression

N/A, not applicable.

There was consistent evidence across the main (multivariable regression and propensity score regression) and additional analyses that women who initiated or continued antidepressants during pregnancy were more likely to have contact with health-care services at various times during and after pregnancy. These include the number of GP consultations (including consultations for depression, and self-harm where there were sufficient numbers available in analyses), GP referrals for depression and outpatient contacts and inpatient stays for mental health problems. Women who initiated or continued antidepressants in pregnancy were also more likely to continue to be prescribed an antidepressant 2 years following the end of pregnancy.

Child neurodevelopmental outcomes: triangulation of results for initiating or continuing an antidepressant during pregnancy

Table 26 summarises the evidence from the various analyses on child neurodevelopmental outcomes in relation to the mother's initiation compared with no initiation of antidepressants during pregnancy, and *Table 27* provides the summary of the evidence from analyses of these outcomes for continuation compared with discontinuation of antidepressants for depression in pregnancy.

TABLE 26 Summary of results of child neurodevelopmental outcomes for initiation compared with no initiation of antidepressants in pregnancy

	Analytical approach					
Child outcome	**Multivariable regression**	**Propensity score-matched regression**	**Instrumental variable analysis**	**Treatment-discordant pregnancies**	**Negative control analysis**	**Variation by indication for antidepressants**
Offspring autism	Little evidence for greater risk	Evidence for greater risk among initiators	Little evidence for greater risk	N/A: insufficient numbers	Little evidence for unmeasured confounding (both associations null)	Little evidence for confounding by indication (both associations null)
Offspring ADHD	Weak evidence for greater risk among initiators	Little evidence for greater risk although point estimates consistent with multivariable regression	Little evidence for greater risk	N/A: insufficient numbers	Little evidence for unmeasured confounding (both associations null)	Little evidence for confounding by indication (overlapping 95% CIs)
Offspring intellectual disability	Little evidence for greater risk	Little evidence for greater risk	Little evidence for greater risk	N/A: insufficient numbers	Little evidence for unmeasured confounding (both associations null)	Little evidence for confounding by indication (overlapping 95% CIs)

N/A, not applicable.

TABLE 27 Summary of results of child neurodevelopmental outcomes for continuation vs. discontinuation of antidepressants in pregnancy

	Analytical approach					
Child outcome	**Multivariable regression**	**Propensity score-matched regression**	**Instrumental variable analysis**	**Treatment-discordant pregnancies**	**Negative control analysis**	**Variation by indication for antidepressants**
Offspring autism	Little evidence for greater risk	Little evidence for greater risk	Little evidence for greater risk	Little evidence for greater risk	Little evidence of association with antidepressants prescribed during or before pregnancy	Little evidence for association with antidepressants prescribed for depression or other conditions
Offspring ADHD	Little evidence for greater risk	Little evidence for greater risk	Little evidence for greater risk	Little evidence for greater risk	Little evidence of association with antidepressants prescribed during or before pregnancy	Little evidence for association with antidepressants prescribed for depression or other conditions
Offspring intellectual disability	Little evidence for greater risk	Little evidence for greater risk	Little evidence for greater risk	Little evidence for greater risk	Little evidence of association with antidepressants prescribed during or before pregnancy	Little evidence for association with antidepressants prescribed for depression or other conditions

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There was consistent evidence that continuation of antidepressants into pregnancy was not associated with a higher risk of autism, ADHD or intellectual disability compared with discontinuing them before pregnancy in our main and supplementary analyses. The evidence was less consistent for the analyses on initiation compared with no initiation of antidepressants during pregnancy, and the lack of precision owing to smaller number and wider CIs was a disadvantage. For autism, propensity score-matched analyses showed some evidence of an association for women who initiated an antidepressant compared with those who did not initiate an antidepressant in pregnancy, and the CIs of other analyses were wide; therefore, we were unable to rule out an association with certainty. There was also evidence for stronger associations for higher doses of antidepressants prescribed, although this may reflect the severity of underlying depression. There was also some evidence of higher risk with antidepressants that have low and moderate SERT affinity than those with high SERT affinity antidepressants. High SERT affinity antidepressants are typically first-line antidepressants, which may be prescribed for milder forms of depression, although these groupings may not have strong empirical support so should be considered with caution. There was weak evidence in terms of higher point estimates for first trimester compared with later initiation, although the CIs were wide. Finally, there was variation by type of antidepressant, with higher risk estimates with tricyclics than SSRIs, and variation of risk estimates within individual antidepressants. All of these latter analyses have to be interpreted with caution because of the lack of statistical power and further work on larger samples will be able to address this limitation.

There was also weak evidence of an association between prescribing variation in the results for ADHD risks in relation to initiation or no initiation of antidepressants in pregnancy in the regression analysis with similarly raised point estimates in propensity score analysis but wide CIs crossing the null. There was also some variation for these in additional analyses although all suffered from low statistical power.

There was little evidence of any increase in risk of intellectual disability for either initiation or continuation of antidepressants in pregnancy consistently across the main and additional analyses, although CIs were wide in all cases.

Strengths

This study had a number of strengths. It was based on a large primary care sample in the UK that is broadly representative of the UK population. Prospectively recorded data were recorded from medical records minimising the possibility of recall bias.

The study benefited from valuable input from our experienced PPI co-leads and the PPI group comprising women with lived experience of perinatal depression. We received input on our plans and results throughout the life of the study, including important input on issues related to our research questions, the interpretation of results and how they might be perceived, and ongoing help in relation to meaningful dissemination of the findings.

To our knowledge, this is the first study on this topic to conceptualise the research question in terms of a clinical trial, with an attempt to emulate two distinct clinical scenarios, that is the decision to initiate or not initiate an antidepressant during pregnancy or the decision to continue or not continue and antidepressant during pregnancy; therefore, the results may support clinical decision-making for these distinct scenarios. Furthermore, our treatment groups comprised women with an underlying history of depression, that is women who would be potentially eligible for RCTs of initiation or continuation of antidepressants in pregnancy. Therefore, we attempted like-with-like comparisons as would be undertaken in randomised trials. This is particularly important where the risk of an outcome, for example offspring autism, is likely to be elevated in groups of women with the underlying indication of prescribing antidepressants. However, previous studies have included either general population comparison groups or less-specific comparison groups, such as women with a history of a mental illness but not specifically depression.

Another important strength of this study is the primary care setting. Although depression is overwhelmingly managed in primary care, most previous studies have had diagnostic data only for the underlying reason for antidepressant prescribing from secondary care samples. This would have underascertained depression in previous studies and thus compounded the potential problem of confounding by indication, a key issue raised in almost all previous studies.

The base sample we had was large for both initiation compared with no initiation and continuation compared with discontinuation of antidepressants. However, due to the offspring outcomes being relatively rare, there was still a problem with statistical power, most apparent in outcomes related to initiation compared with no initiation of antidepressants in pregnancy, particularly in causal inference approaches applied within smaller subsets. This can be ameliorated in future studies using CPRD, as the sample size with research quality data is continuously increasing. This issue of power also highlights why it is unlikely that it will be feasible to have RCT evidence to study such long-term offspring outcomes. Even if ethically and logistically permissible, such RCTs will require the recruitment of very large samples of pregnant women with several years of post-pregnancy follow-up.

A major strength of this study is the use of a range of causal inference methods, all of which have their own strengths and limitations. This project could be a template of how studies of medication use during pregnancy may make use of such methods to triangulate the results for better understanding of any potential causal mechanisms. However, a limitation for some of these approaches was the lack of statistical power, leading to wide CIs specially in the investigation of initiation of antidepressants and child neurodevelopmental outcomes.

Limitations

Several limitations of this study should be considered.

First, although we have noted the key strength of using primary care data to ascertain depression more completely, the possibility of measurement error in depression should be acknowledged. The terms we used to define depression included symptom codes such as 'low mood'. This was because it is well established that UK GPs have been increasingly making use of symptom codes as opposed to diagnostic codes since the introduction of the Quality Outcomes Framework even when antidepressants are being prescribed.[77] Therefore, CPRD studies ascertaining depression solely through Read codes for a diagnosis of depression are likely to have low sensitivity.

Second, this study, like others on this topic, used prescription data and, therefore, it is not possible to comment on the adherence to the treatment prescribed.

Third, although we used a number of causal methods, several of the analyses which may have been more informative regarding causal estimates (e.g. the IV analysis), lacked precision because of small numbers.

Fourth, we could define outcomes only based on their presence in the medical records, and consultations typically record problems and diagnoses than measures of improvement. This was problematic in studying women's outcomes for whom we were interested in studying potential benefits of antidepressant prescribing. We concluded that several of the outcomes that we studied, for example number of GP consultations following prescription of antidepressants, were intrinsically linked to the exposure (prescribing) as doctors would routinely follow-up patients who they prescribe medications to. For this reason, medical record data to study measures of effectiveness or improvement are limited in the absence of robust outcome measures routinely recorded in medical records.

Finally, we studied a range of maternal outcomes and long-term neurodevelopmental outcomes. However, there may be outcomes that do not fit into specific diagnostic categories we used. The

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decision regarding benefits or harms of medications is more complex and there may be other outcomes that are important to individuals who are considering these decisions.

Clinical implications

The most common clinical scenario in relation to antidepressant prescribing in pregnancy is of women who need to decide whether to continue or discontinue their antidepressants when planning pregnancy or after discovering they are pregnant. Women who continued antidepressants in pregnancy in this study had more severe depression and continued to need antidepressants for a longer period, received more frequent input from primary care and greater frequency of referrals to secondary mental health care. In this group of women, there was no increase in risk of offspring autism, ADHD or intellectual disability compared with women who discontinued antidepressant treatment.

Fewer women in the population needed to initiate antidepressants during pregnancy. Our study found that these women too had greater clinical need, were followed up more frequently in primary care, were more likely to be referred to secondary mental health care services and be prescribed antidepressants at 2-year follow-up. There was no strong evidence suggestive of risks of offspring ADHD or intellectual disability but a potential association with offspring autism would need further investigation, although there is a possibility that this is finding was observed due to chance or residual confounding.

The findings of this research may help clinicians and women make decisions; however, prescribing during pregnancy should always be a decision based on the clinical presentation and individual preferences after taking into account a broader range of factors than this study investigated.

Research implications

The CPRD is a powerful resource for perinatal pharmacoepidemiology. As the database is continually updated, a follow-up study on this topic would provide larger numbers and more precision in the results in relation to the outcomes of initiation of antidepressants during pregnancy, as well as longer period of follow-up.

Collection of standard outcome measures of depression in CPRD practices could allow for more robust assessment of effectiveness of antidepressants.

This study found variation of the relative risks for the neurodevelopmental outcomes by different antidepressants. As larger data sets become available, this information may be useful to understand outcomes of individual medications with more precision.

Our PPI work highlighted that there may be a wider set of outcomes (e.g. pregnancy loss or cardiac anomalies in offspring) that may be of interest to women in the decision-making process. These could be addressed in future work.

The methods used herein could be used as a template for pharmaco-epidemiological studies of other medications during pregnancy and provide an efficient approach towards clinical guidance in the absence of randomised trial evidence.

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Data-sharing statement

The analytic code for this study can be requested from the corresponding author. The CPRD data cannot be shared due to licencing agreements.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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