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Risks and benefits of psychotropic medication in pregnancy: cohort studies based on UK electronic primary care health records

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Abstract

Risks and benefits of psychotropic medication in pregnancy: cohort studies based on UK electronic primary care health records

Irene Petersen,[1]* Rachel L McCrea,[1] Cormac J Sammon,[1] David PJ Osborn,[2] Stephen J Evans,[3] Phillip J Cowen,[4] Nick Freemantle[1] and Irwin Nazareth[1]

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Background: Although many women treated with psychotropic medication become pregnant, no psychotropic medication has been licensed for use in pregnancy. This leaves women and their health-care professionals in a treatment dilemma, as they need to balance the health of the woman with that of the unborn child. The aim of this project was to investigate the risks and benefits of psychotropic medication in women treated for psychosis who become pregnant.

Objective(s): (1) To provide a descriptive account of psychotropic medication prescribed before pregnancy, during pregnancy and up to 15 months after delivery in UK primary care from 1995 to 2012; (2) to identify risk factors predictive of discontinuation and restarting of lithium (multiple manufacturers), anticonvulsant mood stabilisers and antipsychotic medication; (3) to examine the extent to which pregnancy is a determinant for discontinuation of psychotropic medication; (4) to examine prevalence of records suggestive of adverse mental health, deterioration or relapse 18 months before and during pregnancy, and up to 15 months after delivery; and (5) to estimate absolute and relative risks of adverse maternal and child outcomes of psychotropic treatment in pregnancy.

Design: Retrospective cohort studies.

Setting: Primary care.

Participants: Women treated for psychosis who became pregnant, and their children.

Interventions: Treatment with antipsychotics, lithium or anticonvulsant mood stabilisers.

Main outcome measures: Discontinuation and restarting of treatment; worsening of mental health; acute pre-eclampsia/gestational hypertension; gestational diabetes; caesarean section; perinatal death; major congenital malformations; poor birth outcome (low birthweight, preterm birth, small for gestational age, low Apgar score); transient poor birth outcomes (tremor, agitation, breathing and muscle tone problems); and neurodevelopmental and behavioural disorders.

Data sources: Clinical Practice Research Datalink database and The Health Improvement Network primary care database.

Results: Prescribing of psychotropic medication was relatively constant before pregnancy, decreased sharply in early pregnancy and peaked after delivery. Antipsychotic and anticonvulsant treatment increased over the study period. The recording of markers of worsening mental health peaked after delivery. Pregnancy was a strong determinant for discontinuation of psychotropic medication. However, between 40% and 76% of women who discontinued psychotropic medication before or in early pregnancy restarted treatment by 15 months after delivery. The risk of major congenital malformations, and neurodevelopmental and behavioural outcomes in valproate (multiple manufacturers) users was twice that in users of other anticonvulsants. The risks of adverse maternal and child outcomes in women who continued antipsychotic use in pregnancy were not greater than in those who discontinued treatment before pregnancy.

Limitations: A few women would have received parts of their care outside primary care, which may not be captured in this analysis. Likewise, the analyses were based on prescribing data, which may differ from usage.

Conclusions: Psychotropic medication is prescribed before, during and after pregnancy. Many women discontinue treatment before or during early pregnancy and then restart again in late pregnancy or after delivery. Our results support previous associations between valproate and adverse child outcomes but we found no evidence of such an association for antipsychotics.

Future work: Future research should focus on (1) curtailing the use of sodium valproate; (2) estimating the benefits of psychotropic drug use in pregnancy; and (3) investigating the risks associated with lifestyle choices that are more prevalent among women using psychotropic drugs.

Funding details: The National Institute for Health Research Health Technology Assessment programme.

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List of abbreviations

AHD	additional health data
BMI	body mass index
BNF	*British National Formulary*
CI	confidence interval
CPRD	Clinical Practice Research Datalink
DDD	defined daily dose
EDD	estimated delivery date
EUROCAT	European surveillance of congenital abnormalities
GP	general practitioner
HTA	Health Technology Assessment
ICD	*International Classification of Diseases*
IQ	intelligence quotient
IQR	interquartile range
LEAP	lived experience advisory panel
LMP	last menstrual period
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
PPI	patient and public involvement
RCT	randomised controlled trial
RR	risk ratio
RRR	relative risk ratio
RRR_{adj}	adjusted relative risk ratio
SD	standard deviation
SGA	small for gestational age
THIN	The Health Improvement Network

Plain English summary

Many women with bipolar disorder and schizophrenia become pregnant, but there is a lack of information about the advantages and disadvantages of using psychotropic drugs such as antipsychotics, valproate (multiple manufacturers) and lithium (multiple manufacturers) to treat these conditions in pregnancy. This makes it difficult for women and their health-care professionals to decide whether or not these should be used in pregnancy.

We used anonymised information from a large database of general practitioner (GP) records to investigate when women were taking psychotropic drugs. We then used information recorded by the GPs to examine if the drug had any impact on pregnancy outcomes. As there are three main types of psychotropic drug (antipsychotics, anticonvulsants and lithium) we did our study separately for each type.

The number of pregnant women using antipsychotics and anticonvulsants increased over time but the number using lithium did not. Many women stopped drug treatment before pregnancy or in early pregnancy and started again in late pregnancy or after they delivered. Women who were prescribed antipsychotics in pregnancy had worse pregnancy outcomes. However, they were also more likely to be obese, drink, smoke, be prescribed other medication and use illicit drugs than women not prescribed antipsychotics. These factors may, to some extent, be associated with the worse pregnancy outcomes. Women who used anticonvulsants in pregnancy had worse child outcomes than those who did not. In particular, women who were prescribed one anticonvulsant drug, valproate, in pregnancy had an increased risk of giving birth to a child with major malformations.

Scientific summary

Background

The onset of psychoses (schizophrenia and bipolar disorder) in women usually occurs within childbearing age and long-term treatment is often required, including a mixture of psychotropic medication such as antipsychotics, lithium (multiple manufacturers) and anticonvulsant mood stabilisers, for example valproate (multiple manufacturers), lamotrigine (Lamictal®, GlaxoSmithKline) and carbamazepine (multiple manufacturers). Antipsychotics are increasingly being prescribed not just for schizophrenia, but also for bipolar disorder and severe depression and valproate is also commonly prescribed to women of childbearing age.

Although many women treated with psychotropic medication become pregnant or plan pregnancy, no psychotropic medication has been licenced for use in pregnancy. This leaves women and their health-care professionals in a treatment dilemma, as they need to balance the health of the woman with that of the unborn child. Advice on treatment varies across countries. The 2014 National Institute for Health and Care Excellence (NICE) guidelines for antenatal and postnatal mental health [NICE. *Antenatal and Postnatal Mental Health: Clinical Management and Service Guidance.* London: NICE; 2014] clearly state that valproate should not be offered for acute or long-term treatment of a mental health problem in women of childbearing potential. Likewise, the guidelines suggest that lithium should not be prescribed to women who are planning a pregnancy or who are pregnant, unless there has been a poor response to antipsychotic medication.

In recognition of the lack of evidence on the risks and benefits of psychotropic medication in pregnancy and the difficulties encountered in evaluating this issue using a traditional randomised controlled trial design, the National Institute for Health Research Health Technology Assessment (HTA) programme commissioned research utilising information derived from established databases. The commissioned call was titled 'What are the risks and benefits of psychotropic drugs in women treated for psychosis who become pregnant?'. The 'health technology' to be evaluated was psychotropic medications that included antipsychotics, lithium and anticonvulsant mood stabilisers prescribed to women with psychosis (bipolar disorder or schizophrenia or overlap syndromes) and whose symptoms are controlled on treatment and who become pregnant.

The focus of our investigations was to compare the relative benefits and harms of these different drugs on the mother and the child, both when prescribed during pregnancy and when discontinued.

Objectives

- Provide a descriptive account of psychotropic medication prescribed before pregnancy, during pregnancy and up to 15 months after delivery in UK primary care from 1995 to 2012.
- Identify risk factors predictive of discontinuation and restarting of lithium, anticonvulsant mood stabilisers and antipsychotic medication.
- Examine the extent to which pregnancy is a determinant for discontinuation of psychotropic medication.
- Examine prevalence of records suggestive of adverse mental health, deterioration or relapse 18 months before and during the course of pregnancy and up to 15 months after delivery.
- Estimate absolute and relative risks of adverse maternal and child outcomes of psychotropic treatment in pregnancy.

Methods

Data source

We used data from The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD), two large primary care databases that provide continuous anonymised longitudinal general practice data on the patients' clinical and prescribing records and include data from >10% of the UK population.

We created a cohort of pregnant women using data from THIN for the period 1 January 1995–31 December 2012. We subsequently linked the pregnant women's clinical records to that of their children. In order to increase the sample for our last objective we combined records from THIN and the CPRD and removed duplicated records from THIN.

Target population and study participants

The target population was women with psychosis (bipolar disorder, schizophrenia or overlap syndromes) who were in receipt of antipsychotics, lithium and anticonvulsant mood stabilisers, and who became pregnant. Some women receive psychotropic medication prior to formal diagnoses and others may never have a diagnosis of psychosis recorded in their electronic primary care health records. For antipsychotics and lithium, we therefore opted for the most sensitive approach and included all women who were treated with these medications prior to pregnancy in our studies, irrespective of whether or not they had a record of psychosis in their electronic health records. On the other hand, anticonvulsant mood stabilisers are prescribed for various indications. We therefore identified all women prescribed an anticonvulsant mood stabiliser, but for some analyses then limited our analyses to those with a history of psychosis (including bipolar disorder) or a recent record of depression.

Intervention

The intervention comprised (1) antipsychotics (atypical and typical), (2) lithium or (3) anticonvulsant mood stabilisers (lamotrigine, valproate and carbamazepine).

Studies

The project was divided into two parts: a descriptive section and an analytic section.

Part 1 of the project included five studies that examined (1) the prevalence of psychotropic treatment prescribing in and around pregnancy; (2) patterns of recording that indicate worsening of mental health; (3) time trends in prescribing of psychotropic medication; (4) discontinuation and factors associated with discontinuation of psychotropic medication in pregnancy; and (5) restarting and factors associated with restarting of psychotropic medication.

Part 2 of the project included a number of cohort studies. For each class of psychotropic drugs (i.e. antipsychotics, lithium and anticonvulsant mood stabilisers) we performed two studies, one which was based on a pregnancy cohort to examine the maternal outcomes and another which was based on a subset of linked mother–child pairs to examine child outcomes.

Outcome measures

Discontinuation and restarting of treatment; worsening of mental health; acute pre-eclampsia/gestational hypertension; gestational diabetes; caesarean section; perinatal death; major congenital malformations; poor birth outcome (low birthweight, preterm birth, small for gestational age, low Apgar score); transient poor birth outcomes (tremor, agitation, breathing and muscle tone problems); and neurodevelopmental and behavioural disorders.

Results

In total, 495,953 pregnancies were included in the study from 1 January 1995 to 31 December 2012. The general patterns of prescribing of psychotropic medication around pregnancy were similar for the three classes of psychotropic medication; it was relatively constant before pregnancy, decreased sharply in early pregnancy and then increased after delivery to equal or even surpass pre-pregnancy levels.

Entries made for mental health hospital admission or invoking of the Mental Health Act [Great Britain. *Mental Health Act 1983*. London: The Stationery Office; 1983] more than tripled just after delivery in comparison to the period just before pregnancy [prevalence ratio (PR) 3.16, 95% confidence interval (CI) 1.86 to 5.60] and recording of psychosis, mania and hypomania followed similar patterns with a doubling just after delivery (PR 2.02, 95% CI 1.53 to 2.69). The recording of suicide attempts, overdose or deliberate self-harm declined during pregnancy, but rose after delivery, but only to half of what it was prior to pregnancy (PR 0.55, 95% CI 0.48 to 0.63).

Since 2007, both antipsychotic and anticonvulsant treatment have increased both before and during pregnancy with a shift from typical to atypical antipsychotics. By 2011/12 carbamazepine was superseded by lamotrigine before, during and after pregnancy and valproate was the most commonly prescribed anticonvulsant mood stabiliser before pregnancy. Lithium was rarely prescribed, with annual prescribing after delivery almost halving in the study period.

Pregnancy is a strong determinant for discontinuation of psychotropic medication and overall patterns of discontinuation of psychotropic medication were remarkably similar. By the sixth week of pregnancy only 54% of women continued to receive further atypical antipsychotic prescriptions, 37% anticonvulsant mood stabilisers, 35% typical antipsychotics and 33% lithium. By the start of third trimester, 38% continued to receive atypical antipsychotics, 27% lithium, 19% typical antipsychotics and 14% anticonvulsant mood stabilisers.

Few factors (dose, age and comedication) predicted continuation of psychotropic treatment in pregnancy, but women with a record of epilepsy who were prescribed anticonvulsants were much more likely to continue medication in pregnancy than women with a record of psychosis or depression. In general, few women switched psychotropic medication before or in pregnancy.

Depending on the psychotropic drug prescribed, between 40% and 76% of women who discontinued psychotropic medication before or in early pregnancy had restarted treatment at 15 months after delivery. There were no clear predictors of restarting of treatment within 6 months of delivery.

Women prescribed psychotropic medication in pregnancy were in general slightly older, and a larger proportion were smokers, obese and had records of illicit drug use and alcohol problems.

Women prescribed antipsychotic medication in pregnancy were not at higher risk of giving birth to a child with major congenital malformations [relative risk ratio (RRR) 1.74, 95% CI 0.93 to 3.25], but they were at higher risk of giving birth by caesarean section (RRR 1.36, 95% CI 1.12 to 1.64) and giving birth to a child with poor birth outcomes (RRR 2.44, 95% CI 1.71 to 3.47), transient poor birth outcomes (RRR 2.62, 95% CI 1.52 to 4.52) and neurodevelopmental and behavioural disorders (RRR 1.58, 95% CI 1.04 to 2.40) than women not prescribed antipsychotics. These associations were confounded by health and lifestyle factors and concomitant medication use, and, after adjustment, none were statistically significant.

Women prescribed anticonvulsant mood stabilisers in pregnancy were at higher risk of delivering by caesarean section [adjusted relative risk ratio (RRR_{adj}) 1.14, 95% CI 1.04 to 1.26] and giving birth to a child with major congenital malformations (RRR_{adj} 2.05, 95% CI 1.53 to 2.74), poor birth outcomes (RRR_{adj} 1.33, 95% CI 1.06 to 1.67), transient poor birth outcomes (RRR_{adj} 1.76, 95% CI 1.30 to 2.38) and neurodevelopmental or behavioural disorders (RRR_{adj} 1.73, 95% CI 1.42 to 2.09) than women not treated, but no differences were seen when comparing with women who discontinued treatment before pregnancy.

Women who were prescribed valproate in pregnancy were about three times as likely to give birth to a child with major congenital malformations (RRR_{adj} 3.15, 95% CI 1.98 to 5.13) or to give birth to a child who later had records of neurodevelopmental or behavioural disorders (RRR_{adj} 2.83, 95% CI 2.11 to 3.81) in comparison with women not prescribed anticonvulsant mood stabilisers. Comparing the women who continued valproate in pregnancy with women who discontinued treatment prior to pregnancy attenuated these risks somewhat, whereas comparing them with women prescribed other anticonvulsant mood stabilisers in pregnancy attenuated the risks further. However, a significant difference in risk remained, with those who continued valproate treatment being around twice as likely to give birth to a child with major congenital malformations (RRR_{adj} 1.85, 95% CI 1.01 to 3.39) or to give birth to a child who later had records of neurodevelopmental or behavioural disorders (RRR_{adj} 2.10, 95% CI 1.43 to 3.08) as women who were prescribed other anticonvulsant mood stabilisers in pregnancy.

Limiting the analyses on anticonvulsants to women with a record of psychosis or depression, the risk of giving birth to a child with poor birth outcomes was twofold higher in women who continued treatment in pregnancy than in those not prescribed anticonvulsant mood stabilisers (RRR_{adj} 2.38, 95% CI 1.27 to 4.47), but in comparison with those who discontinued treatment before pregnancy there was no significant difference after adjustment.

Conclusion

The use of psychotropic drugs around pregnancy has increased with an increasing number of women using atypical antipsychotics, lamotrigine and, the potentially teratogenic drug, valproate. However, our findings indicate that many women discontinue treatment before or during early pregnancy and then restart again in late pregnancy or after delivery. Lithium continues to be prescribed around pregnancy but its use is decreasing.

Our results support previous findings of associations between valproate prescribed in pregnancy and major congenital malformations as well as neurodevelopmental or behavioural disorders. In contrast, our results suggest the increased risk of adverse pregnancy outcomes in women who continue antipsychotic treatment in pregnancy may be associated with health and lifestyle factors (obesity, smoking, alcohol abuse, concomitant medication and illicit drug use) rather than specific drug effects. It was not possible to investigate the risk associated with lithium use or anticonvulsant use specifically for psychoses owing to the small numbers of women in these groups.

Implications for health care

The results of our study highlight the relationship between general health and lifestyle factors and risks of adverse maternal and child outcomes in women who are prescribed psychotropic medication in pregnancy. Health-care providers should be alerted to the fact that many of the women prescribed psychotropic medication may be at a heightened risk of giving birth to a child with major congenital malformations and other adverse outcomes, perhaps because of obesity, alcohol abuse, illicit drug use and concomitant use of anticonvulsants.

Recommendations for future research

Future research should focus on (1) describing the utilisation and curtailing the use of valproate in women of childbearing potential; (2) quantifying the potential benefits of psychotropic treatment in pregnancy; (3) investigating the risks associated with alcohol abuse, illicit drug use, obesity, smoking and other lifestyle choices that are more prevalent among women using psychotropic medication in pregnancy.

Funding

Funding for this study was provided by the HTA programme of the National Institute for Health Research.

Chapter 1 Background, aims and objectives

Background

Onset of psychoses and psychotropic treatment

The onset of psychoses (schizophrenia and bipolar disorder) in women usually occurs within childbearing age and long-term treatment is often required, including a mixture of psychotropic medication such as antipsychotics, lithium and anticonvulsant mood stabilisers, for example valproate, lamotrigine and carbamazepine (see *Table 1* for trade names and manufacturers).[1–6] In 2007 in the UK, women with a diagnosis of schizophrenia aged between 18 and 44 years received antipsychotic treatment for more than 50% of the time they were registered with a general practice. However, antipsychotics are being increasingly prescribed not just for schizophrenia, but also for bipolar disorder and severe depression.[2,7,8] A second UK study revealed that in 2009, 233 out of 682 (34%) women of childbearing age who had bipolar disorder received two or more prescriptions of valproate.[2] Atypical antipsychotics in combination with lithium are also often prescribed to women of this age group.[2,4]

Pregnancy and psychotropic treatment dilemma

Although many women treated with psychotropic medication become pregnant or plan pregnancy,[9–11] no psychotropic medication has been licenced for use in pregnancy.[12,13] This leaves women and their health-care professionals in a treatment dilemma as they need to balance the health of the women with that of the unborn child.[1,14–16] Advice on treatment varies across countries and in some instances standard psychiatric advice is that women should maintain pharmacological treatment across the perinatal period,[17] however, some psychotropic medications are known to have teratogenic and adverse neurodevelopmental effects.[4,12,18] Thus, the 2014 National Institute for Health and Care Excellence (NICE) guidelines[12] for antenatal and postnatal mental health clearly state that valproate should not be offered for acute or long-term treatment of a mental health problem in women of childbearing potential. Likewise, the guidelines suggest that lithium should not be prescribed to women who are planning a pregnancy or who are pregnant, unless there has been a poor response to antipsychotic medication.[12] The evidence base for adverse effects of other psychotropic medications is sparse. Although antipsychotic drugs are often used in the treatment of both schizophrenia and bipolar disorder in pregnancy, several reviews conclude that there is a paucity of information on the risks and benefits of pharmacological treatment of psychoses in pregnancy in the absence of large and well-designed prospective studies.[1,14,17,19,20] This is further supported by a Cochrane review from 2004,[21] updated in 2009,[22] which concluded that no randomised controlled trials (RCTs) have been conducted to establish whether the benefits of taking antipsychotic drugs outweigh the risks for pregnant or postpartum women. Similarly, limited information is available for anticonvulsant mood stabilisers other than valproate,[18] even though the prescribing of drugs such as lamotrigine has been on the rise for more than a decade.

In recognition of the lack of evidence on the risks and benefits of psychotropic medication in pregnancy and the difficulties encountered in evaluating this issue using a traditional RCT design, in 2001, the National Institute for Health Research Health Technology Assessment (HTA) programme commissioned research utilising information derived from established databases. The commissioned call was titled 'What are the risks and benefits of psychotropic drugs in women treated for psychosis who become pregnant?' (HTA reference number 11/35/06). The 'health technology' to be evaluated in this call was psychotropic medications that included antipsychotics, lithium and anticonvulsant mood stabilisers prescribed to women with psychosis (bipolar disorder or schizophrenia or overlap syndromes) and whose symptoms are controlled on treatment and who become pregnant. The focus of the investigation was to compare the relative benefits and harms of these different drugs on the mother and the child, when prescribed both during pregnancy and when discontinued.

This project was hence designed in response to this commissioned call. We used data from two large UK clinical databases – The Health Improvement Network (THIN) and the Clinical Practice Research Datalink (CPRD) – to study 'real-life' prescribing of psychotropic medication just before, during and after pregnancy and to examine the absolute and relative risks of adverse maternal and child outcomes in women who use psychotropic medication in pregnancy.

Structure of the report

In this chapter of the report we include a description of the overall aim and the specific objectives. *Chapter 2* then presents the overall methodology: the data sources, the development of the pregnancy cohorts and the linked mother–child cohorts, the study sample and target populations, and the 'health technology' (i.e. the psychotropic medications). This will be followed by the results of five descriptive studies in *Chapter 3* with a focus on psychotropic drug utilisation, discontinuation and restarting of treatment. In *Chapter 4* we report the results of a series of cohort studies that examine the absolute and relative risks of adverse maternal and child outcomes associated with psychotropic medication that emerged from the analyses of the data, followed by a synthesis and discussion of strength and limitations (see *Chapter 5*), conclusions and recommendations for future research (see *Chapter 6*) and a descriptive account of our work with patients and the public (see *Chapter 7*).

Aim and objectives

The overall aim of the project was to ascertain the risks and benefits of psychotropic medication in women treated for psychosis who become pregnant.

The specific objectives were to:

- provide a descriptive account of psychotropic medication prescribed before pregnancy, during pregnancy and up to 15 months after delivery in UK primary care from 1995 to 2012
- identify risk factors predictive of discontinuation and restarting of lithium, anticonvulsant mood stabilisers and antipsychotic medication
- examine the extent to which pregnancy is a determinant for discontinuation of psychotropic medication
- examine prevalence of records suggestive of adverse mental health, deterioration or relapse 18 months before and during the course of pregnancy and up to 15 months after delivery
- estimate absolute and relative risks of adverse maternal and child outcomes of psychotropic treatment in pregnancy.

Chapter 2 Methods

In this chapter we describe the data sources for the project (THIN and the CPRD) and how the pregnancy cohorts and mother–child cohorts were developed. We also describe our study samples and the 'health technology' under evaluation, that is, the psychotropic medication.

UK electronic primary care health records

We used data from two electronic health records data sources, THIN and the CPRD (formerly known as the General Practice Research Database). The Department of Primary Care and Population Health at University College London has a licence for full access to all of the THIN data. Hence, we used data from THIN to address four of our five objectives, but for our final objective (i.e. to calculate absolute and relative risks of adverse effects of discontinuation compared with continuation of psychotropic medication in pregnancy on maternal and child outcomes) we supplemented our sample of pregnant women and their children in THIN with a sample of pregnant women who have been prescribed psychotropic medication either before and/or during pregnancy and their linked children from the CPRD in order to obtain a larger study sample. Below, we provide a description of the two data sources and information about how the cohorts of pregnant women and the linked mother–child cohort were derived.

The Health Improvement Network primary care database and the Clinical Practice Research Datalink

The Health Improvement Network and the CPRD are two large primary care databases that provide continuous anonymised longitudinal general practice data on patients' clinical and prescribing records and include data from > 10% of the UK population, (www.csdmruk.imshealth.com/; www.cprd.com/intro.asp). Both databases collect data from general practices that use Vision computer software (In Practice Systems, London) (www.inps4.co.uk/vision) to manage patient consultations and health records. Diagnoses and symptoms are recorded by practice staff using Read codes, which is a hierarchical coding system including more than 100,000 codes.[23,24] Although the Read code system can be mapped to the *International Classification of Diseases*, Tenth Edition (ICD-10), the Read codes also include a number of symptoms and administrative codes.[24] Information on weight, height, smoking habits, alcohol intake and illicit drug problems is also recorded as well as information on antenatal care and birth details, pregnancy outcomes and postnatal care. Prescriptions are issued electronically and directly recorded on the general practice computer systems and thus captured in specific therapy records that hold information on dates of prescription and generic names. Some information is also available on quantity and dosage, although this information is not always complete. In addition, the databases hold individual patient-level information about year of birth (month of birth for individuals < 15 years of age), date of registration, date of death and date of transfer out of the practice. There is also a household identifier, which is the same for individuals who are registered with the same practice and live in the same household. However, some household identifiers include more than one household. This may, for example, be the case where several people live in a block of flats (e.g. flat 2A, flat 2B). In THIN, social deprivation is recorded for each individual by quintiles of Townsend scores, based on information from the 2001 census[25] In the CPRD, social deprivation information is available for practices that have signed up to their linkage scheme (www.cprd.com/recordLinkage/), but we did not have access to Townsend scores for this project from the CPRD.

Over 98% of the UK population are registered with a general practitioner (GP) (family doctor)[26] and the databases are broadly representative of the UK population.[27,28] However, Blak *et al.*[27] demonstrated that THIN contains slightly more patients who lived in the most affluent areas (23.5% in THIN vs. 20% nationally). Although antenatal care is often shared between general practice staff and midwives, the GP remains responsible for women's general medical care during pregnancy, including prescribing of

medicines. Some women with psychosis also receive care from local NHS mental health trusts, but most mental health trusts have limited prescribing budgets; therefore, for most women, prescribing of psychotropic medication remains with GPs during pregnancy and hence this information is available in THIN and the CPRD.

Although computerisation of general practices started as early as the late 1980s, few practices used computers initially. It was, however, in the mid-1990s that an increasing number of general practices became fully computerised[29] and in this study we utilised data from 1 January 1995, or when general practices met data quality standards.[28–30]

Pregnancy cohort and mother–child cohorts

We created a cohort of pregnant women using data from THIN for the period 1 January 1995–31 December 2012. We subsequently linked the pregnant women's clinical records to those of their children if they were registered with the same general practice. Details on how the cohort was created and the decisions that were made to identify a suitable cohort for further analysis are described below. We also describe how we linked mothers and children, and finally how we identified women receiving psychotropic treatments within these cohorts.

Pregnancy cohort

Our pregnancy cohort was based on the recorded date of delivery of the women, the postnatal care record, the first day of last menstrual periods (LMPs) and the estimated delivery dates (EDDs).

The Health Improvement Network includes records that are made as a part of clinical management in primary care; therefore, some pregnancy and antenatal records may not represent actual pregnancies, but they represent historical information. Furthermore, some pregnancies may result in early terminations (either selective or spontaneous abortions/miscarriages) and in these instances little information is recorded in the electronic health records, making it impossible to determine the start and duration of the pregnancy. We therefore derived a set of rules for the inclusion of pregnancies in our cohort. Every pregnancy was ascertained using two different types of information as follows:

- LMP date
- antenatal record
- delivery record
- postnatal care record
- child whose GP record could be matched to the current pregnancy.

Further, we ensured that if we had information only on LMP and antenatal records, the latest antenatal record should be at least 105 days after the first date of the LMP (i.e. equivalent to 15 weeks' gestation). Only a very small proportion (1%) of the pregnancy cohort was identified from LMP and antenatal records alone.

In total, we identified 495,953 pregnancies in 365,138 women who were permanently registered with one of the general practices that contributed data to THIN in the period between 1 January 1995 and 31 December 2012. This cohort was used as the basis for selecting the target population for our examination of psychotropic medication prescribed before pregnancy, during pregnancy and up to 15 months after delivery; changes in severity of illness during the course of pregnancy and in the period after delivery; and for assessing the absolute and relative risks of adverse maternal pregnancy outcomes.

Duration of pregnancy

In accordance with clinical practice in the UK, the first day of the LMP was considered as the start of pregnancy. As the clinical records do not always hold direct information about the pregnancy length, we estimated the duration of the pregnancy based on information on gestation and maturity of the fetus and/or baby as entered on the electronic record. For women where there was no information available on length of pregnancy or no indications that suggested a child was born pre or post term, we made the assumption that the pregnancy lasted the normal course of 280 days (40 weeks).

Linked mother–child cohorts

Pregnant women and their potential children were linked if they were both registered with the same general practice and shared the same family/household identifier. Furthermore, the date of delivery and the child's month of birth were required to be near to each other (within 6 months) and the child should have been registered with the general practice within 6 months of birth.

We excluded mother–child pairs when several possible mothers could be linked to a child (< 0.2%). This could have occurred if two women from a block of flats (who would have shared the same household/family identifier) were pregnant at the same time. In cases where the child was registered with another general practice, linkage with the mother was not possible. This was also not done in instances where the mother and child moved to a different practice shortly after the birth of the child. We also excluded pregnancies from the mother–child cohort where there were two or more children associated with the same delivery.

We first identified mother–child pairs in THIN. They were combined with records from the CPRD and together used as the target populations to examine the absolute and relative risks of adverse effects of discontinuation compared with continuation of psychotropic medication on child outcomes.

Combining records from The Health Improvement Network and the Clinical Practice Research Datalink

Inspired by previous research that utilised data from both THIN and the CPRD and demonstrated that combining clinical records from these two databases is feasible,[31] we combined our cohorts derived from THIN with data from the CPRD, including pregnant women who have been prescribed psychotropic medication before and/or during pregnancy as well as a cohort of linked mother–child pairs.

We provide a brief description on how we combined the data from THIN and the CPRD, and the process used to remove records that were duplicated from those practices that contributed to both databases.

Although THIN and the CPRD receive raw data from general practices that use the Vision clinical software system, the two databases are structured in slightly different ways. The CPRD data were first reformatted such that the data structure was similar to that of THIN. We then derived a matching algorithm between the two databases based on patient registration data, medical records and patient demographics. As the two databases overlap at practice level, practices deemed to have a sufficient number of matching individuals were taken to be the same practice. THIN records for such practices were excluded and the CPRD records maintained for further analysis. Further details are provided in *Appendix 1*.

Study sample and target population

The target population for this project was women with psychosis (bipolar disorder, schizophrenia or overlap syndromes) who are in receipt of antipsychotics, lithium and anticonvulsant mood stabilisers, and who became pregnant. Some women receive psychotropic medication prior to formal diagnoses and others may never have a diagnosis of psychosis recorded in their electronic primary care health records. For antipsychotics and lithium, we therefore opted for the most sensitive approach and included all women who were treated with these medications prior to pregnancy in our studies, irrespective of whether or not they had a record of psychosis in their electronic health records. On the other hand, anticonvulsant mood stabilisers are prescribed for various indications. We therefore identified all women prescribed an anticonvulsant mood stabiliser, but for some analyses then limited our analyses to those with a history of psychosis (including bipolar disorder) or a recent record of depression (in the 3 years prior to the start of pregnancy).

Psychotropic medication

The 'health technology' under investigation in this project was (1) antipsychotics (atypical and typical); (2) lithium; or (3) anticonvulsant mood stabilisers. *Table 1* provides a list of the generic names of each of the treatments.

TABLE 1 Generic and trade names of psychotropic medications

Antipsychotics			
Typical	**Atypical**	**Lithium**	**Anticonvulsant mood stabilisers**
Asenapine (Sycrest®, Lundbeck)	Amisulpride (Solian®, Sanofi Synthelabo)	Lithium Camcolit®, Norgine; Li-Liquid®, Rosemont; Liskonum®, GSK; Litarex®, Dumex; Lithonate®, Approve Prescription Services; Phasal®, Lagap; Priadel®, Sanofi)	Carbamazepine (Arbil®, Ranbaxy; Carbagen®, Generics; Epimaz®, Ivax; Tegretol®, Novartis; Teril®; Timonil®, CP Pharmaceuticals)
Benperidol (Anquil®, Archimedes; Benquil®, Concord)	Aripiprazole (Abilify®, Otsuka)		Lamotrigine (Lamictal®, GSK)
Chlorpromazine (Chloractil®, DDSA Pharmaceuticals; Largactil®, Sanofi-Aventis)	Clozapine (Clozaril®, Novartis; Denzapine®, Merz; Zaponex®, Ivax)		Sodium valproate (Epilim®, Sanofi-Aventis; Epilim Chrono®, Sanofi-Aventis; Episenta®, Desitin; Orlept®, Wockhardt)
Chlorprothixene	Olanzapine (Zypadhera®, Lilly; Zyprexa®, Lilly)		Valproic acid (Convulex®, Pharmacia; Depakote®, Sanofi Synthelabo)
Droperidol (Thalamonal®, Janssen; Droleptan®, Janssen-Cilag; Xomolix®, ProStrakan)	Paliperidone (Invega®, Janssen-Cilag; Xeplion®, Janssen)		Valproate semisodium (Convulex®, Pharmacia; Depakote®, Sanofi Synthelabo)
Flupentixol (Depixol®, Lundbeck; Fluanxol®, Lundbeck)	Quetiapine (Atrolak®, Accord; Biquelle®, Aspire; Ebesque®, Ashbourne; Mintreleq®, CEB Pharma Ltd; Seotiapim®, Sandoz; Seroqul®, AstraZeneca; Sondate®, Teva; Zaluron®, Fontus)		

TABLE 1 Generic and trade names of psychotropic medications (*continued*)

Antipsychotics			
Typical	**Atypical**	**Lithium**	**Anticonvulsant mood stabilisers**
Fluphenazine (Decazate®, Berk; Modecate®, Sanofi Synthelabo; Moditen®, Sanofi-Aventis; Motipress®, Sanofi Synthelabo; Motival®, Sanofi-Aventis)	Risperidone (Risperdal®, Janssen-Cilag)		
Fluspirilene (Redeptin®, Fluspirilene)			
Haloperidol (Dozic®, Rosemont; Fortunan®, Steinhard; Haldol®, Janssen-Cilag; Serenace®, Ivax)			
Levomepromazine (Levinan®, Link; Nozinan®, Sanofi-Aventis)			
Loxapine (Loxapac®, Wyeth)			
Oxypertine (Integrin®, Sterling Winthrop)			
Pericyazine (Neulactil®, JHC Healthcare)			
Perphenazine (Fentazin®, Goldshield; Triptafen®, AMCo)			
Pimozide (Orap®, Eumedica)			
Pipotiazine (Piportil®, JHC Healthcare)			
Promazine (Sparine®, Genus)			
Remoxipride (Roxima®, AstraZeneca)			
Sertindole (Serdolect®, Lundbeck)			
Sulpiride (Dolmatil®, Sanofi-Aventis; Sulparex®, BMS; Sulpitil®, Pfizer; Sulpor®, Rosemont)			
Thiopropazate			
Thioproperazine			
Thioridazine (Melleril®, Novartis; Rideril®, DDSA Pharmaceuticals)			
Trifluoperazine (Stelazine®, Goldshield)			
Trifluperidol (Triperidol®, Lagap)			
Zotepine (Zolpetil®, Movianto)			
Zuclopenthixol (Clopixol®, Lundbeck)			

Amco, Amdipharm Mercury Company Limited; BMS, Bristol-Myers Squibb; GSK, GlaxoSmithKline.

We used all antipsychotics listed in the *British National Formulary* (BNF)[32] chapter 4.2.1, except prochlorperazine, which is primarily prescribed for morning sickness in pregnancy (nausea gravidarum, emesis gravidarum). For anticonvulsant mood stabilisers, we focused on the three most commonly prescribed anticonvulsant mood stabilisers;[33] lamotrigine, carbamazepine and valproate (sodium valproate, valproic acid and valproate semisodium) listed in the BNF chapter 4.8. For lithium, we included lithium carbonate and lithium citrate listed in the BNF chapter 4.2.3.

Data analysis and statistical software

Data analysis conducted for each study is described in further detail in *Chapters 3* and *4*. Stata (version 13.1) (StataCorp LP, College Station, TX, USA) was used for all data management and analysis.

Ethics and scientific approvals

The scheme for THIN to obtain and provide anonymous patient data to researchers was approved by the NHS South-East Multicenter Research Ethics Committee in 2002. The CPRD has been granted Multiple Research Ethics Committee approval (05/MRE04/87) to undertake purely observational studies, with external data linkages, including Hospital Episode Statistics and Office for National Statistics (ONS) mortality data. The work of the CPRD is also covered by the National Information Governance Board for Health and Social Care – Ethics and Confidentiality Committee approval Ethics and Confidentiality Committee (a) 2012. Scientific approval for use of THIN data for this study was obtained from Cegedim Strategic Data Medical Research's Scientific Review Committee (protocol number 13–059) and scientific approval for use of CPRD data was obtained from Independent Scientific Advisory Committee (protocol number 14_087R).

Chapter 3 Psychotropic medication prescribed before pregnancy, during pregnancy and up to 15 months after delivery

Introduction

In order to understand the risks and benefits of psychotropic medication in pregnancy, it is important to also have an overview of the utilisation of these medications before and during pregnancy. This has been the subject of a number of recent studies conducted in Europe and North America.[34–41] Epstein *et al.*[39] examined use of psychotropic medication using data from Tennessee Medicaid to conduct a retrospective cohort study of nearly 300,000 women enrolled in the database throughout pregnancy from 1985 to 2005. This study reported significant increases in the use of anticonvulsants among mothers with pain and other psychiatric disorders, but a decrease in the use of lithium and typical antipsychotics.[39] Two studies[37,40] based on pharmacy dispensing data from the USA estimated the prevalence of anticonvulsant mood stabilisers and antipsychotics dispensed during pregnancy over the period 2001–7 from 11 US health plans participating in the Medication Exposure in Pregnancy Risk Evaluation Program involving 585,615 deliveries. One study[37] reported a sharp increase in the use of atypical antipsychotics from 0.33% [95% confidence interval (CI) 0.29% to 0.37%)] in 2001 to 0.82% (95% CI 0.76% to 0.88%) in 2007, while the use of typical antipsychotics remained stable. The other study[40] estimated that in 2001 there were 15.7 women receiving anticonvulsant mood stabilisers per 1000 deliveries in the USA, increasing to 21.9 per 1000 deliveries in 2007. A more recent study[34] based on data from THIN demonstrated that for anticonvulsant mood stabilisers the overall prevalence of prescribing in pregnancy has remained at the same level, between 0.4% and 0.6% between 1994 and 2009; however, the prevalence of prescribing of individual types of anticonvulsants has changed over time with lamotrigine becoming increasingly common.[34]

A study based on one of the UK primary care databases, the CPRD, including records from 1989 to 2010, found that among 420,000 pregnancies, treatment with antipsychotics (excluding prochlorperazine) followed a u-shaped pattern, with 0.15% of all women having a prescription in the 3 months before pregnancy, a decline during pregnancy (0.07–0.08% in the second and the third trimester) and an increase in the first 3 months after delivery, to 0.15%.[36] A dramatic decline in the dispensing of antipsychotics in the second and third trimester was also observed in the American dispensing data.[37] UK data suggest that the rate of discontinuation of anticonvulsant mood stabilisers depends on whether or not the woman has a record of epilepsy or bipolar disorder.[34] Thus, women with bipolar disorder were much more likely to discontinue treatment than women with epilepsy, although the medications were the same.[34] Petersen *et al.*[35] studied discontinuation of antidepressants in pregnancy and found that only 1060 (20%) out of 5229 women who were on antidepressant treatment 3 months before they became pregnant received further treatment after the first 6 weeks of their pregnancy (when the woman is likely to become aware of her pregnancy).

Limited information is available on the proportion of women who discontinued psychotropic medication just before or during pregnancy and who then restarted medication in either the course of being pregnant or in the post-partum period. However, studies on antidepressants indicate that reintroduction of antidepressant treatment in pregnancy is common. Cohen *et al.*[42] followed 54 non-depressed pregnant women who had discontinued antidepressant treatment around the time of conception. Of these women, 23 (42%) restarted antidepressant therapy during pregnancy, with nearly half of them ($n = 11$) doing so in the first trimester. Another study followed 70 women who discontinued antidepressants, and of these, 40 (57%) restarted treatment, almost half in the first trimester of pregnancy.[43] The major determinant of treatment reintroduction was relapse of the disorder, as noted from women who scored higher on

depression and anxiety measures in cases where treatment was reintroduced.[39] Lithium and other mood stabilisers may on the other hand be introduced for preventative measures rather than to treat relapse. In fact, NICE guidance[12] recommends that lithium may be stopped in early pregnancy, but reintroduced in the third trimester in the case of women at high risks of relapse.

Methods

Studies

We conducted five studies to evaluate utilisation and recording of mental health in primary care; these were (1) the prevalence, initiation and termination of prescribing of psychotropic medication at 6 months before pregnancy, during pregnancy and up to 15 months after delivery; (2) the patterns of recording that indicate worsening of mental health at 18 months before pregnancy, during the course of pregnancy and up to 15 months after delivery; (3) the time trends in prescribing of psychotropic medication around and during pregnancy over the calendar period 1995–2012; (4) the extent of discontinuation and factors associated with discontinuation of psychotropic medication in pregnancy; and (5) the extent of restarting and factors associated with restarting psychotropic medication in pregnancy. Below we provide further details on each study in turn.

Study participants

We used data from women in the pregnancy cohort derived from THIN. As a minimum inclusion criterion, we required that women were registered with the practice throughout their pregnancy. For each of the individual studies, we introduced further inclusion criteria, detailed in the analysis section.

For the studies on discontinuation and restarting psychotropic medication, we randomly selected one pregnancy from the women who had records of more than one eligible pregnancy (antipsychotics, $n = 19$; lithium, $n = 1$; and anticonvulsant mood stabilisers, $n = 2$). Pregnancies that ended in miscarriage or termination were excluded from all four studies as it was impossible to determine the start and end dates of these pregnancies.

Psychotropic medication, prescription intervals and dose

Most psychotropic prescribing occurred over monthly intervals. For $> 98\%$ of women prescribed antipsychotics in the year prior to pregnancy, the median gap between prescriptions was < 3 months (91 days) and similar patterns were observed for other psychotropic medication. We considered a new episode of treatment if a woman had not received psychotropic medication prescriptions in the past 3 months (91 days). Likewise, if a woman received no further prescriptions after 3 months, she was deemed to have discontinued an episode of treatment. The date of initiation was considered as the date the first prescription was issued for that episode. The date of termination was considered as the date of the last prescription issued in the episode.

For antipsychotics we also calculated the average daily dose during the period from 4–6 months before the start of pregnancy by dividing the total amount of drugs prescribed over the period by the expected total duration of the relevant prescriptions. Durations were estimated with the help of the enhanced dosage determination method developed by the University of Nottingham Division of Epidemiology and Public Health (further details can be obtained from the data providers of THIN, IMS Health). The mass of each antipsychotic drug was standardised into units of the defined daily dose (DDD) for maintenance treatment of psychosis.[44]

Prevalence, initiation and termination of psychotropic treatment: study participants, outcomes and data analysis

Study participants

We included women from the pregnancy cohort who registered with their general practice in the relevant time periods.

Outcomes

Our outcomes were (1) prevalence of prescribing before pregnancy (6 months before), during pregnancy and after delivery [up to 15 months after delivery (approximately 24 months after conception)]; and (2) proportions of individuals who initiated, terminated or received isolated psychotropic prescriptions before and during pregnancy, and after delivery.

Data analysis

Prevalence

We provided estimates of the prevalence for each 3-month period (trimester in pregnancy) from 6 months prior to pregnancy to 15 months after delivery. Prevalence was estimated for each class of psychotropic medication as the number of women who received a prescription in the relevant time period (numerator), divided by the number of women in the cohort in the relevant time period (denominator). Women were included in the denominator for the prevalence estimates if they were registered with a practice for at least 1 day during the relevant period.

For antipsychotics and anticonvulsant mood stabilisers we further stratified the analyses according to treatment prescribed. For antipsychotics we stratified by typical and atypical antipsychotics, and for anticonvulsant mood stabilisers we stratified the analysis by lamotrigine, valproates and carbamazepine. We estimated prevalence ratios (PRs) for each 3-month period using the period from 1 to 3 months before pregnancy as a reference.

Multiple psychotropic medications

In order to gain a better understanding of drugs prescribed from the BNF chapter on the central nervous system, we explored prescription of multiple classes of drugs from antipsychotics (BNF chapter 4.2.1 and 4.2.2), lithium and anticonvulsants (BNF chapter 4.8.1), as well as antidepressants (BNF chapter 4.3), anxiolytics (BNF chapter 4.1.2) and hypnotics (BNF chapter 4.1.1). We estimated the number of women who were in receipt of more than one psychotropic medication in the 4–6 months before pregnancy.

Start and end of prescribing episodes and isolated prescriptions

For each 3-month period (trimester in pregnancy) we also estimated the number of individuals who started or ended a prescribing episode and the number of individuals who received an isolated prescription (no preceding or subsequent prescriptions within 91 days).

Patterns of recording that indicate worsening of mental health: 18 months before pregnancy, during the course of pregnancy and up to 15 months after delivery

Study participants

We included women from the pregnancy cohort who registered with their general practice in the relevant time periods.

Outcomes

Our outcomes were records of suicide attempts, overdose and deliberate self-harm, hospital admissions, invoking under the Mental Health Act[45] and entries of Read codes for psychosis, mania and hypomania. We combined the codes into three sets of outcomes: (1) suicide attempts, overdose or deliberate self-harm; (2) hospital admissions or examination under section under Mental Health Act; and (3) entries of psychosis, mania or hypomania.

Further details regarding the definition of outcomes and Read codes are provided in *Appendix 1*.

Data analysis

We provided estimates of the prevalence for each outcome group for each 3-month period (trimester in pregnancy) from 18 months prior to pregnancy to 15 months after delivery. Prevalence estimates were made for each of the three sets of outcomes by dividing the number of women who had a relevant record(s) (numerator) by the number of women who were registered with their general practice and thus in the cohort in the relevant time period (denominator). Women were included in the denominator for the prevalence estimates if they were registered with a practice for at least 1 day during the relevant period. They were included in the numerator if they had a least one Read code within the relevant record group. Some women may have contributed to several record groups.

The prevalence for each record group was plotted against time in relation to the pregnancy. We estimated PRs for each 3-month period using the period 1–3 months before pregnancy as a reference.

Time trends in prevalence of psychotropic medication treatment around and during pregnancy

Study participants

We included women from the pregnancy cohort who were registered with their general practice in the relevant time periods.

Outcomes

Our outcomes were annual prevalence of psychotropic treatment in (1) the 6 months before pregnancy; (2) pregnancy after the first 6 weeks of gestation (when the pregnancy is likely to be known); and (3) the first 6 months after delivery. Separate estimates were made for antipsychotics, anticonvulsant mood stabilisers and lithium. We provided the estimates by year of delivery for every 2-year period.

Data analysis

Prevalence was estimated as described in the previous section (see *Patterns of recording that indicate worsening of mental health: 18 months before pregnancy, during the course of pregnancy and up to 15 months after delivery*). Estimates were made separately for the 6 months before pregnancy, during pregnancy (after the first 6 weeks of gestation) and in the first 6 months after delivery.

We accounted for variation in the denominator before and after pregnancy. Hence, for women to be included in the estimates for before pregnancy they had to be registered with their general practice for the 6 months before pregnancy. Likewise, women had to be registered for at least 6 months after pregnancy to be included in the estimates for after delivery.

Discontinuation and factors associated with discontinuation of psychotropic medication in pregnancy

Study participants

This study included both a cohort of pregnant women and a comparison cohort of women who were not pregnant but who were prescribed psychotropic drugs, in order to examine the impact of pregnancy on discontinuation of these medications.

We included women from the pregnancy cohort and selected women who:

- contributed data for at least 6 months before the pregnancy and throughout their pregnancy
- received continuous psychotropic medication before they became pregnant, that is, women were selected if they received prescriptions between 4 and 6 months (inclusive) before they became pregnant
- received at least one further prescription in the 3 months before the start of pregnancy.

Thus, we focused on women who received two or more prescriptions of psychotropic medication in the 6 months leading up to pregnancy.

We excluded women with a miscarriage, abortion or delivery in the 6 months prior to the start of their pregnancy since these women's decisions about whether or not to discontinue medication might have been influenced by their previous pregnancy.

For the comparison cohort, we identified a cohort of twice as many women also in receipt of the relevant psychotropic prescriptions, but who were not pregnant for at least 12 months before and 24 months after a randomly selected index date. We stratified these groups such that the age distribution was similar in the pregnant and non-pregnant samples.

Outcomes

Our outcomes were (1) the time to last consecutive prescription of psychotropic medication in pregnancy; and (2) the factors associated with continuation of prescribed psychotropic medication in pregnant women. These included age, the average daily dosage (for antipsychotics), the length of time that the medication had been prescribed prior to pregnancy, prescription of other psychotropic medication (antidepressants, mood stabilisers or antipsychotics), records of illicit drug or alcohol problems, obesity, parity, social deprivation and ethnicity). While there is no direct measurement of severity of illness, the average daily dosage of antipsychotics and length of time the treatment had been prescribed prior to pregnancy may be indicative of the severity of illness.

Many other factors may impact on the decision to continue or discontinue psychotropic medication in pregnancy. We chose, however, to examine the variables described above, as they were available from primary care electronic health records.

Data analysis

We used Kaplan–Meier plots to examine time to last psychotropic prescription, and performed separate analyses for each class of psychotropic medication (antipsychotics, lithium and anticonvulsant mood stabilisers). We followed pregnant and non-pregnant women who were prescribed any of the three classes of psychotropic medication from 3 months before the pregnancy (or the index date for the non-pregnant women) and identified when they had their last consecutive prescription (identified as < 91 days after the previous prescription). We ended follow-up after 220 days (2 months before delivery). In the case of a premature delivery this was sooner than 220 days with follow-up ending at the time of delivery. Although we defined stopping psychotropic medication as the date of issue of the last prescription, we are aware that some women would have continued taking the drug beyond this point. The data were further stratified for atypical and typical antipsychotics and for different dosages of antipsychotics. In the case of anticonvulsant mood stabilisers the data were stratified by lamotrigine, carbamazepine and valproate and

also by indication for prescription (i.e. distinctions were made between those who had an electronic health record of epilepsy, psychosis/depression or none of these).

In the pregnant cohort we examined whether or not continuation of antipsychotic and anticonvulsant mood stabiliser prescribing beyond 6 weeks of pregnancy was associated with the factors listed above using a Poisson regression model. We estimated the univariate relative risk ratios (RRRs) for each of the variables as well as the RRR adjusted for age and average daily dose. For antipsychotics we also examined if women switched between typical and atypical treatments.

For lithium we provided percentages and their CIs, but did not embark on further statistical analyses, as so few women received lithium prescriptions beyond 6 weeks of pregnancy.

Restarting and factors associated with restarting psychotropic medication in pregnancy

Study participants

In this study we began by using the same cohorts of women as used in the studies on discontinuation (see *Chapter 3, Discontinuation and factors associated with discontinuation of psychotropic medication in pregnancy*), that is, women who were treated with psychotropic medication in the 6 months before they became pregnant. We then selected subsets of women who discontinued psychotropic treatments just before they reached 6 weeks of pregnancy.

Outcomes

Our outcomes were (1) time to first new psychotropic prescription; (2) the proportion of women who restarted psychotropic medication by 6 months after delivery; and (3) the factors/characteristics of the women associated with restarting of prescribed psychotropic medication. We included the following factors/characteristics: age, the average daily dosage (for antipsychotics), length of time the psychotropic medication had been prescribed prior to pregnancy and prescription of other psychotropic medication (antidepressants, mood stabilisers or antipsychotics).

Data analysis

We used Kaplan–Meier plots to examine time to renewal of prescribing the psychotropic prescriptions after the start of the pregnancy. Follow-up was censored at the earliest of the following: 15 months after delivery, 31 December 2012 or when the woman left the general practice. We conducted separate analyses for each class of psychotropic medication (antipsychotics, lithium and anticonvulsant mood stabilisers) and with antipsychotics we stratified our analyses for atypical and typical antipsychotics. For anticonvulsant mood stabilisers we performed the analysis for women who had a record of psychoses or depression.

We estimated the proportion with 95% CIs of women who had discontinued medication before 6 weeks of pregnancy and restarted treatment by 6 months after delivery. The characteristics of these women were tabulated and contrasted to women who had not restarted psychotropic medication by 6 months after delivery. For antipsychotics, we estimated the univariate RRRs for each of the variables as well as RRRs adjusted for age and average daily dose. For lithium and anticonvulsant mood stabilisers we did not attempt further analysis, as the numbers were too small to produce meaningful results.

Changes to the protocol

We originally planned to undertake an evaluation of changes in severity of mental illness from the period commencing 18 months before the start of pregnancy up to 15 months after the delivery of the baby. This analysis was deemed infeasible, as it was not possible to 'grade' the severity of mental illness in an individual merely from their Read code entries. Instead we decided to explore how the entries varied more generally over this time period by choosing a number of outcomes suggestive of adverse mental health, deterioration or relapse and we then estimated 3-month (trimester in pregnancy) prevalence.

Results

Below we report the results on:

(a) prevalence, initiation and termination of psychotropic treatment
(b) patterns of recording that indicate worsening of mental health
(c) time trends in prevalence of psychotropic treatment around and during pregnancy over the calendar period 1995–2012
(d) discontinuation and factors associated with continuation of psychotropic medication in pregnancy
(e) restarting and factors associated with restarting psychotropic medication in pregnancy.

Prevalence, initiation and terminations of psychotropic treatment: 6 months before pregnancy, during pregnancy and up to 15 months after delivery

Overall, 495,953 pregnancies were included in the study from 1 January 1995 to 31 December 2012. Below we describe the results of our studies on the prevalence, initiation and termination of psychotropic treatment. Parts of this work have been published elsewhere.[46,47]

Prevalence of psychotropic treatment before, during and after delivery

In the 1–3 months before the start of pregnancy 1051 out of 495,624 (0.21%) women were prescribed antipsychotics (*Table 2*), 78 out of 495,624 (0.015%) were prescribed lithium and 2046 out of 495,624 (0.41%) were prescribed anticonvulsant mood stabilisers (*Table 3*). Only 165 out of 52,998 (0.31%) of the women prescribed an anticonvulsant drug had a record of psychosis or depression (see *Table 3*).

During pregnancy the prevalence of antipsychotics and lithium prescribing fell dramatically. Hence, 554 out of 495,953 (0.11%) were prescribed antipsychotics and 33 out of 495,953 (0.006%) lithium in the second trimester. The corresponding PRs of antipsychotics and lithium prescribing relative to the period from 1–3 months before pregnancy were 0.53 (95% CI 0.47 to 0.58) and 0.42 (95% CI 0.27 to 0.64), respectively (*Table 4* and *Figure 1*). In the case of anticonvulsant mood stabilisers there was only a small decline in the prevalence of prescribing in pregnancy, 1782 out of 495,953 (0.36%) were prescribed in the second trimester and the PR was 0.87 (95% CI 0.82 to 0.93) (see *Table 4* and *Figure 1*). In the case of those prescribed anticonvulsant mood stabilisers who had a record of psychosis or depression the level of prescribing in the second trimester fell dramatically, with 57 out of 53,012 (0.11%) being prescribed an anticonvulsant mood stabiliser in the second trimester. The PR in the second trimester was 0.35 (95% CI 0.25 to 0.47) (see *Table 4* and *Figure 1*).

For the period after delivery the prevalence of both antipsychotic and lithium treatment were higher in the period between 4 months and 15 months after delivery than before pregnancy. In the case of anticonvulsant mood stabilisers the prevalence after pregnancy remained similar to that before pregnancy irrespective of whether or not the sample was limited to women with psychoses or depression (see *Table 4* and *Figure 1*). The three most commonly prescribed typical antipsychotics in pregnancy were chlorpromazine, trifluoperazine and flupentixol and for atypical antipsychotics, it was quetiapine, olanzapine, and risperidone (see *Table 2*). For anticonvulsant mood stabilisers, carbamazepine was primarily prescribed in pregnancy followed by lamotrigine and valproate (see *Table 3*), but this has changed over time, see *Time trends in prevalence of psychotropic medication treatment around and during pregnancy over the calendar period 1995–2012*.

TABLE 2 Numbers of women prescribed antipsychotic drugs before, during and after pregnancy in the total pregnancy cohort

Prescribed antipsychotic	4–6 months before pregnancy	1–3 months before pregnancy	First trimester	Second trimester	Third trimester	1–3 months after delivery	4–6 months after delivery	7–9 months after delivery	10–12 months after delivery	13–15 months after delivery
Any antipsychotic	999	1051	992	554	509	987	1157	1127	1092	1065
Any typical	550	594	596	301	258	533	582	558	536	519
Chlorpromazine	120	134	185	110	81	114	117	109	98	101
Trifluoperazine	118	111	110	61	50	103	98	100	100	94
Flupentixol	112	125	86	28	15	108	123	123	115	130
Promazine	24	26	88	30	41	17	18	16	36	36
Thioridazine	96	97	52	20	17	83	114	97	89	77
Haloperidol	36	37	36	30	36	59	42	47	39	32
Sulpiride	15	11	9	10	10	30	33	24	23	17
Pericyazine	6	20	11	4	3	10	15	14	15	11
Zuclopenthixol	6	8	3	5	5	7	5	4	7	6
Fluphenazine	15	20	7	1	0	11	11	17	13	14
Perphenazine	11	10	5	2	2	6	10	14	9	8
Levomepromazine	2	2	6	2	0	2	3	5	5	4
Droperidol	1	4	2	0	0	1	3	3	3	2
Loxapine	1	1	1	0	0	0	0	0	0	0
Trifluperidol	0	0	1	0	0	0	0	0	0	0
Pimozide	0	0	0	0	1	1	1	0	0	0
Pipotiazine	0	0	0	0	0	0	1	0	0	1
Paliperidone	0	0	0	0	0	0	1	1	1	1

Prescribed antipsychotic	4–6 months before pregnancy	1–3 months before pregnancy	First trimester	Second trimester	Third trimester	1–3 months after delivery	4–6 months after delivery	7–9 months after delivery	10–12 months after delivery	13–15 months after delivery
Any atypical	473	485	427	265	263	485	604	597	579	573
Quetiapine	173	200	171	113	112	177	209	211	209	214
Olanzapine	154	157	149	101	108	199	243	229	219	207
Risperidone	90	85	70	30	25	76	107	125	118	111
Aripiprazole	40	45	37	20	18	37	42	35	41	40
Amisulpride	21	17	9	4	3	13	28	19	17	19
Clozapine	0	1	1	0	0	0	0	0	1	0
Total pregnancies	476,270	495,624	495,953	495,953	493,672	495,894	473,358	456,040	439,313	423,192

TABLE 3 Numbers of women prescribed the three main anticonvulsant mood stabilisers and lithium before, during and after pregnancy in the total pregnancy cohort

Prescribed drug	4–6 months before pregnancy	1–3 months before pregnancy	First trimester	Second trimester	Third trimester	1–3 months after delivery	4–6 months after delivery	7–9 months after delivery	10–12 months after delivery	13–15 months after delivery
Lithium	84	78	58	33	37	69	98	110	104	105
Any of the three ACMS	1991	2046	1991	1782	1741	1965	1957	1922	1862	1819
Carbamazepine	830	859	822	706	706	799	780	795	776	749
Lamotrigine	687	727	748	707	696	718	722	687	666	639
Valproate	629	607	556	472	436	562	577	555	545	556
Total pregnancies	476,270	495,624	495,953	495,953	493,672	495,894	473,358	456,040	439,313	423,192
Women with a record of psychosis or depression										
Any of the three ACMS	160	165	135	57	55	121	151	159	149	152
Carbamazepine	77	82	65	23	26	59	61	68	61	53
Valproate	68	66	47	19	17	50	68	66	66	77
Lamotrigine	19	21	24	16	15	16	26	28	26	26
Total pregnancies	51,718	52,998	53,012	53,012	52,736	53,006	50,487	48,489	46,546	44,711

ACMS, anticonvulsant mood stabilisers.

TABLE 4 Prevalence ratios (95% CI) for the prevalence of prescribing psychotropic drugs in the total pregnancy cohort

Prescribed antipsychotic	4–6 months before pregnancy	1–3 months before pregnancy	First trimester	Second trimester	Third trimester	1–3 months after delivery	4–6 months after delivery	7–9 months after delivery	10–12 months after delivery	13–15 months after delivery
Any antipsychotic	0.99 (0.91 to 1.08)	1	0.94 (0.86 to 1.03)	0.53 (0.47 to 0.58)	0.49 (0.44 to 0.54)	0.94 (0.86 to 1.02)	1.15 (1.06 to 1.25)	1.17 (1.07 to 1.27)	1.17 (1.08 to 1.28)	1.19 (1.09 to 1.29)
Any typical	0.96 (0.86 to 1.08)	1	1.00 (0.89 to 1.13)	0.51 (0.44 to 0.58)	0.44 (0.38 to 0.51)	0.90 (0.80 to 1.01)	1.03 (0.91 to 1.15)	1.02 (0.91 to 1.15)	1.02 (0.90 to 1.15)	1.02 (0.91 to 1.15)
Any atypical	1.01 (0.89 to 1.15)	1	0.88 (0.77 to 1.00)	0.55 (0.47 to 0.64)	0.54 (0.47 to 0.63)	1.00 (0.88 to 1.14)	1.30 (1.16 to 1.47)	1.34 (1.18 to 1.51)	1.35 (1.19 to 1.52)	1.38 (1.22 to 1.56)
Lithium	1.12 (0.81 to 1.55)	1	0.74 (0.52 to 1.06)	0.42 (0.27 to 0.64)	0.48 (0.31 to 0.71)	0.88 (0.63 to 1.24)	1.32 (0.97 to 1.79)	1.53 (1.14 to 2.08)	1.50 (1.11 to 2.04)	1.58 (1.17 to 2.14)
Any of the three ACMS	1.01 (0.95 to 1.08)	1	0.97 (0.91 to 1.03)	0.87 (0.82 to 0.93)	0.85 (0.80 to 0.91)	0.96 (0.90 to 1.02)	1.00 (0.94 to 1.07)	1.02 (0.96 to 1.09)	1.03 (0.96 to 1.09)	1.04 (0.98 to 1.11)
Any of the three ACMS limited to women with SMI or recent depression	0.99 (0.79 to 1.24)	1	0.82 (0.65 to 1.03)	0.35 (0.25 to 0.47)	0.33 (0.24 to 0.46)	0.73 (0.58 to 0.93)	0.96 (0.77 to 1.21)	1.05 (0.84 to 1.32)	1.03 (0.82 to 1.29)	1.09 (0.87 to 1.37)

ACMS, anticonvulsant mood stabilisers; SMI, severe mental illness.

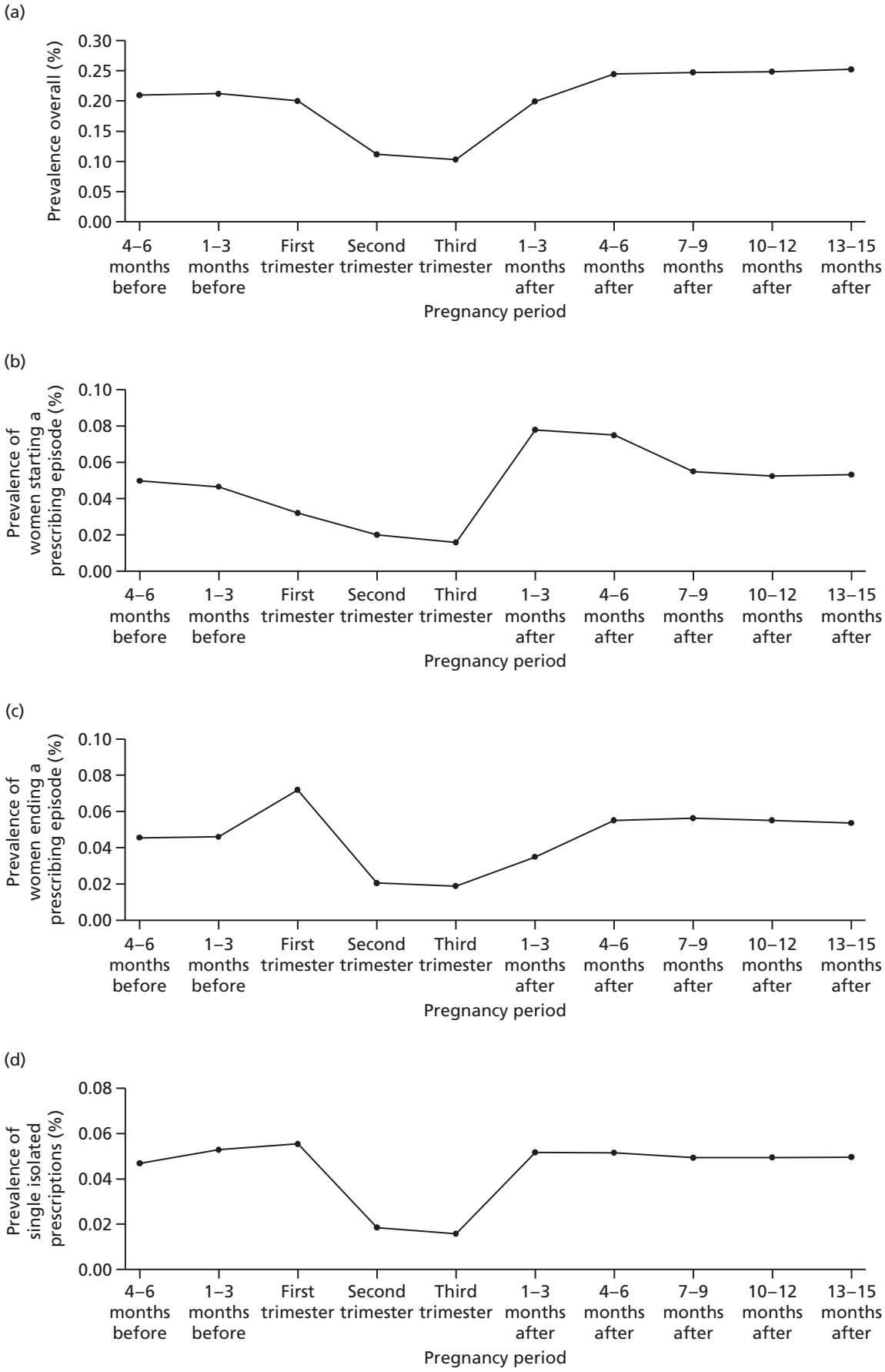


FIGURE 1 Overall prevalence of antipsychotics (a–d), lithium (e–h) and anticonvulsant mood stabilisers (i–l) (women with a record of psychosis or depression) prescribing in the total pregnancy cohort along with levels of starting and ending a prescribing episode and single prescriptions.

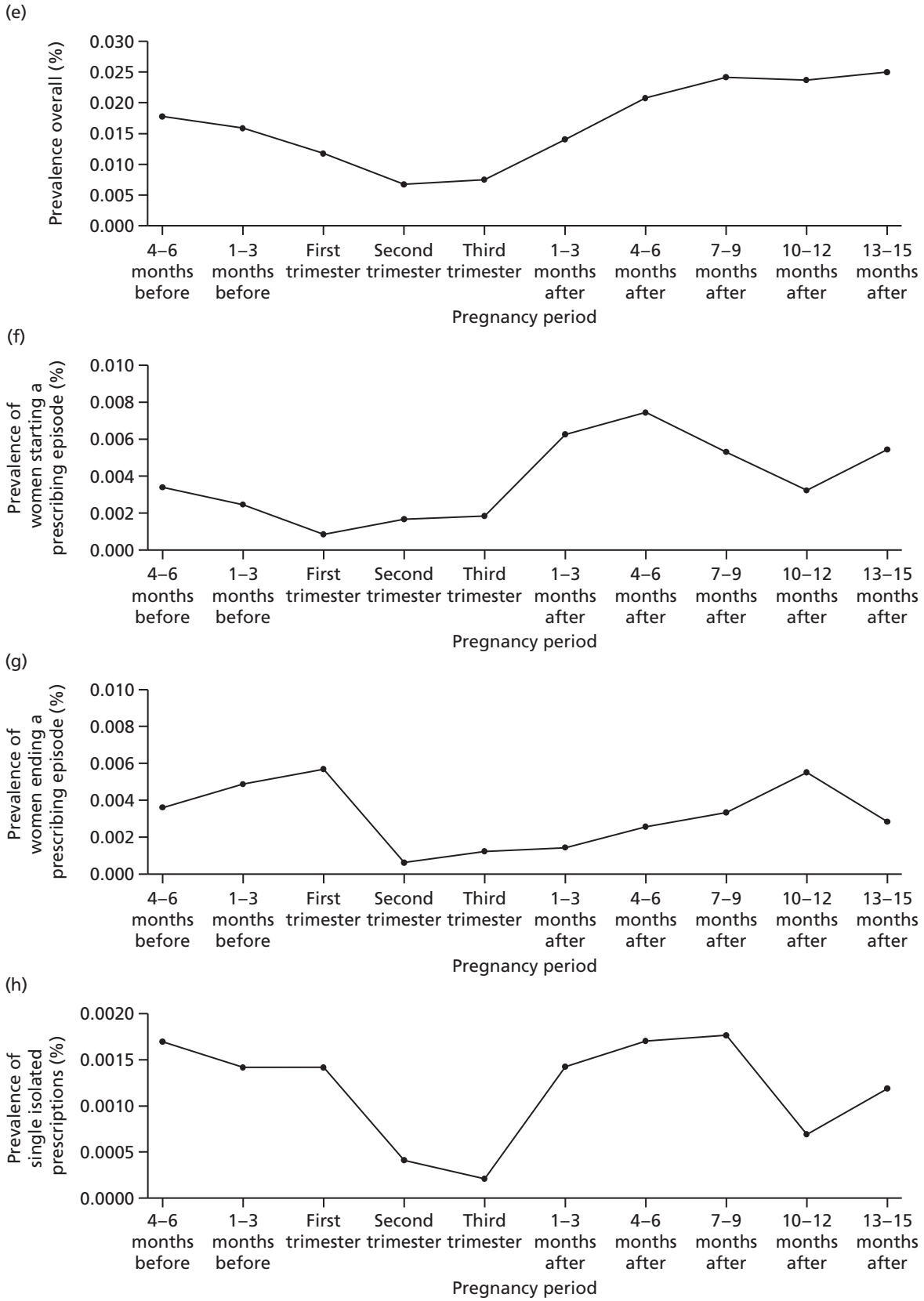


FIGURE 1 Overall prevalence of antipsychotics (a–d), lithium (e–h) and anticonvulsant mood stabilisers (i–l) (women with a record of psychosis or depression) prescribing in the total pregnancy cohort along with levels of starting and ending a prescribing episode and single prescriptions. (*continued*)

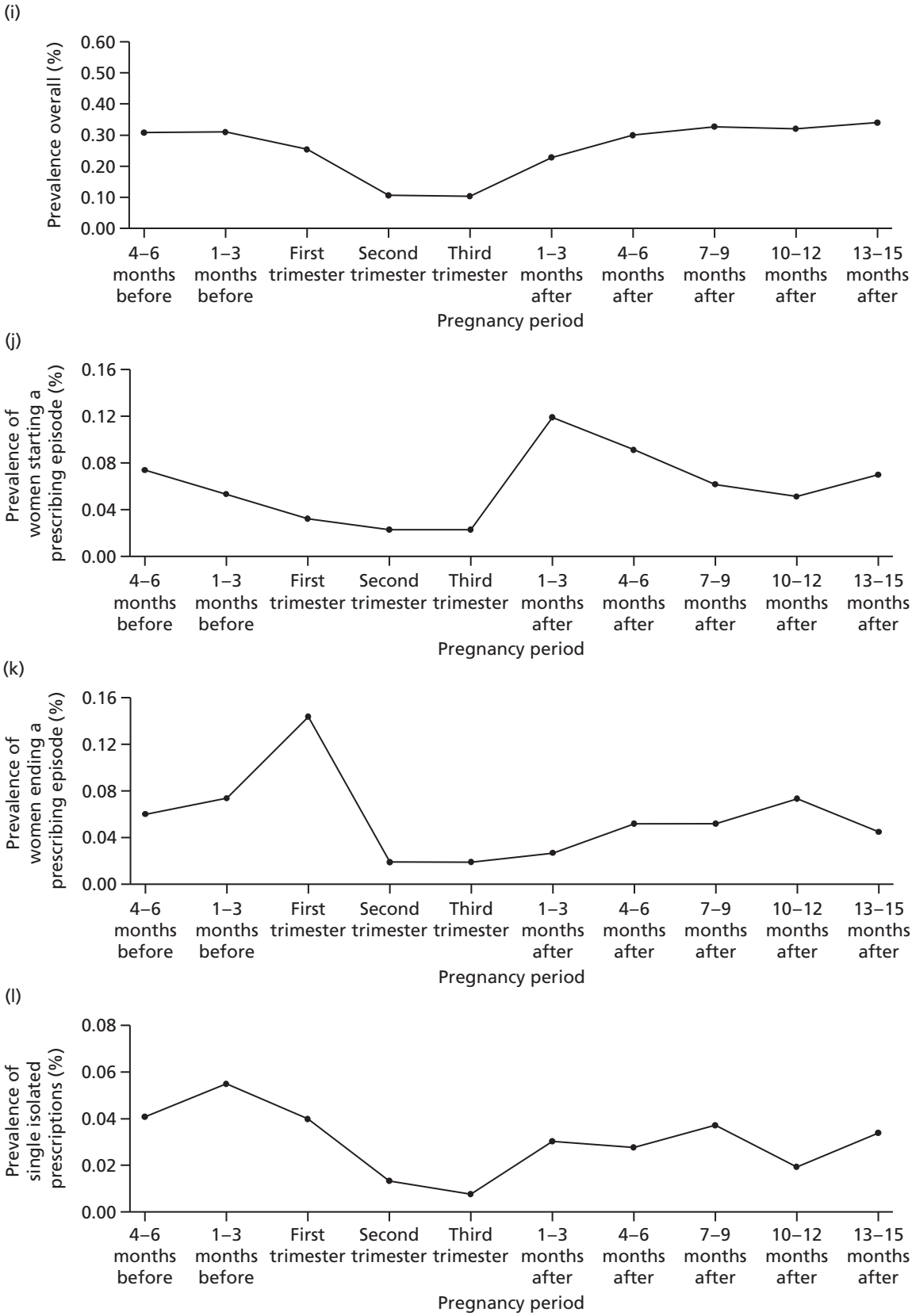


FIGURE 1 Overall prevalence of antipsychotics (a–d), lithium (e–h) and anticonvulsant mood stabilisers (i–l) (women with a record of psychosis or depression) prescribing in the total pregnancy cohort along with levels of starting and ending a prescribing episode and single prescriptions. (*continued*)

Multiple psychotropic medications

Considering the six relevant classes of drugs [antipsychotics (BNF chapters 4.2.1 and 4.2.2); lithium and anticonvulsants (BNF chapter 4.8.1); antidepressants (BNF chapter 4.3); anxiolytics (BNF chapter 4.1.2) and hypnotics (BNF chapter 4.1.1)], in about 6% (28,305/495,953) of all pregnancies, the women received one class of psychotropic medication in the 4–6 months before they became pregnant, whereas < 1% received prescriptions from two to five classes (*Table 5*). The most typical combinations were antidepressants and hypnotics [1256 (0.25%)] and antidepressants and anxiolytics [906 (0.18%)]. Antipsychotics and antidepressants were prescribed in combination to 387 individuals, equivalent to 0.08% of the full pregnancy cohort, but to 38% (387/999) of the women prescribed antipsychotics 4–6 months before pregnancy. Anticonvulsant and antidepressants were prescribed to 317 (0.06%) of the full pregnancy cohort (*Table 6*), but to 16% (317/1991) of those who received anticonvulsant mood stabilisers 4–6 months before pregnancy.

TABLE 5 Numbers of pregnancies in which women received prescriptions from more than one category of the six classes of medication listed in the text in the 4–6 months before pregnancy

Number of drug categories	Frequency	Per cent[a]
0	463,950	93.55
1	28,305	5.71
2	3156	0.64
3	456	0.09
4	73	0.01
5	13	< 0.01

a Percentage of 495,953 pregnancies.

TABLE 6 Most common combinations of drug categories being prescribed to women in the 4–6 months before pregnancy

Combination	Frequency	Per cent[a]
Antidepressant and hypnotic	1256	0.25
Antidepressant and anxiolytic	906	0.18
Antipsychotic and antidepressant	387	0.08
Anticonvulsant and antidepressant	317	0.06
Antidepressant, anxiolytic and hypnotic	187	0.04
Anxiolytic and hypnotic	122	0.02
Antipsychotic, antidepressant and hypnotic	80	0.02
Antipsychotic, antidepressant and anxiolytic	53	0.01
Anticonvulsant and anxiolytic	40	0.01
Anticonvulsant, antidepressant and anxiolytic	40	0.01
Antipsychotic, antidepressant, anxiolytic and hypnotic	35	0.01
Antipsychotic, anticonvulsant and antidepressant	34	0.01

a Percentage of 495,953 pregnancies.

Initiation of psychotropic treatment, termination of psychotropic treatment and isolated psychotropic prescriptions

Although very few women were prescribed a new episode of antipsychotics, lithium or anticonvulsant mood stabilisers immediately before and during pregnancy (see *Figure 1*), there was a sharp rise in the proportion of women initiating new episodes in the first 6 months after delivery (see *Figure 1*). In contrast, a large number of women terminated treatments before and during pregnancy. Thus, the highest proportion of women terminating treatments were found in the 1–3 months before pregnancy and during the first pregnancy trimester (see *Figure 1*).

In general there were few women who received a single isolated prescription of psychotropic medication and there were even fewer women who received such during the second and third pregnancy trimester (see *Figure 1*).

Patterns of recording that indicate worsening of mental health: 18 months before pregnancy, during the course of pregnancy and up to 15 months after delivery

Overall, 495,953 pregnancies were included in the study from 1 January 1995 to 31 December 2012.

Below, we describe the annual prevalence of each of the three sets of outcomes: (1) suicide attempts, overdose or deliberate self-harm; (2) mental health hospital admission or examination in relation to the Mental Health Act;[45] and (3) psychosis, mania or hypomania before, during and after delivery over the calendar period 1995–2012.

In general, relatively few women had any entries in their records that suggested deterioration or change of severity of mental illnesses in the period before and during pregnancy as well as after delivery (see *Figure 2*). The recording of suicide attempts, overdose or deliberate self-harm was relatively constant in the 18 months prior to pregnancy (*Figure 2* and *Table 7*). During pregnancy the prevalence declined and relative to the period of 1–3 months before pregnancy the PR was 0.11 (95% CI 0.08 to 0.14) in the third trimester. It rose after pregnancy, but was still only half of what it was prior to pregnancy (see *Table 7*). The entries made of mental health hospital admissions or invoking of the Mental Health Act[45] more than tripled just after delivery in comparison to the period of 1–3 months before pregnancy (PR 3.16, 95% CI 1.86 to 5.60) (see *Table 7*). Records of psychosis, mania or hypomania followed similar patterns with a doubling just after delivery in comparison to the 1–3 months before pregnancy (PR 2.02, 95% CI 1.53 to 2.69) (see *Table 7*).

Time trends in prevalence of psychotropic medication treatment around and during pregnancy over the calendar period 1995–2012

Overall, 495,953 pregnancies were included in the study from 1 January 1995 to 31 December 2012. Below we describe annual prevalence for each of the three classes of psychotropic medication (antipsychotics, lithium and anticonvulsant mood stabilisers) before, during and after delivery over the calendar period 1995–2012. The work on antipsychotics and lithium has been published in part elsewhere.[46,47]

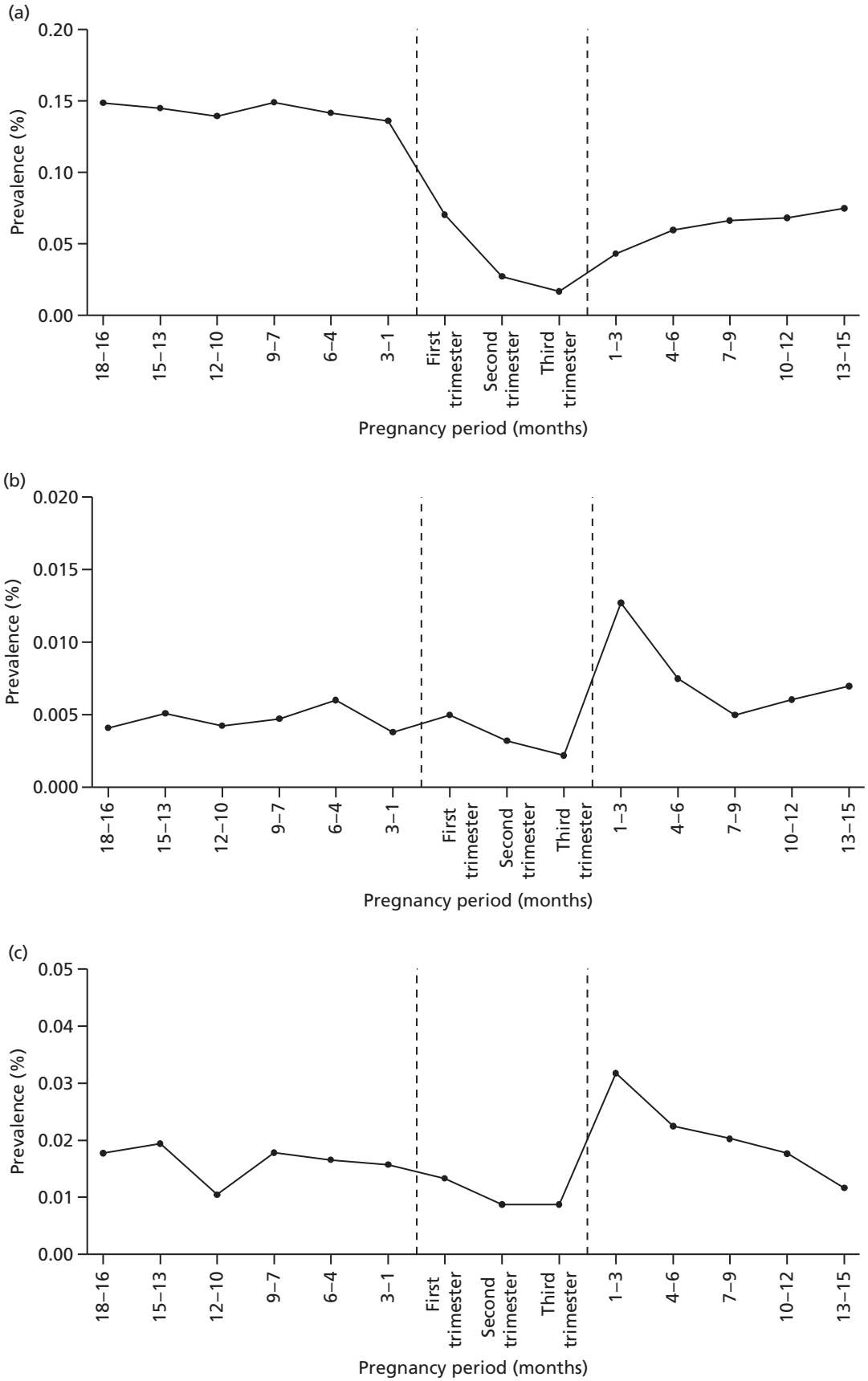


FIGURE 2 Prevalence recording of (a) suicide attempts, overdose or self-harm; (b) mental health hospital admission; and (c) psychosis, mania or hypomania, from 18 months before the start of pregnancy up to 15 months after delivery.

TABLE 7 Prevalence ratios (95% CI) for the prevalence of symptoms over time in the full pregnancy cohort

Prescribed antipsychotic	4–6 months before pregnancy	1–3 months before pregnancy	First trimester	Second trimester	Third trimester	1–3 months after delivery	4–6 months after delivery	7–9 months after delivery	10–12 months after delivery	13–15 months after delivery
Suicide attempt, overdose or deliberate self-harm	1.03 (0.92 to 1.15)	1	0.50 (0.44 to 0.57)	0.19 (0.15 to 0.23)	0.11 (0.08 to 0.14)	0.31 (0.26 to 0.36)	0.43 (0.37 to 0.50)	0.48 (0.42 to 0.55)	0.50 (0.43 to 0.57)	0.55 (0.48 to 0.63)
Hospital admissions or MHA examination	1.53 (0.83 to 2.91)	1	1.26 (0.66 to 2.44)	0.79 (0.37 to 1.64)	0.58 (0.25 to 1.28)	3.16 (1.86 to 5.60)	1.98 (1.11 to 3.66)	1.26 (0.65 to 2.46)	1.60 (0.86 to 3.05)	1.79 (0.97 to 3.37)
Psychosis, mania or hypomania	1.05 (0.76 to 1.46)	1	0.86 (0.61 to 1.21)	0.54 (0.36 to 0.79)	0.53 (0.35 to 0.78)	2.02 (1.53 to 2.69)	1.38 (1.02 to 1.88)	1.24 (0.90 to 1.70)	1.13 (0.81 to 1.56)	0.74 (0.50 to 1.07)

MHA, Mental Health Act.[45]

Overall, annual prescribing in the 6 months before pregnancy and during pregnancy of both antipsychotics and anticonvulsant mood stabilisers was relatively stable from 1995 to 2006, but increased from around 2007 (*Figure 3*). By 2011/12, just under 0.4% were prescribed antipsychotics in the 6 months before pregnancy and just under 0.3% received antipsychotic treatment in pregnancy by 2011/12, suggesting a more than 50% increase since 1995/6. For anticonvulsant mood stabilisers the prevalence figures for women with a record of psychoses or depression for 2011/12 were 0.6% before pregnancy, 0.26% during pregnancy and 0.36% after delivery. Hence the treatment prevalence has almost doubled since 1995/6 (see *Figure 3*).

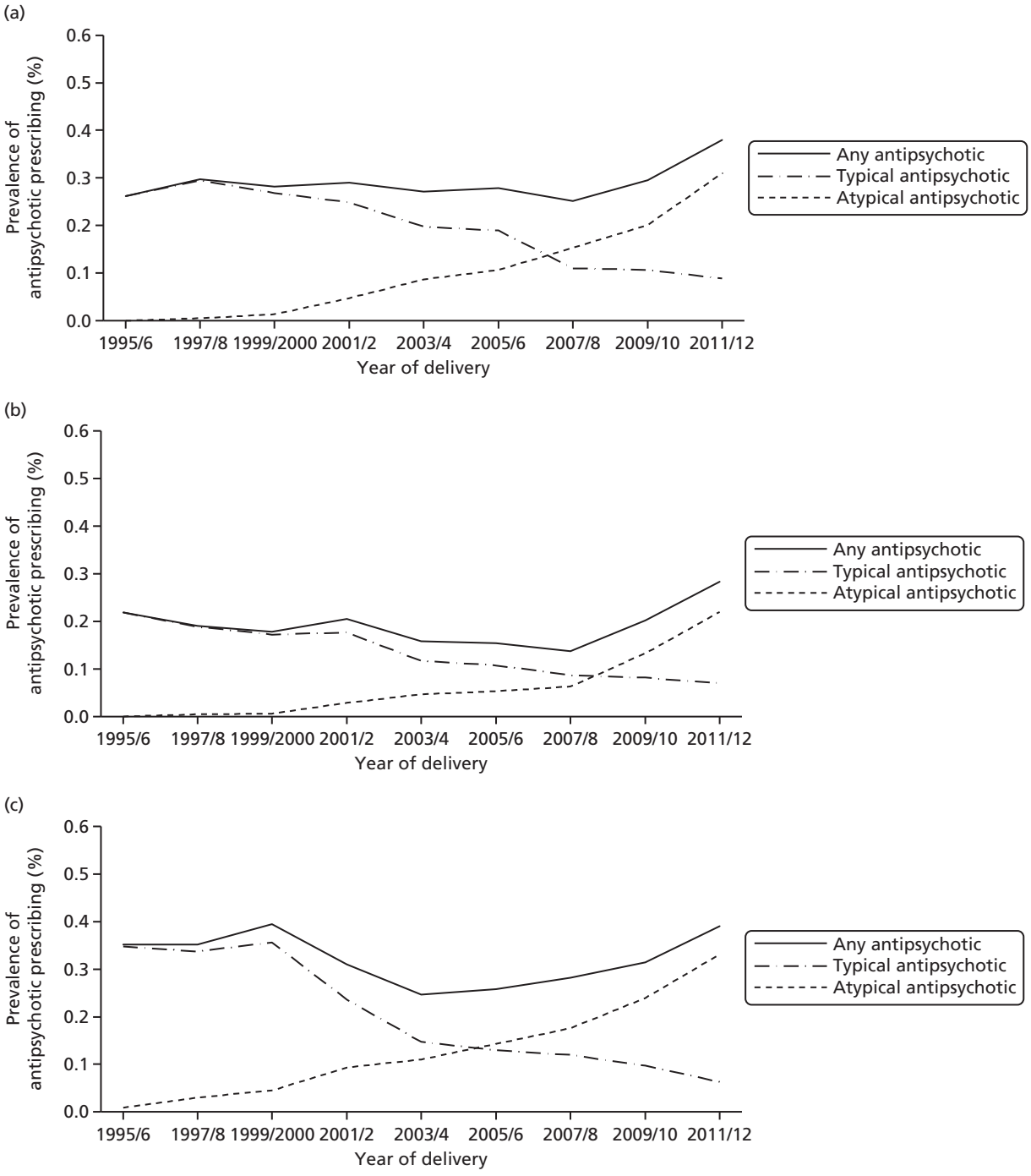


FIGURE 3 Prevalence of prescribing over calendar period 1995–2012. Prescribing of antipsychotics (a) in the 6 months before pregnancy; (b) during pregnancy; (c) 6 months after delivery; lithium (d) in the 6 months before pregnancy; (e) during pregnancy; (f) 6 months after delivery; anticonvulsant mood stabilisers (g) in the 6 months before pregnancy; (h) during pregnancy; and (i) 6 months after delivery.

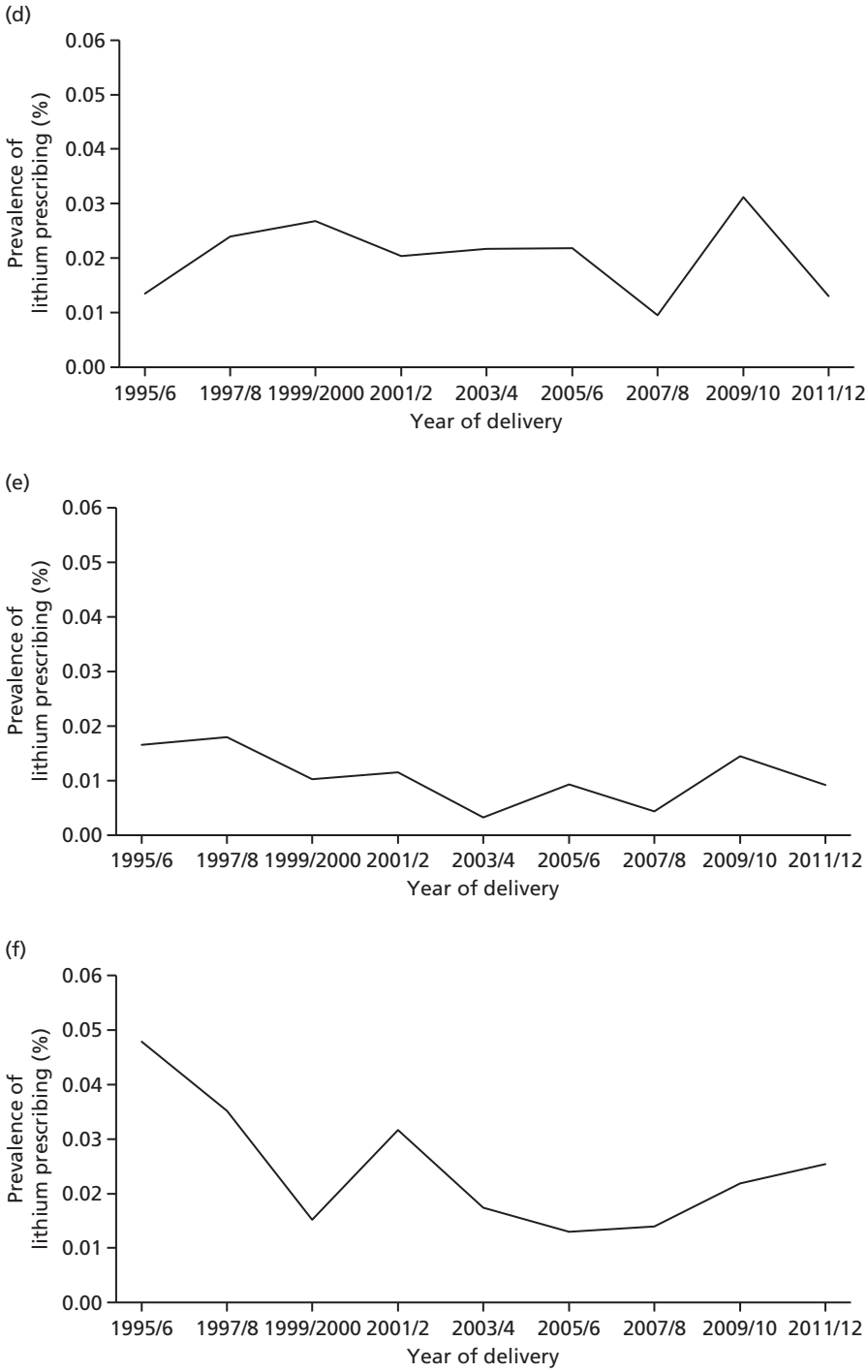


FIGURE 3 Prevalence of prescribing over calendar period 1995–2012. Prescribing of antipsychotics (a) in the 6 months before pregnancy; (b) during pregnancy; (c) 6 months after delivery; lithium (d) in the 6 months before pregnancy; (e) during pregnancy; (f) 6 months after delivery; anticonvulsant mood stabilisers (g) in the 6 months before pregnancy; (h) during pregnancy; and (i) 6 months after delivery. (*continued*)

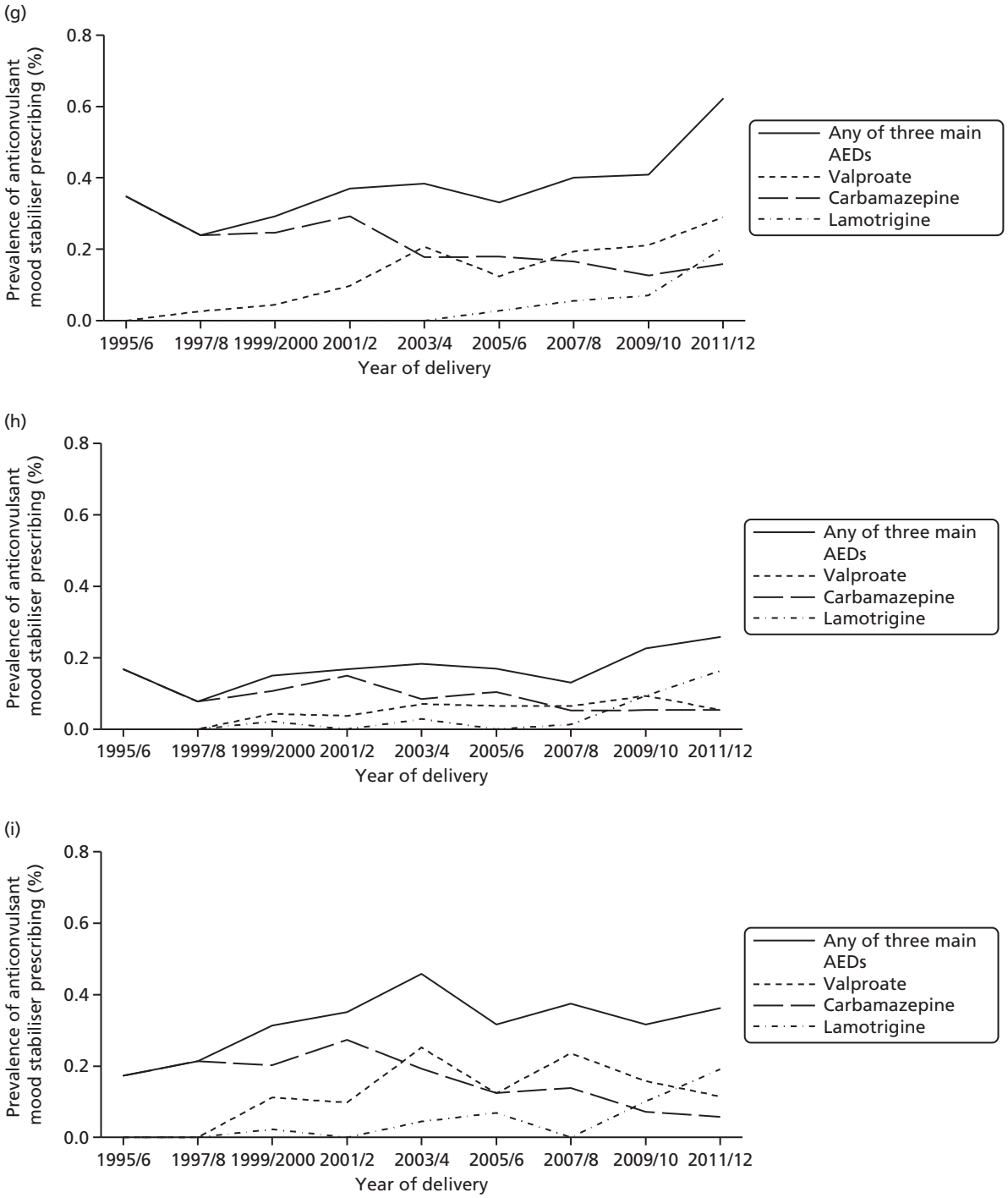


FIGURE 3 Prevalence of prescribing over calendar period 1995–2012. Prescribing of antipsychotics (a) in the 6 months before pregnancy; (b) during pregnancy; (c) 6 months after delivery; lithium (d) in the 6 months before pregnancy; (e) during pregnancy; (f) 6 months after delivery; anticonvulsant mood stabilisers (g) in the 6 months before pregnancy; (h) during pregnancy; and (i) 6 months after delivery. (*continued*)

Prescribing of typical antipsychotics has been declining since 1997/8, whereas prescribing of atypical antipsychotics has been increasing. Thus, atypical antipsychotics were more commonly prescribed before pregnancy, during pregnancy and after delivery after 2007/8 (see *Figure 3*). For anticonvulsant mood stabilisers, prescribing of carbamazepine has declined, whereas both valproate and lamotrigine have gradually increased before pregnancy (see *Figure 3*). By 2011/12, carbamazepine was superseded by lamotrigine before, during and after pregnancy and valproate was the most commonly prescribed anticonvulsant mood stabiliser before pregnancy (see *Figure 3*).

Lithium was rarely prescribed; before pregnancy the annual prevalence of lithium prescribing ranged between 0.01% and 0.03%, and during pregnancy between 0.003% and 0.018%. The annual prevalence in the 6 months after delivery declined from 0.048% in 1995/6 to 0.015 in 1999/2000 (see *Figure 3*).

Discontinuation and factors associated with continuation of psychotropic medication in pregnancy

We identified 207 women receiving typical antipsychotics, 279 receiving atypical antipsychotics, 52 receiving lithium and 93 with a record of psychoses or depression receiving anticonvulsant mood stabilisers in the 4–6 months before the start of their pregnancy.

Although many women discontinued psychotropic medication either before or early in pregnancy the proportion varied between psychotropic treatments. Women prescribed atypical antipsychotics were least likely to discontinue treatment in pregnancy and 150 out of 279 (54%) received further prescriptions after 6 weeks of pregnancy (when the woman is likely to become aware of the pregnancy). In contrast, only 73 out of 207 (35%) women received further prescriptions of typical antipsychotics, 17 out of 52 (33%) lithium and 34 out of 93 (37%) anticonvulsant mood stabilisers after 6 weeks of pregnancy. By the start of the third trimester the figures were 107 out of 279 (38%) for atypical antipsychotics, 39 out of 207 (19%) for typical antipsychotics, 14 out of 52 (27%) for lithium and 13 out of 93 (14%) for anticonvulsant mood stabilisers.

We report below, additional results from studies on discontinuation of psychotropic medication in pregnancy and factors associated with continuation for each of the classes of psychotropic medication (antipsychotics, lithium and anticonvulsant mood stabilisers) Parts of this work have been published elsewhere.[46,47]

Discontinuation of antipsychotics

Pregnant and non-pregnant women prescribed atypical antipsychotics discontinued at similar rates up to the start of pregnancy (or index date) (*Figure 4*). However, pregnant women were more likely to discontinue atypical antipsychotics than non-pregnant women (see *Figure 4b*).

For women on typical antipsychotics there was a substantial difference in the rates of discontinuation between pregnant and non-pregnant women even before the pregnancy (see *Figure 4a*) and the gap became wider in early pregnancy (see *Figure 4a*). The comparisons with non-pregnant women, however, suggest that awareness of the pregnancy may not be the only reason for stopping antipsychotics. About 75% of non-pregnant women continued both typical and atypical antipsychotics throughout the follow-up period (see *Figure 4*).

The rates of discontinuation differed by dose and type of antipsychotics (*Figure 5*). Among women receiving prescriptions of less than one-quarter of the DDD of typical antipsychotics, only 29 out of 118 (25%) continued prescriptions after 6 weeks. For women on atypical antipsychotics the figure was 24 out of 52 (46%) after 6 weeks (see *Figure 5*).

Women on a high dose (DDD > 1) of typical antipsychotics were highly likely to discontinue prescriptions prior to pregnancy in contrast to women on a high dose (DDD > 1) of atypical antipsychotics (see *Figure 5*). Three out of 15 women on high dose typical antipsychotics were on depots prior to the start of pregnancy.

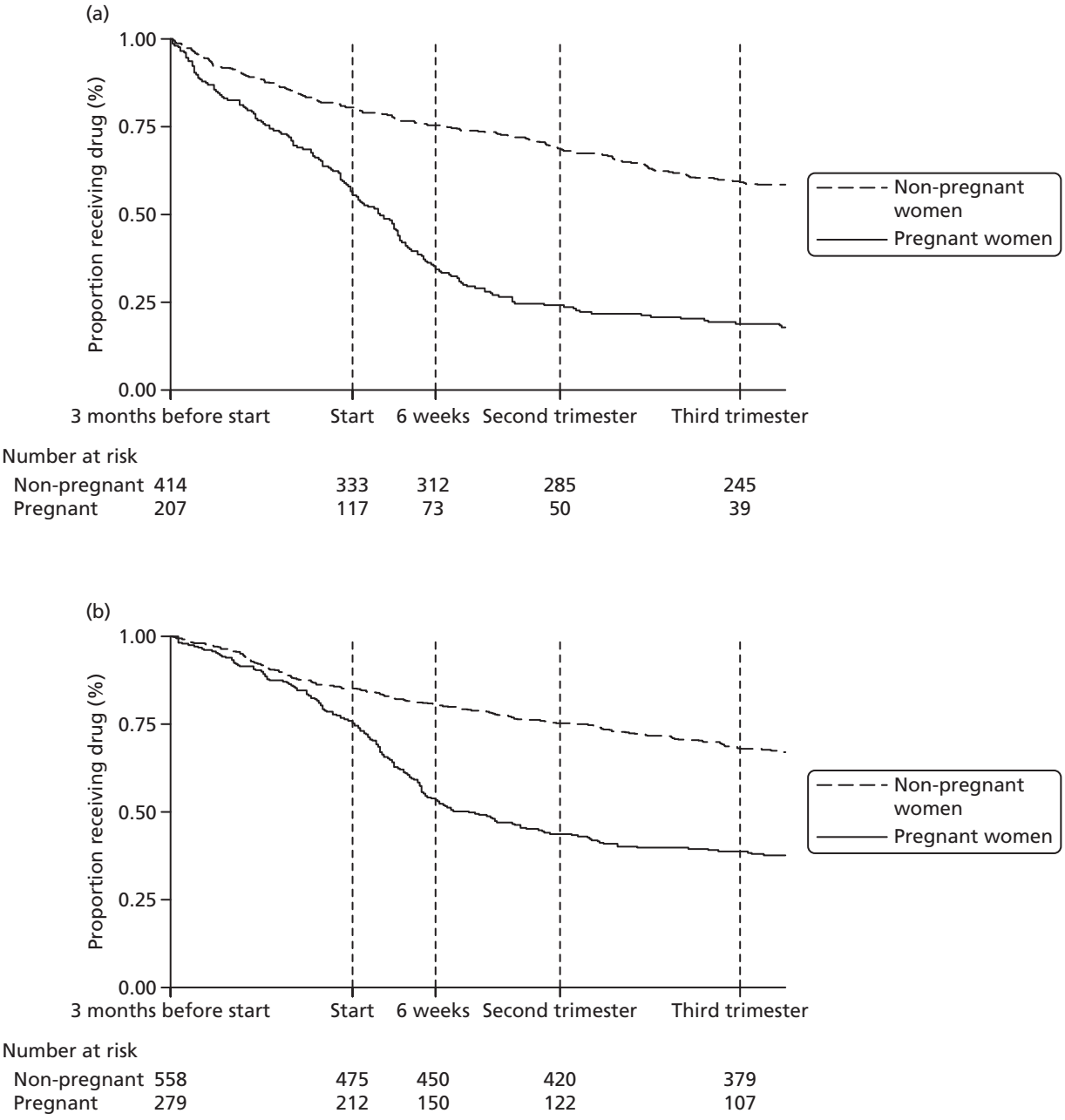
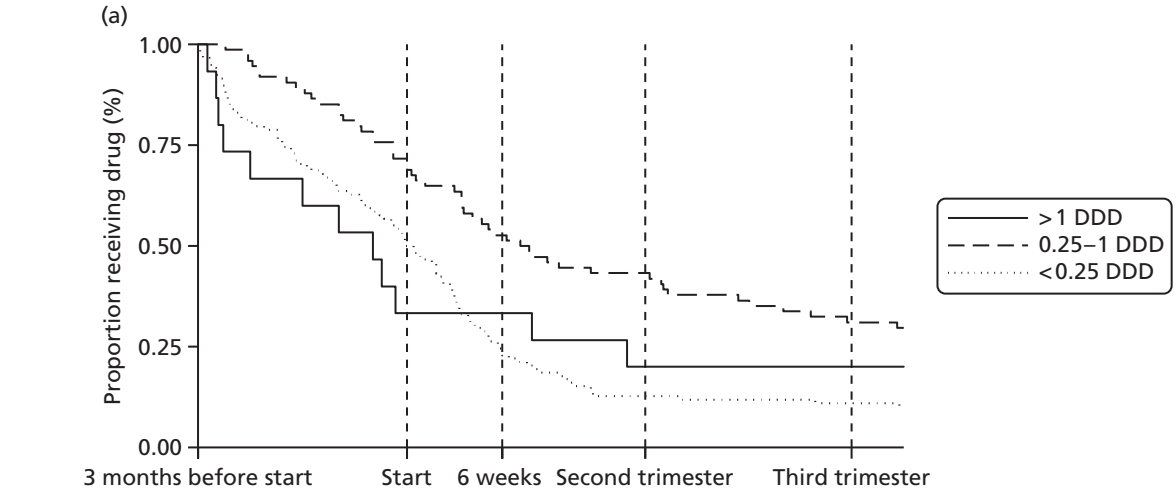
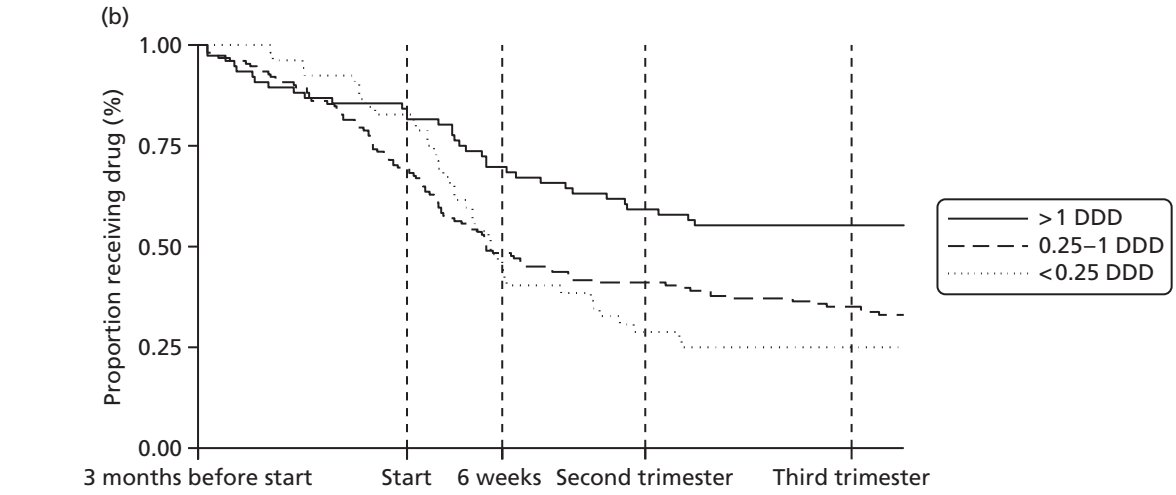


FIGURE 4 Discontinuation of antipsychotic drugs in pregnant and non-pregnant women by (a) typical; and (b) atypical antipsychotics.



Number receiving drug:

>1 DDD	15	5	5	3	3
0.25–1 DDD	74	53	39	32	23
<0.25 DDD	118	59	29	15	13



Number receiving drug:

>1 DDD	76	64	53	45	41
0.25–1 DDD	151	105	73	62	53
<0.25 DDD	52	43	24	15	13

FIGURE 5 Discontinuation of antipsychotic drugs in pregnant women, by dose, in women who were prescribed (a) typical; and (b) atypical antipsychotics.

Factors associated with continuation of antipsychotics

Factors associated with continuation of receiving antipsychotic prescriptions beyond 6 weeks of pregnancy for typical antipsychotics included age and durations of treatment prior to pregnancy (*Table 8*). Those aged ≥ 35 years were more than three times as likely to continue treatment compared with those < 25 years [risk ratio (RR) 3.09, 95% CI 1.76 to 5.44]. The effect of age attenuated slightly after adjustment for dose. Likewise, those who had received continuous treatment for > 12 months prior to pregnancy were also more likely to continue treatment in pregnancy compared with those who had received < 6 months of continuous treatment prior to pregnancy (RR 3.12, 95% CI 1.97 to 4.95). This was still the case after adjustment for age and dose (RR 2.48, 95% CI 1.54 to 3.99). For atypical antipsychotics, length and dose of prior prescribing were also associated with continuation in pregnancy (*Table 9*). However, those aged 30–34 years were the most likely to continue prescriptions in pregnancy (see *Table 9*). For other factors examined (diagnosis of severe mental illnesses, also taking antidepressants and mood stabilisers, social deprivation, estimated parity, obesity, smoking, records of alcohol problems, illicit drug use and ethnicity) none of the adjusted effect sizes was larger than 1.67 or lower than 0.64 (see *Tables 8* and *9*).

TABLE 8 Factors associated with receiving typical antipsychotics prescriptions beyond 6 weeks after the estimated pregnancy start date

	Typical antipsychotics (*N* = 207)						
		Unadjusted			Adjusted		
Factors	*n*	RR	95% CI	*p*-value	RR	95% CI	*p*-value
Average daily dose (in units of DDD)				***< 0.001***			***0.011***
< 0.25 DDD	118	1			1		
0.25–1 DDD	74	2.14	1.46 to 3.15		1.78	1.22 to 2.60	
> 1 DDD	15	1.36	0.62 to 2.97		1.25	0.58 to 2.68	
Age band				***< 0.001***			***< 0.001***
< 25 years	53	1			1		
25–29 years	42	1.49	0.74 to 2.99		1.34	0.68 to 2.62	
30–34 years	59	1.22	0.62 to 2.43		1.15	0.58 to 2.29	
≥ 35 years	53	3.09	1.76 to 5.44		2.60	1.47 to 4.59	
Continuous prior time on antipsychotics				***< 0.001***			***0.001***
< 6 months	98	1			1		
6–12 months	34	1.92	1.03 to 3.57		1.78	0.97 to 3.26	
> 12 months	75	3.12	1.97 to 4.95		2.48	1.54 to 3.99	
SMI diagnosis code				***0.018***			***0.404***
No	160	1			1		
SMI diagnosis code	47	1.57	1.08 to 2.27		1.17	0.81 to 1.71	
Also taking an antidepressant				***0.238***			***0.566***
No	66	1			1		
Taking an antidepressant	141	0.80	0.55 to 1.16		0.90	0.64 to 1.28	
Also taking a mood stabiliser				***0.033***			***0.281***
No	191	1			1		
Taking a mood stabiliser	16	1.68	1.04 to 2.71		1.31	0.80 to 2.12	

continued

TABLE 8 Factors associated with receiving typical antipsychotics prescriptions beyond 6 weeks after the estimated pregnancy start date (*continued*)

	Typical antipsychotics (*N* = 207)						
		Unadjusted			Adjusted		
Factors	*n*	RR	95% CI	*p*-value	RR	95% CI	*p*-value
Townsend quintile				***0.562***			***0.440***
1	16	1			1		
2	22	0.85	0.35 to 2.05		0.72	0.32 to 1.61	
3	36	0.67	0.28 to 1.56		0.64	0.29 to 1.43	
4	61	1.14	0.57 to 2.28		1.07	0.57 to 1.99	
5	68	0.98	0.48 to 1.99		0.89	0.47 to 1.68	
Unrecorded	4						
Estimated parity				***0.103***			***0.159***
0	84	1			1		
1	57	1.47	0.91 to 2.40		1.34	0.87 to 2.08	
2	44	1.82	1.13 to 2.93		1.65	1.06 to 2.57	
3 or more	22	1.39	0.72 to 2.69		1.52	0.80 to 2.90	
Obesity status				***0.771***			***0.759***
Not obese	186	1			1		
Obese	21	1.09	0.61 to 1.95		1.09	0.63 to 1.90	
Smoking status				***0.912***			***0.602***
Non-smoker	106	1			1		
Smoker	101	1.02	0.71 to 1.48		1.09	0.78 to 1.53	
Alcohol problems				***0.154***			***0.094***
No	191	1			1		
Yes	16	1.47	0.87 to 2.50		1.59	0.92 to 2.75	
Illicit drug use				***0.941***			***0.866***
No	181	1			1		
Yes	26	0.98	0.56 to 1.72		1.05	0.60 to 1.84	
Ethnicity							
Other	204	1			1		
Black or minority ethnic	3	Could not be estimated – all three continue receiving prescriptions					

RR, risk ratio; SMI, severe mental illness.

Notes

Adjustment variables: dose and age band.

TABLE 9 Factors associated with receiving atypical antipsychotics prescriptions beyond 6 weeks after the estimated pregnancy start date

	Atypical antipsychotics (*N* = 279)						
		Unadjusted			Adjusted		
Factors	*n*	RR	95% CI	*p*-value	RR	95% CI	*p*-value
Average daily dose (in units of DDD)				***0.002***			***0.003***
< 0.25 DDD	52	1			1		
0.25–1 DDD	151	1.05	0.75 to 1.47		1.04	0.74 to 1.47	
> 1 DDD	76	1.51	1.09 to 2.10		1.48	1.06 to 2.07	
Age band				***0.147***			***0.201***
< 25 years	53	1			1		
25–29 years	74	1.24	0.84 to 1.83		1.23	0.84 to 1.80	
30–34 years	82	1.50	1.04 to 2.15		1.45	1.02 to 2.08	
≥ 35 years	70	1.34	0.92 to 1.97		1.31	0.90 to 1.92	
Continuous prior time on antipsychotics				***< 0.001***			***0.001***
< 6 months	100	1			1		
6–12 months	53	1.34	0.93 to 1.93		1.34	0.93 to 1.94	
> 12 months	126	1.78	1.34 to 2.35		1.67	1.27 to 2.21	
SMI diagnosis code				***0.005***			***0.073***
No	136	1			1		
SMI diagnosis code	143	1.39	1.11 to 1.74		1.25	0.98 to 1.59	
Also taking an antidepressant				***0.097***			***0.402***
No	96	1			1		
Taking an antidepressant	183	0.83	0.67 to 1.03		0.91	0.73 to 1.13	
Also taking a mood stabiliser				***0.098***			***0.574***
No	232	1			1		
Taking a mood stabiliser	47	1.23	0.96 to 1.58		1.08	0.83 to 1.40	
Townsend quintile				***0.880***			***0.805***
1	26	1			1		
2	32	1.10	0.70 to 1.74		1.07	0.68 to 1.67	
3	52	0.93	0.59 to 1.45		0.87	0.56 to 1.35	
4	72	0.93	0.61 to 1.42		0.87	0.57 to 1.33	
5	85	1.03	0.69 to 1.54		0.94	0.63 to 1.41	
Unrecorded	12						
Estimated parity				***0.474***			***0.511***
0	110	1			1		
1	89	0.89	0.70 to 1.15		0.92	0.72 to 1.18	
2	49	0.79	0.57 to 1.11		0.82	0.58 to 1.14	
3 or more	31	0.82	0.55 to 1.22		0.80	0.54 to 1.18	

continued

TABLE 9 Factors associated with receiving atypical antipsychotics prescriptions beyond 6 weeks after the estimated pregnancy start date (*continued*)

	Atypical antipsychotics (*N* = 279)						
		Unadjusted			Adjusted		
Factors	*n*	RR	95% CI	*p*-value	RR	95% CI	*p*-value
Obesity status				***0.055***			***0.119***
Not obese	223	1			1		
Obese	56	1.26	1.00 to 1.59		1.21	0.95 to 1.53	
Smoking status				***0.875***			***0.935***
Non-smoker	142	1			1		
Smoker	137	0.98	0.79 to 1.22		0.99	0.80 to 1.23	
Alcohol problems				***0.595***			***0.385***
No	264	1			1		
Yes	15	1.12	0.73 to 1.73		1.22	0.78 to 1.90	
Illicit drug use				***0.370***			***0.340***
No	246	1			1		
Yes	33	1.15	0.85 to 1.55		1.16	0.85 to 1.58	
Ethnicity				***0.087***			***0.214***
Other	249	1			1		
Black or minority ethnic	30	1.28	0.97 to 1.69		1.20	0.90 to 1.59	

SMI, severe mental illness.
Notes
Adjustment variables: dose and age band.

Switch between typical and atypical antipsychotic treatment

In general, few women switched between typical and atypical antipsychotic treatment just before or in pregnancy. Only 5 out of 207 (2.4%) women switched from typical to atypical antipsychotics and 9 out of 279 (3.2%) switched from atypical to typical antipsychotics. However, among the more frequently used antipsychotics, switching levels were high for two drugs: 12 out of 50 women (24.0%) switched from risperidone to another antipsychotic, while 9 out of 48 (18.8%) switched from trifluoperazine to another antipsychotic.

Discontinuation of lithium

For lithium, there was a substantial difference in the rates of discontinuation between pregnant and non-pregnant women (*Figure 6*). Only 14 out of 52 (27%) continued lithium treatment after the start of the third trimester. Of the non-pregnant women, 80 out of 104 (77%) continued lithium treatment beyond this period (see *Figure 6*).

Factors associated with continuation of lithium

A greater proportion of those who continued lithium in pregnancy had been prescribed an antidepressant (47%) or antipsychotic (53%) in addition to lithium during the 4–6 months before pregnancy (compared with 34% prescribed antidepressants or antipsychotics in those who stopped). In addition, a greater proportion of those who continued lithium were having their first child (59% vs. 40%) or had been receiving continuous lithium prescriptions for < 6 months (47% vs. 31%). However, the small numbers of women involved mean that the CIs for these percentages are wide and generally overlap (*Table 10*).

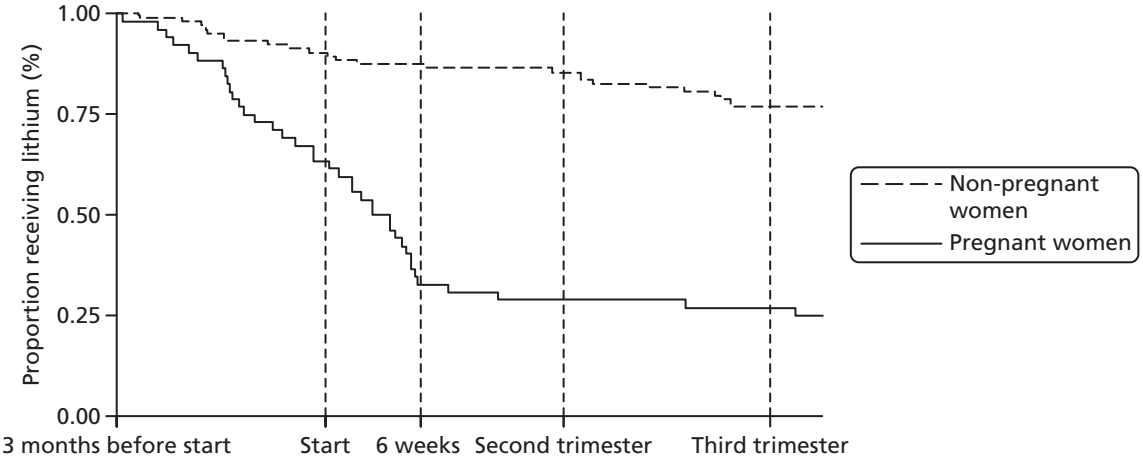


FIGURE 6 Discontinuation of lithium in pregnant and non-pregnant women.

TABLE 10 Factors associated with continued lithium prescribing beyond 6 weeks after the estimated pregnancy start

	Stopped before 6 weeks (*N* = 35)			Continued beyond 6 weeks (*N* = 17)		
Factors	***n***	**%**	**95% CI**	***n***	**%**	**95% CI**
Age band						
< 25 years	5	14.3	5.9 to 30.8	0	0.0	–
25–29 years	8	22.9	11.5 to 40.2	4	23.5	8.6 to 50.1
30–34 years	10	28.6	15.7 to 46.2	7	41.2	20.2 to 66.0
≥ 35 years	12	34.3	20.2 to 51.9	6	35.3	16.0 to 60.9
Prior continuous time on lithium						
< 6 months	11	31.4	17.9 to 49.0	8	47.1	24.5 to 70.8
6–12 months	6	17.1	7.7 to 34.0	2	11.8	2.7 to 38.8
> 12 months	18	51.4	34.7 to 67.8	7	41.2	20.2 to 66.0
Estimated parity						
0	14	40.0	24.8 to 57.4	10	58.8	34.0 to 79.8
1	13	37.1	22.5 to 54.6	4	23.5	8.6 to 50.1
2	6	17.1	7.7 to 34.0	3	17.6	5.4 to 44.4
3 or more	2	5.7	1.4 to 21.1	0	0.0	–
Also taking an antidepressant	12	34.3	20.2 to 51.9	8	47.1	24.5 to 70.8
Also taking an antipsychotic	12	34.3	20.2 to 51.9	9	52.9	29.2 to 75.5
Also taking an anticonvulsant	6	17.1	7.7 to 34.0	3	17.6	5.4 to 44.4

Switch from lithium to antipsychotic treatment

Of the 39 women who discontinued lithium before the end of follow-up at 220 days, six received at least two prescriptions for an antipsychotic in the 91 days after lithium discontinuation. However, five of these were already receiving an antipsychotic prior to lithium discontinuation, so only one could be classed as having 'switched' treatment. We cannot exclude the possibility that some of the other five may have started a new antipsychotic while gradually tapering off lithium.

Discontinuation of anticonvulsant mood stabilisers

We identified 1175 women receiving anticonvulsant mood stabilisers in the period of 4–6 months before the start of their pregnancy. Of these, 1007 had a record of epilepsy, 62 had a record of psychosis, 31 had a record of depression and 75 did not have a record of any of these indications. Among the 93 women with a record of psychosis or depression, there was a substantial difference in the rates of discontinuation between pregnant and non-pregnant women (*Figure 7*). This was the case even before the pregnancy started (see *Figure 7*). As for antipsychotics and lithium, the comparisons with non-pregnant women suggest that awareness of the pregnancy may not be the only reason for stopping treatment, as about 70% of non-pregnant women continued anticonvulsant mood stabilisers throughout the follow-up period (see *Figure 7*).

Although the numbers were small, there appeared to be no substantial difference in the rate of discontinuation between women who were prescribed lamotrigine, carbamazepine or valproates (*Figure 8*).

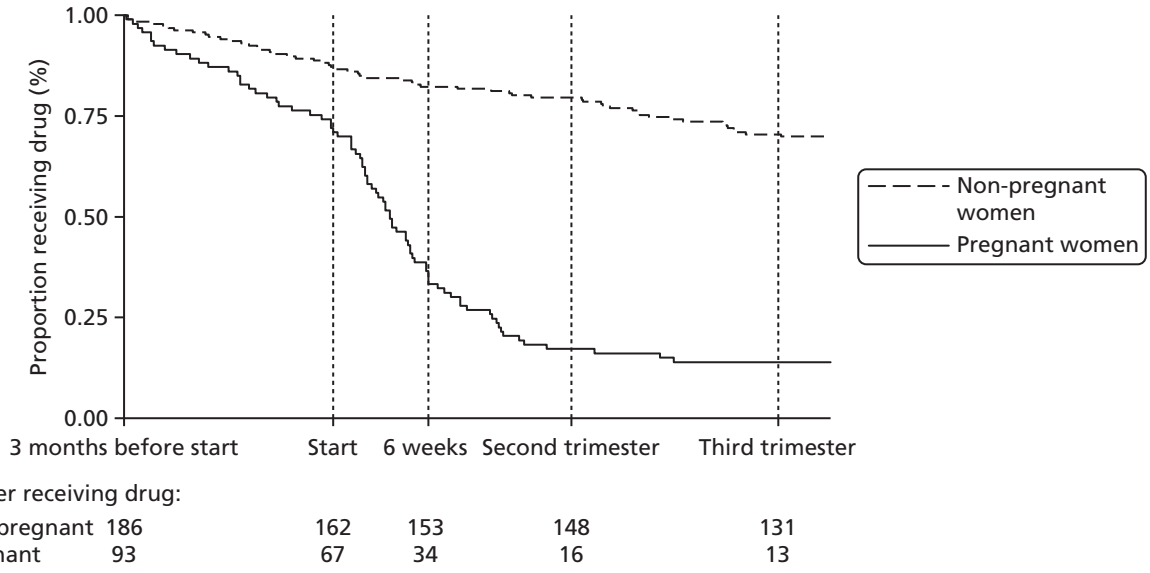
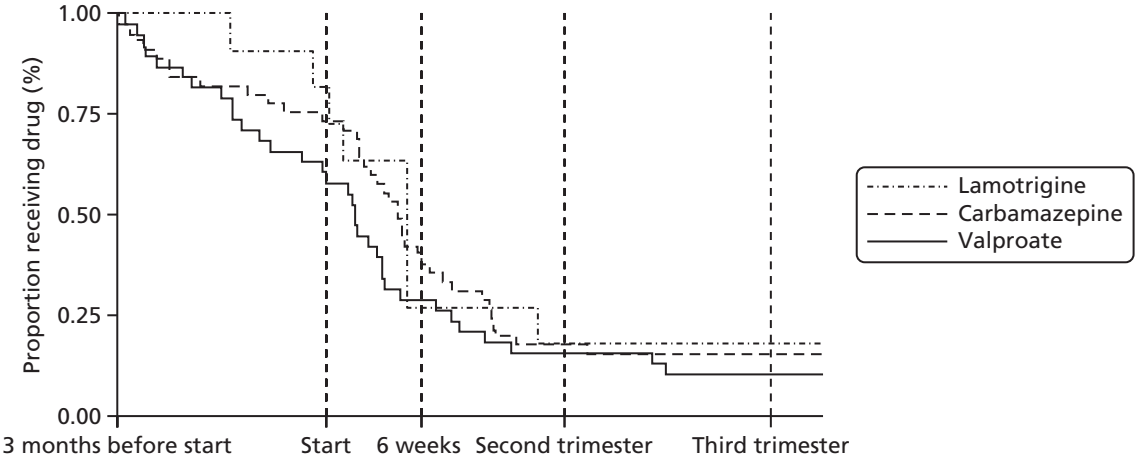


FIGURE 7 Discontinuation of anticonvulsant mood stabilisers in pregnant and non-pregnant women with a record of psychosis or depression.



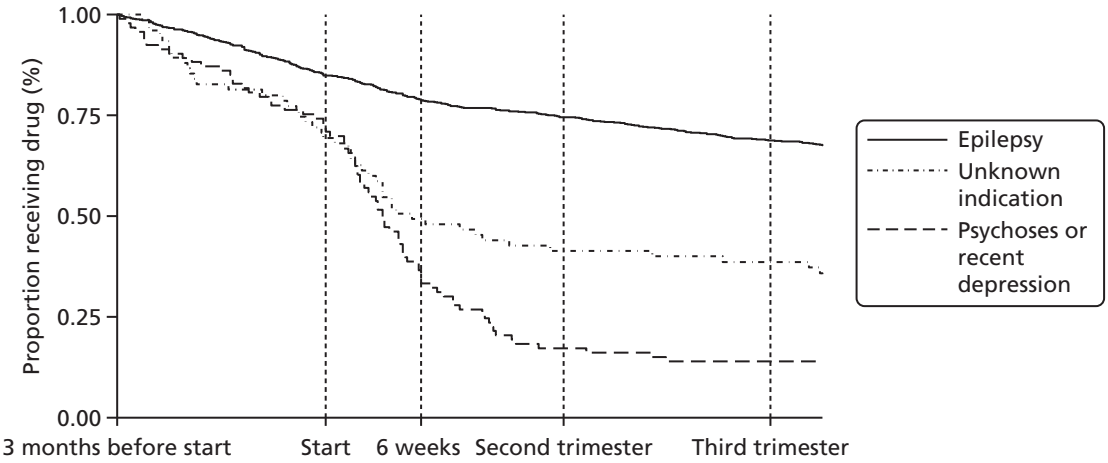
Number receiving drug:

Lamotrigine	11	9	5	2	2
Carbamazepine	45	33	18	8	7
Valproate	38	23	11	6	4

FIGURE 8 Discontinuation of anticonvulsant mood stabilisers in pregnant women with a record of psychosis or depression, by drug.

Discontinuation of anticonvulsant mood stabilisers in women with a record of epilepsy compared with women with other or unknown indications

There was a sharp contrast in rates of discontinuation between women with a record of epilepsy who were prescribed anticonvulsant mood stabilisers and women who had a record of psychosis or depression or unknown indications (*Figure 9*). Hence, among women who had a record of epilepsy 795 out of 1007 (79%) continued to be prescribed anticonvulsant mood stabilisers beyond 6 weeks of pregnancy (see *Figure 9*) compared with 34 out of 93 (37%) for women with records of psychoses or depression (see *Figure 9*).



Number receiving drug:

Epilepsy	1007	855	795	751	686
Unknown indication	75	52	37	31	29
SMI or recent depression	93	67	34	16	13

FIGURE 9 Discontinuation of anticonvulsant mood stabilisers in pregnant women with a record of epilepsy, psychosis, depression or unknown indications. SMI, severe mental illness.

Factors associated with continuation of anticonvulsant mood stabilisers

Factors associated with continuation of receiving anticonvulsant mood stabiliser prescriptions beyond 6 weeks of pregnancy for women with a record of psychoses or depression included duration of treatment prior to pregnancy, lithium treatment and obesity, although after adjustment for age the association with lithium was no longer statistically significant (*Table 11*). Those who had received continuous treatment for > 12 months prior to pregnancy were more likely to continue treatment in pregnancy compared with those who had received < 6 months of continuous treatment prior to pregnancy (RR 2.56, 95% CI 1.27 to 5.15) (see *Table 11*). This was still the case after adjustment for age (RR 2.47, 95% CI 1.23 to 4.95) (see *Table 11*). For other factors examined (age, diagnosis of severe mental illnesses, also taking antidepressants and antipsychotics, social deprivation, estimated parity, smoking, records of alcohol problems, illicit drug use and ethnicity) none of the adjusted effect sizes was statistically significant although the CIs were relatively wide for some estimates (see *Table 11*).

TABLE 11 Factors associated with receiving anticonvulsant mood stabilisers beyond 6 weeks after the estimated pregnancy start date in women with a record of psychoses or depression

		Unadjusted			Adjusted		
Factors	***n***	**RR**	**95% CI**	***p*-value**	**RR**	**95% CI**	***p*-value**
Age band				***0.394***			
< 25 years	9	1					
25–29 years	22	0.72	0.27 to 1.87				
30–34 years	35	0.64	0.26 to 1.59				
> 35 years	27	1.08	0.47 to 2.49				
Continuous prior time on ACMS				***0.026***			***0.020***
< 6 months	41	1			1		
6–12 months	12	2.56	1.10 to 5.97		2.77	1.27 to 6.02	
> 12 months	40	2.56	1.27 to 5.15		2.47	1.23 to 4.95	
SMI diagnosis code				***0.308***			***0.433***
No	31	1			1		
SMI diagnosis code	62	1.39	0.74 to 2.61		1.29	0.68 to 2.45	
Also taking an antidepressant				***0.699***			***0.733***
No	38	1			1		
Taking an antidepressant	55	1.12	0.64 to 1.95		1.10	0.63 to 1.91	
Also taking an antipsychotic				***0.152***			***0.247***
No	58	1			1		
Taking an antipsychotic	35	1.47	0.87 to 2.50		1.37	0.80 to 2.34	
Also taking lithium				***0.043***			***0.056***
No	87	1			1		
Taking lithium	6	1.93	1.02 to 3.66		2.21	0.98 to 4.97	

TABLE 11 Factors associated with receiving anticonvulsant mood stabilisers beyond 6 weeks after the estimated pregnancy start date in women with a record of psychoses or depression (*continued*)

		Unadjusted			Adjusted		
Factors	*n*	RR	95% CI	*p*-value	RR	95% CI	*p*-value
Townsend quintile				***0.933***			***0.886***
1	16	1			1		
2	11	1.16	0.40 to 3.40		0.96	0.32 to 2.90	
3	15	0.85	0.28 to 2.61		0.71	0.24 to 2.15	
4	30	1.17	0.49 to 2.80		1.09	0.46 to 2.58	
5	17	1.32	0.52 to 3.33		1.18	0.48 to 2.90	
Unrecorded	4						
Estimated parity				***0.383***			***0.425***
0	43	1			1		
1	29	0.86	0.48 to 1.53		0.85	0.47 to 1.53	
2	12	0.38	0.10 to 1.41		0.37	0.10 to 1.34	
3 or more	9	0.50	0.14 to 1.80		0.56	0.15 to 2.08	
Obesity status				***0.020***			***0.010***
Not obese	80	1			1		
Obese	13	1.89	1.11 to 3.24		2.11	1.20 to 3.73	
Smoking status				***0.174***			***0.137***
Non-smoker	56	1			1		
Smoker	37	1.45	0.85 to 2.47		1.50	0.88 to 2.56	
Alcohol problems				***0.867***			***0.893***
No	88	1			1		
Yes	5	1.10	0.36 to 3.35		1.07	0.42 to 2.71	
Illicit drug use				***0.122***			***0.114***
No	80	1			1		
Yes	13	1.60	0.88 to 2.89		1.56	0.90 to 2.69	
Ethnicity				***0.376***			***0.454***
Other	87	1			1		
Black or minority ethnic	6	0.44	0.07 to 2.71		0.49	0.08 to 3.14	

ACMS, anticonvulsant mood stabilisers; SMI, severe mental illness.

Notes

Adjustment variable: age.

Restarting and factors associated with restarting psychotropic medication in pregnancy

We identified 134 women who discontinued typical antipsychotics and 129 women who discontinued atypical antipsychotics before 6 weeks of pregnancy. The figures were 35 for lithium and 59 for anticonvulsant mood stabilisers prescribed to women with a record of psychosis or depression. The proportion of women who restarted treatment (i.e. received additional prescriptions after > 91 days of a gap) varied between psychotropic treatments. At 15 months after delivery, the proportion of restarting treatment was highest for lithium (0.76) and lowest for typical antipsychotics (0.40). We report below additional results from studies on restarting of psychotropic medication in pregnancy and factors associated with restarting for each of the classes of psychotropic medication (antipsychotics, lithium and anticonvulsant mood stabilisers).

Restarting of antipsychotics

Of the 134 women who discontinued typical antipsychotics, the proportion of women who had restarted at the EDD, 6 months and 15 months after delivery was 0.17, 0.33 and 0.40, respectively (*Figure 10*).
Of the 129 women who discontinued atypical antipsychotics, the proportion of women who had restarted treatment at the EDD was 0.23. The proportion of women who had restarted at 6 and 15 months after delivery was 0.44 and 0.52, respectively (see *Figure 10*).

Factors associated with restarting treatment of antipsychotics

There were 44 individuals who had restarted typical antipsychotics and 55 who had restarted atypical antipsychotics by 6 months after delivery. The factors associated with restarting antipsychotic treatment for typical antipsychotics was the average daily dose prescribed and whether or not the women had been prescribed an anticonvulsant mood stabiliser before they became pregnant. Thus, women receiving the DDD or higher were nearly three times as likely to restart treatment by 6 months after delivery compared with women receiving less than one-quarter of the DDD level before and after pregnancy for typical antipsychotics (RR 2.88, 95% CI 1.75 to 4.74) (see *Table 12*). Women who were also receiving mood stabilisers (anticonvulsants or lithium) were twice as likely to restart typical antipsychotic treatment by 6 months after delivery (RR 2.09, 95% CI 1.21 to 3.59) (*Table 12*). There were no associations with age, prior duration of treatment or antidepressant treatment prior to pregnancy.

For atypical antipsychotics there were no significant associations between any of the factors measured at 6 months prior to pregnancy (age, dose, prior duration of treatment, antidepressant treatment or mood stabilisers) and restarting treatment by 6 months after delivery (*Table 13*).

Restarting of lithium

Of the 35 women who discontinued lithium, the proportion of women who restarted treatment by the EDD was 0.26. The proportion of women who had restarted at 6 and 15 months after delivery was 0.64 and 0.76, respectively (*Figure 11*).

Factors associated with restarting treatment of lithium

There were 22 women who had restarted lithium by 6 months after delivery. Tabulation of factors potentially associated with restarting of lithium treatment (age, prior duration of treatment, antidepressant treatment or antipsychotic treatment) by 6 weeks after delivery suggests some variation between women who restarted and those who did not (*Table 14*). However, the overall numbers were small and CIs were wide.

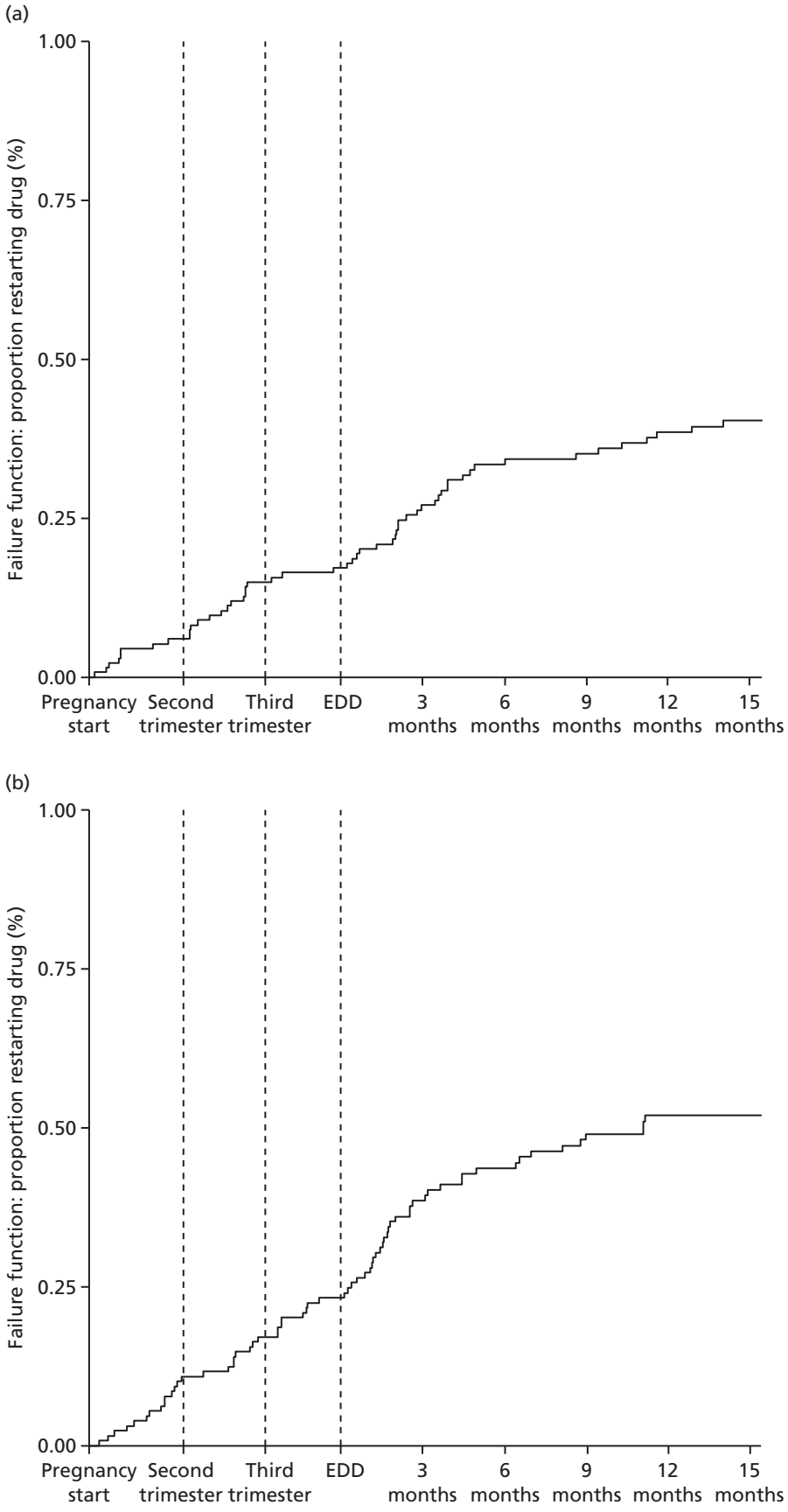


FIGURE 10 Proportions of women restarting antipsychotics among those who discontinued by 6 weeks of pregnancy (Kaplan–Meier failure functions). (a) Typical antipsychotics and (b) atypical antipsychotics.

TABLE 12 Factors associated with restarting typical antipsychotics by 6 months after delivery

	Typical antipsychotics ($N = 134$, $n = 44$ restarted)						
		Unadjusted			Adjusted		
Factors	*n*	RR	95% CI	*p*-value	RR	95% CI	*p*-value
Age band				***0.494***			***0.536***
< 25 years	42	1			1		
25–29 years	29	1.45	0.69 to 3.04		1.43	0.70 to 2.91	
30–34 years	44	1.53	0.78 to 2.98		1.49	0.79 to 2.80	
> 35 years	19	1.77	0.83 to 3.77		1.65	0.79 to 3.46	
Average daily dose (in units of DDD)				***< 0.001***			***< 0.001***
< 0.25 DDD	89	1			1		
0.25–1 DDD	35	1.27	0.72 to 2.26		1.20	0.67 to 2.15	
> 1 DDD	10	2.97	1.87 to 4.71		2.88	1.75 to 4.74	
Continuous prior time on antipsychotics				***0.066***			***0.153***
< 6 months	80	1			1		
6–12 months	22	1.82	1.00 to 3.30		1.72	0.92 to 3.21	
> 12 months	32	1.75	1.01 to 3.03		1.55	0.89 to 2.68	
Also taking an antidepressant				***0.367***			***0.834***
No	39	1			1		
Taking an antidepressant	95	0.79	0.48 to 1.31		0.95	0.57 to 1.57	
Also taking a mood stabiliser				***0.002***			***0.008***
No	127	1			1		
Taking a mood stabiliser	7	2.33	1.36 to 3.99		2.09	1.21 to 3.59	

Adjustment variables: dose and age band. Antidepressants and mood stabilisers (lithium or anticonvulsants) recorded in the 4–6 months prior to the start of pregnancy.

TABLE 13 Factors associated with restarting atypical antipsychotics by 6 months after delivery

	Atypical antipsychotics ($N = 129$, $n = 55$ restarted)						
		Unadjusted			Adjusted		
Factors	*n*	RR	95% CI	*p*-value	RR	95% CI	*p*-value
Age band				***0.425***			***0.487***
< 25 years	31	1			1		
25–29 years	36	0.86	0.45 to 1.64		0.91	0.48 to 1.73	
30–34 years	31	1.25	0.70 to 2.22		1.27	0.71 to 2.27	
≥ 35	31	1.33	0.76 to 2.34		1.34	0.77 to 2.35	
Average daily dose (in units of DDD)				***0.364***			***0.454***
< 0.25 DDD	28	1			1		
0.25–1 DDD	78	1.36	0.75 to 2.46		1.35	0.75 to 2.43	
> 1 DDD	23	1.62	0.83 to 3.17		1.53	0.79 to 2.99	
Continuous prior time on antipsychotics				***0.836***			***0.840***
< 6 months	62	1			1		
6–12 months	26	0.85	0.49 to 1.49		0.86	0.47 to 1.57	
> 12 months	41	0.92	0.58 to 1.45		0.90	0.57 to 1.41	
Also taking an antidepressant				***0.646***			***0.353***
No	38	1			1		
Taking an antidepressant	91	1.11	0.70 to 1.76		1.25	0.78 to 1.98	
Also taking a mood stabiliser				***0.322***			***0.516***
No	112	1			1		
Taking a mood stabiliser	17	1.29	0.78 to 2.13		1.20	0.70 to 2.06	

Adjustment variables: dose and age band. Antidepressants and mood stabilisers (lithium or anticonvulsants) recorded in the 4–6 months prior to the start of pregnancy.

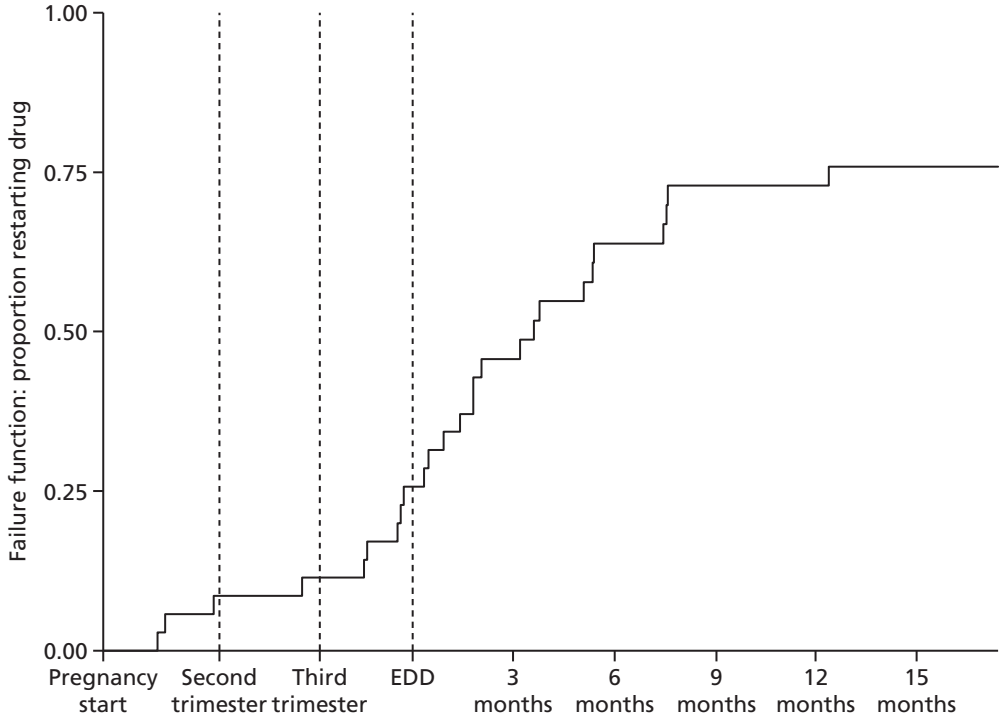


FIGURE 11 Proportions of women restarting lithium among those who discontinued by 6 weeks of pregnancy (Kaplan–Meier failure functions).

TABLE 14 Factors associated with restarting lithium prescriptions by 6 months after delivery

	Restarted before 6 months (*N* = 22)			Did not restart (*N* = 13)		
Factors	*n*	%	95% CI	*n*	%	95% CI
Age band						
< 25 years	3	13.6	4.2 to 36.5	2	15.4	3.5 to 48.0
25–29 years	5	22.7	9.3 to 45.9	3	23.1	6.9 to 54.7
30–34 years	9	40.9	21.9 to 63.0	1	7.7	0.9 to 43.0
≥ 35 years	5	22.7	9.3 to 45.9	7	53.8	26.5 to 79.1
Continuous prior time on lithium						
< 6 months	8	36.4	18.5 to 59.0	3	23.1	6.9 to 54.7
6–12 months	5	22.7	9.3 to 45.9	1	7.7	0.9 to 43.0
> 12 months	9	40.9	21.9 to 63.0	9	69.2	38.7 to 88.9
Also taking an antidepressant	6	27.3	12.2 to 50.4	6	46.2	20.9 to 73.5
Also taking an anticonvulsant	4	18.2	6.6 to 41.2	2	15.4	3.5 to 48.0
Also taking an antipsychotic	8	36.4	18.5 to 59.0	4	30.8	11.1 to 61.3

Antidepressants, anticonvulsants and antipsychotics recorded in the 4–6 months prior to the start of pregnancy.

Restarting of anticonvulsant mood stabilisers

Of the 59 women with a record of psychosis or depression who discontinued anticonvulsant mood stabilisers the proportion of women who restarted treatment at the EDD was 0.29. The proportion of women who had restarted at 6 and 15 months after delivery was 0.58 and 0.64, respectively (*Figure 12*).

Factors associated with restarting treatment of anticonvulsant mood stabilisers

There were 34 women who had restarted anticonvulsant mood stabilisers by 6 months after delivery. Tabulation of factors potentially associated with restarting of treatment with anticonvulsant mood stabilisers (age, prior duration of treatment, antidepressant treatment or antipsychotic treatment) by 6 weeks after delivery suggest some differences between women who restarted and those who did not (*Table 15*). However, the overall numbers were small and CIs were wide.

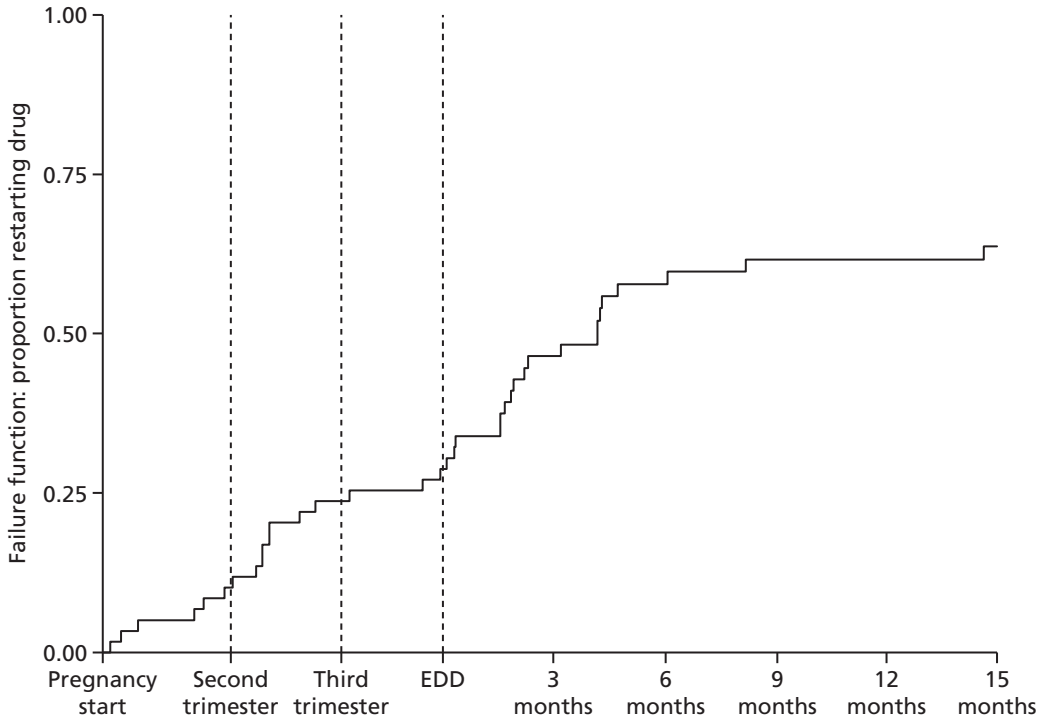


FIGURE 12 Proportions of women restarting anticonvulsant mood stabilisers among those who discontinued by 6 weeks of pregnancy (Kaplan–Meier failure functions).

TABLE 15 Factors associated with restarting anticonvulsant mood stabilisers prescriptions by 6 months after delivery

	Restarted before 6 months (*N* = 34)			Did not restart (*N* = 25)		
Factors	***n***	**%**	**95% CI**	***n***	**%**	**95% CI**
Age band						
< 25 years	4	11.8	4.3 to 28.2	1	4.0	0.5 to 25.1
25–29 years	8	23.5	11.9 to 41.2	7	28.0	13.5 to 49.1
30–34 years	13	38.2	23.2 to 55.9	12	48.0	28.9 to 67.7
≥ 35 years	9	26.5	14.0 to 44.2	5	20.0	8.3 to 41.0
Continuous prior time on anticonvulsants						
< 6 months	17	50.0	33.2 to 66.8	16	64.0	43.1 to 80.6
6–12 months	4	11.8	4.3 to 28.2	2	8.0	1.9 to 28.2
> 12 months	13	38.2	23.2 to 55.9	7	28.0	13.5 to 49.1
Also taking an antidepressant	18	52.9	35.9 to 69.3	16	64.0	43.1 to 80.6
Also taking lithium	0	0	–	2	8.0	1.9 to 28.2
Also taking an antipsychotic	12	35.3	20.8 to 53.1	7	28.0	13.5 to 49.1

Antidepressants, lithium and antipsychotics recorded in the 4–6 months prior to the start of pregnancy.

Discussion

In the previous section we reported the results of the five (drug utilisation) studies. Below we discuss the findings from each of these studies in turn.

Prevalence, initiation and termination of psychotropic treatment around and during pregnancy

Overall, the patterns of psychotropic medication prescribing before and during pregnancy and after delivery were remarkably similar, although the absolute prevalence estimates varied between classes of medication. Following a broad 'u shape' the prevalence was relatively constant before pregnancy, decreased sharply in early pregnancy and increased after delivery to the level of before or even higher. Hence, 0.11% were prescribed antipsychotics, 0.006% lithium and 0.11% were prescribed anticonvulsant mood stabilisers in the second trimester. The prevalence was higher after delivery for atypical antipsychotics and lithium, but remained at the same level before and after pregnancy for typical antipsychotics and anticonvulsant mood stabilisers.

Chlorpromazine, trifluoperazine and flupentixol were the three most commonly prescribed typical antipsychotics in pregnancy and quetiapine, olanzapine, and risperidone were the most commonly prescribed atypical antipsychotics.

We observed a peak in the starting of new prescribing episodes just after delivery for all three classes of psychotropic medication and likewise a peak in termination of prescribing episodes during the first trimester. Single isolated prescriptions were at the lowest during the second and third trimester and that was true of all three classes of psychotropic medications.

A US study based on pharmacy dispensing data from nearly 600,000 deliveries demonstrated a sharp increase in the use of atypical antipsychotics in pregnant women between 2001 and 2007, but estimated that atypical antipsychotics were, on average, dispensed to 26.7 out of 10,000 pregnancies in the second trimester, whereas typical antipsychotics were dispensed to 4.8 out of 10,000 pregnancies in the

second trimester.[37] Our estimates are much lower, but in line with another study,[36] also based on UK primary care data. This study, which covered the period from 1989 to 2010, found that 0.08% were prescribed antipsychotics in the second trimester. A Swedish study identified 570 women who reported use of antipsychotics out of 958,729 pregnancies (equivalent to 0.06%) from the Swedish birth registry between July 1995 and the end of 2005.[48] Maternal drug use in early pregnancy was recorded from interviews performed by the midwife at the first antenatal care visit, usually before the end of the first trimester. It is likely, however, that this study may have underestimated the prevalence of antipsychotic use in pregnant women in the Swedish population.[49] Another study also using Swedish registry data, but from 2005 to 2009 estimated atypical antipsychotic use during pregnancy to be approximately 0.1%.[50]

We found that quetiapine, olanzapine and risperidone were the three most commonly prescribed atypical antipsychotics both before and after pregnancy. This mirrors the patterns of atypical antipsychotics dispensed in the USA[37] and the general prescribing pattern of antipsychotics in the UK.[7]

The utilisation of anticonvulsant mood stabilisers was examined in another US study also based on pharmacy dispensing data from nearly 600,000 pregnancies.[40] This study included benzodiazepines as one of the 'older' anticonvulsant mood stabilisers and the prevalence estimates were primarily driven by the dispensing of these drugs. They found that 0.9% received benzodiazepines at any time in pregnancy while 0.2% received valproic acid derivatives.[40] Of those who were dispensed an old anticonvulsant mood stabiliser 4024 out of 9001 (45%) had an indication of psychiatric disorder, while 2115 out of 3515 (60%) of those dispensed new anticonvulsant mood stabilisers had an indication of psychiatric disorder. Only between 21% and 25% had an indication of epilepsy.[40] A study by Kulaga *et al.*[41] identified 349 epileptic pregnant women within the Quebec Pregnancy Registry and divided these into three groups based on maternal use of anticonvulsant mood stabilisers during pregnancy. Like our study, Kulaga *et al.*[41] also found that the frequency of exposure to anticonvulsant mood stabilisers declined substantially during pregnancy, and in the second trimester was estimated to be 0.22% (95% CI 0.19 to 0.26%).[41] Most women were dispensed anticonvulsant mood stabilisers as monotherapy (79.6%) during pregnancy and the three most prevalent anticonvulsants were carbamazepine (29.9%), valproate (19.7%) and phenytoin (11.5%).[41]

To our knowledge there are no recent estimates of lithium usage or prescribing in pregnancy. However, the study by Reis and Källén[48] identified 79 lithium users among 958,729 pregnancies (< 0.01%) from the Swedish birth registry between July 1995 and the end of 2005. Another study on adverse birth outcome following lithium exposure in pregnancy identified 83 lithium-exposed pregnancies among women who contacted the Israeli Teratology Information Service between 1999 and 2010.[51] Both studies support our findings that lithium is still used by pregnant women, but rarely.

Patterns of recording that indicate worsening of mental health; 18 months before pregnancy, during the course of pregnancy and up to 15 months after delivery

In this exploratory study we observed that recording of suicide attempts, overdose or deliberate self-harm was relatively constant in the 18 months before pregnancy, but declined during pregnancy. Recording of psychosis, mania and hypomania was also slightly lower in the second and third trimester. However, entries increased substantially in the immediate period after delivery, while hospital admissions and the Mental Health Act[45] examinations tripled compared with before pregnancy. Recording of psychosis, mania and hypomania followed similar patterns with a doubling just after delivery.

Comparing the results of this study with the prevalence of psychotropic medications around pregnancy there appears to be a strong correlation in terms of the timing of psychosis, mania and hypomania and the start of new prescribing episodes just after delivery (see *Figure 1*). In contrast, the low level of entries for suicide attempts, overdose or deliberate self-harm during pregnancy may suggest that there were fewer such events. However, it is also possible that some women were less likely to reveal these events to their GP during pregnancy, in particular if they were not in receipt of psychotropic medication.

Time trends in prevalence of psychotropic medication treatment around and during pregnancy

The overall annual prevalence of prescribing in the 6 months before and during pregnancy of both antipsychotics and anticonvulsant mood stabilisers was relatively stable from 1995 to 2006, but increased from around 2007. The total prevalence of antipsychotic treatment has increased by > 50% before and during pregnancy since 1995/6 and the prevalence of anticonvulsant mood stabilisers prescribing in women with a record of psychosis or depression has almost doubled since 1995/6. There has been a shift from typical to atypical antipsychotics in the study period. Likewise, for the anticonvulsant mood stabilisers, carbamazepine has recently been superseded by valproate and lamotrigine. Lithium was rarely prescribed and prescribing fluctuated over time with annual prescribing after delivery almost halved between 1995/6 and 2011/12. We observed a sharp increase in the prevalence of atypical antipsychotic prescribing in pregnancy although this only really 'kicked off' after 2007/8. However, the prescribing of atypical antipsychotics after delivery superseded typical antipsychotics by 2005/6.

Our study findings are consistent with an increase in atypical antipsychotics usage in the general population[8] and an expansion of indications for usage including bipolar disorder and treatment-resistant depression.[2,52] However, there seems to be an even faster growth in dispensing of antipsychotics to pregnant women in the USA, which has increased 2.5-fold between 2001 and 2007.[37]

As mentioned in *Prevalence, initiation and termination of psychotropic treatment around and during pregnancy*, there seem to be no recent estimates of lithium usage or prescribing in pregnancy. However, a UK study also based on primary care data suggests that lithium continues to be prescribed to women of childbearing age with bipolar disorder[2] and that women were prescribed the drug for 30% of the time they were registered with the general practice, which remained constant between 1996 and 2009.[2]

Pharmacy dispensing of anticonvulsant mood stabilisers before and during pregnancy in the USA increased by approximately 40% between 2001 and 2007, with 15.7 women receiving anticonvulsant mood stabilisers per 1000 pregnancies in 2001 and 21.9 per 1000 pregnancies in 2007.[40] As mentioned earlier these estimates include benzodiazepines, which account for a large proportion of the 'older' anticonvulsant mood stabilisers. However, it appears that our overall prevalence estimates for prescribing of anticonvulsant mood stabilisers are roughly the same for women prescribed anticonvulsant mood stabilisers with a record of psychosis or depression.

For some time there has been concern about potential teratogenic and neurodevelopmental effects of valproate.[15,53–58] We were therefore surprised to observe that valproate appears to be the most commonly prescribed mood stabilising anticonvulsant in the 4–6 months before pregnancy in women with a record of psychosis or depression in 2011/12. The NICE guidelines for antenatal and postnatal mental health and for management of bipolar disorders both issued in 2014[12,59] state clearly that valproate should not be prescribed to girls and women of childbearing potential. An American study based on Florida Medicaid beneficiaries suggested that use of valproate in pregnancy has declined for women with epilepsy over the period 1999 –2009, but not for other indications[60] and a Danish registry study suggested that dispensing of lamotrigine has been sharply rising during pregnancy in the period 1996–2006 (the time period of the study).[61] Future investigations should monitor the impact of these guidelines on prescribing.

Discontinuation and factors associated with discontinuation of psychotropic medication in pregnancy

The overall patterns of discontinuation of psychotropic medication around pregnancy were remarkably similar. Thus, many women were not prescribed further psychotropic medication after 6 weeks of pregnancy, suggesting that pregnancy is a major determinant for stopping psychotropic prescribing. By the time the prescription would be due for renewal many women would have been aware of their pregnancy and have decided to stop the medication. Women prescribed lithium were most likely to discontinue treatment with only 17 out of 52 (33%) receiving further prescriptions after 6 weeks of gestation. For the other psychotropic medications the figures were 73 out of 207 (35%) for typical antipsychotics, 34 out of

93 (37%) for anticonvulsant mood stabilisers (in women with a record of psychosis or depression) and 150 out of 279 (54%) for atypical antipsychotics. By the start of third trimester the figures were 13 out of 93 (14%) for anticonvulsant mood stabilisers, 39 out of 207 (19%) for typical antipsychotics, 14 out of 52 (27%) for lithium and 107 out of 279 (38%) for atypical antipsychotics. However, women prescribed anticonvulsant mood stabilisers with an indication of epilepsy were far more likely to continue treatment in pregnancy than women with any other indications. Hence, of women with a record of epilepsy, 795 out of 1007 (79%) continued to be prescribed anticonvulsant mood stabilisers beyond 6 weeks of pregnancy.

Those most likely to continue antipsychotic treatment were those who had received continuous treatment for > 12 months prior to pregnancy. Other determinants for continuation of antipsychotic prescribing in pregnancy included women's age and being on higher pre-pregnancy treatment doses. It appears that a greater proportion of those who continued lithium in pregnancy had also been prescribed antidepressants before they became pregnant, were pregnant with their first child and received lithium for < 6 months before pregnancy. However, the numbers were small and CIs were overlapping. Factors associated with continuation of anticonvulsant mood stabilisers in women with a record of psychosis or depression included duration of previous treatment and obesity.

Previous studies on utilisation of psychotropic medication in pregnancy suggest that many women discontinue treatment either just before or in early pregnancy.[36,37,39,40,49] As we describe in a *Chapter 2*, there was a peak in the termination of prescribing episodes for all three classes of psychotropic medications in the first pregnancy trimester.

The pregnant woman's mental health team/consultant as well as the GP may play a pivotal role in advising an individual woman on continuation of psychotropic medication in pregnancy. This would be in keeping with the recommendations made by national formularies and the NICE guidelines.[12,32,59] As outlined earlier in this document, there are a few very specific recommendations in terms of prescribing of psychotropic medication to pregnant women, but most are non-specific. In many situations this leaves both health-care professionals and the women with a very difficult and complex decision. They will have to weigh up risks to the mother and child of continuation versus discontinuation of medication in each individual case.

The greatest risk of discontinuation of psychotropic medication is the possibility of relapse of mental illness in pregnancy and postpartum. An observational study of mood disorders in 2252 pregnancies and postpartum periods demonstrated that women with bipolar disorders were at particularly high risk of developing major depression in the postpartum period (prevalence: 19% and 29% in women with bipolar I disorder and bipolar II disorder, respectively).[62] Likewise, it has been shown that women with a history of psychotic disorder are at higher risk of postpartum psychiatric illness, in particular non-psychotic anxiety and depressive disorders.[63] The severity of these illnesses is highlighted by case reports of suicide among these women.[16] Aside from the direct effects of discontinuation of psychotropic medication on the mother, the indirect impact on the fetus and child of severe depression and puerperal psychosis also needs to be taken into consideration. Women may have different reasons to discontinue psychotropic medication in pregnancy; some may discontinue because they fear the medication will harm the unborn child and deem that uncertainty of risk to be higher than the potential risk of relapse. Thus, an international survey of nearly 10,000 women reveals a substantial disparity between women's perceived risks and the actual risks of prescribed medication in pregnancy.[64] In this survey women rated the risks of antidepressants on par with smoking and alcohol and almost as dangerous as thalidomide.[64] Indeed only about 20% of around 5000 women who were prescribed antidepressants before pregnancy continued to receive treatment after 6 weeks of gestation.[35] However, some women may discontinue psychotropic medication in this period because they no longer need it. We also observed that a number of women on high-dose typical antipsychotics ceased receiving prescriptions before they became pregnant. This may be a part of pregnancy planning, but could also be explained by the fact that typical antipsychotics are known to reduce fertility by

inducing hyperprolactinaemia. Finally, the comparison of discontinuation between non-pregnant and pregnant women revealed that pregnancy is not the only reason for women to discontinue psychotropic medication. Other factors, such as experience of adverse effects and stigmatisation associated with psychotropic medication may influence continuous prescribing in pregnant as well as non-pregnant women.

As previously demonstrated by Man *et al.*,[34] using a similar approach to this study, the rate of discontinuation of anticonvulsant mood stabilisers in pregnancy is associated with the indications for treatment. Thus, women with a record of epilepsy were much more likely to continue anticonvulsant mood stabilisers in pregnancy compared with women with a record of psychosis or depression. There may be several reasons why we see these differences such as alternative treatment options and advice from specialists. However, a detailed investigation of this was outside the remit of this project.

Restarting and factors associated with restarting of psychotropic medication in pregnancy

Of the women who discontinued psychotropic medication either before or in early pregnancy those who were prescribed lithium were most likely to restart treatment. Thus, within 15 months of delivery three-quarters of the women who had discontinued were again receiving lithium treatment. For anticonvulsant mood stabilisers the proportion of women who had restarted within 15 months after delivery was 0.64. On the other hand approximately half of the women prescribed atypical antipsychotics had restarted by 15 months after delivery and a slightly smaller proportion of women prescribed typical antipsychotics had restarted. Overall, there were no clear predictors of restarting of treatment within 6 months of delivery, although for typical antipsychotics women who received an average daily dose greater than the DDD before pregnancy were about three times as likely to restart treatment as women receiving an average daily dose less than one-quarter of the DDD.

With these data we were unable to determine whether women restarted medication in response to relapse of their mental illness or whether treatments were given to prevent major psychoses or other relapses in the postnatal period, but it is likely that it is a mixture of the two. As discussed in *Discontinuation and factors associated with discontinuation of psychotropic medication in pregnancy* previous research has demonstrated that both women with a psychotic disorder and women with mood disorders are at a particularly high risk of developing major depression and affective psychosis in the postpartum period.[62,63] Some observational studies have sought to compare the risks of relapse of mental illnesses during and after pregnancy in relation to psychotropic treatment.[65–68] Newport *et al.*[65] observed 16 women who stopped lamotrigine treatment for bipolar disorder in pregnancy. All 16 women experienced a new illness episode during the course of the pregnancy in contrast to 3 out of 10 women who continued treatment.[65] In another study[66] more than half (52%) of 42 women who discontinued treatment with lithium in pregnancy experienced a recurrence of bipolar disorder in pregnancy compared with 21% in the year before treatment was discontinued. Viguera *et al.*[66] observed 89 pregnant women with bipolar disorder (euthymic at conception) treated with one or more mood stabilisers. Of these women, 62 discontinued treatment and 86% experienced at least one recurrence in pregnancy. In contrast only 37% of the 27 women who maintained treatment experienced recurrences in pregnancy[66] and similar findings were reported by Cohen *et al.*[42] for antidepressants. The relationship between drug treatment and mental illness is intrinsically difficult to disentangle as the women who continue psychotropic medication during pregnancy may be more likely to be those who are at the highest risk of relapse; this may result in spurious findings suggesting that psychotropic medication may increase risks of adverse mental outcomes or suggest no difference as in the study by Yonkers *et al.*[68] on antidepressant prescribing in pregnancy.

It is likely that some women titrate their medication (for example take one tablet instead of two tablets) and hence 'stretch' a prescription for much longer during pregnancy. In such cases what may have appeared as a restart of treatment (prescription after more than 91 days gap), was actually a delay in picking up a subsequent prescription because of this prescription 'stretching' behaviour.

Chapter 4 Absolute and relative risks of adverse effects of psychotropic medication in pregnancy on maternal and child outcomes

Introduction

In the 1960s the large number of children born with severe birth defects as a result of women's exposure to thalidomide during pregnancy brought focus on the adverse effects of medicines used in pregnancy.[69] Fifty years later, we still know little about the potential adverse effects of exposure to many medicines in pregnancy. For some time there has been concerns over whether or not certain psychotropic medications increase the risks of major congenital malformations.[15,48,53,54] Likewise, there has been some debate since the 1970s whether or not some anticonvulsant mood stabilisers may adversely impact on child development and increase the risk of behavioural disorders.[18] This leaves many pregnant women with serious psychiatric illnesses and also leaves them (and their health-care professionals) in a dilemma, as they have to consider their own health as well as that of their future child, and many women are conflicted in managing the two. The important question for many women who need treatment during pregnancy is whether some treatments are safer than others and although data from electronic health records do not indicate the reasons for discontinuation of psychotropic medication in pregnancy, it is likely, as discussed in *Chapter 3*, that the lack of evidence surrounding the safety of medication in pregnancy may have an impact on the decisions made.

In this chapter, we report the results of a number of studies in which we further examined the potential adverse effects of psychotropic medication prescribed in pregnancy on maternal and child outcome. These effects can broadly be divided into three categories: congenital malformations, adverse developmental and adverse perinatal outcomes. The adverse perinatal outcomes category can be further divided between adverse maternal and child outcomes.

We examined a range of maternal and child outcomes, which have previously been identified in the literature.[14,15,19,48,53–55,70,71] These included maternal outcomes such as pre-eclampsia, gestational diabetes, caesarean section, and perinatal death; child outcomes such as major congenital malformations and adverse birth outcomes such as low Apgar scores, preterm birth, low birthweight, tremor, agitation, any breathing problems; and problems with the infants' muscle tone, which we divide into 'poor birth outcomes' and 'transient poor birth outcomes'. We also conducted exploratory analyses to evaluate potential associations between psychotropic medication treatment in pregnancy and developmental and behavioural outcomes.

Most prior research on psychotropic medication in pregnancy has used 'healthy women', that is, women not prescribed psychotropic medication as their comparison group.[23,38,48] However, these women may differ in terms of individual characteristics and health and lifestyle factors which can confound the associations between psychotropic drug treatment and the pregnancy and birth outcomes. To overcome some of these issues we compared women treated with psychotropic medication in pregnancy with those with records of psychotropic treatment before they became pregnant, but not in pregnancy, as well as with women who had no records of psychotropic treatment up to 24 months before and during pregnancy.

Methods

Studies

For each class of psychotropic drugs (i.e. antipsychotics, lithium and anticonvulsant mood stabilisers) we performed two studies; one of which was based on the pregnancy cohorts to examine maternal outcomes, and another of which was based on the linked mother–child cohort to examine child outcomes.

Participants

Pregnancy cohorts

We included women from the pregnancy cohort who were registered with the general practice for at least 6 months before and throughout their pregnancy. Where a woman had two or more eligible pregnancies, we randomly selected one pregnancy for the analyses.

Mother–child cohorts

We included mothers and children in the mother–child cohort if the mothers were registered with the general practice for at least 6 months before the start of their pregnancy, throughout their pregnancy and had a singleton birth. We excluded mother–child pairs when the child had Down syndrome. If a woman had two or more eligible pregnancies, we randomly selected one for the analyses.

Psychotropic medication exposures

For each class of psychotropic medication (i.e. antipsychotics, lithium and anticonvulsant mood stabilisers) we created four cohorts based on medication prescribed. *Figure 13* provides a graphical representation of how the exposure cohorts were constructed.

Cohort A contained women with records of psychotropic treatment between 4 and 24 months before the start of pregnancy and no evidence of prescriptions issued after 4 weeks prior to pregnancy start.

Cohort B1 contained women with records of psychotropic treatments between 4 and 24 months before the start of pregnancy *and* with evidence of prescriptions issued between 31 and 105 days (inclusive) after the start of pregnancy (which is the critical period for many major congenital malformations).

Cohort B2 contained women with records of psychotropic treatment between 4 and 24 months prior to the start of pregnancy and records of psychotropic treatment within 92 days prior to the delivery date. Thus, cohort B1 and cohort B2 are *not* mutually exclusive.

Cohort C contained women with no records of psychotropic treatment from 24 months before the start of pregnancy through to the delivery date. Start of pregnancy was defined as the first day of LMP or 280 days before delivery if no indication suggested a different duration of pregnancy.

These cohorts were based on prescribing of the psychotropic medication, irrespective of the underlying indication for prescribing.

For the study of anticonvulsant mood stabilisers we defined an additional two sets of subcohorts: (1) cohorts limited to women with a record of psychosis or depression and no records of epilepsy and (2) a cohort of women prescribed valproate in the beginning of pregnancy. For the latter cohort we made comparisons against other anticonvulsant mood stabilisers (lamotrigine and carbamazepine) within cohort B1 as well as against cohort A and C. The reason to select more than one comparison cohort was to investigate the potential issues of confounding. Thus, we anticipated that women who had discontinued treatment (cohort A) just before pregnancy would be more similar both in terms of their measured, but also their unmeasured, characteristics to women who continued treatment in pregnancy (cohort B1 and B2) than women in cohort C.

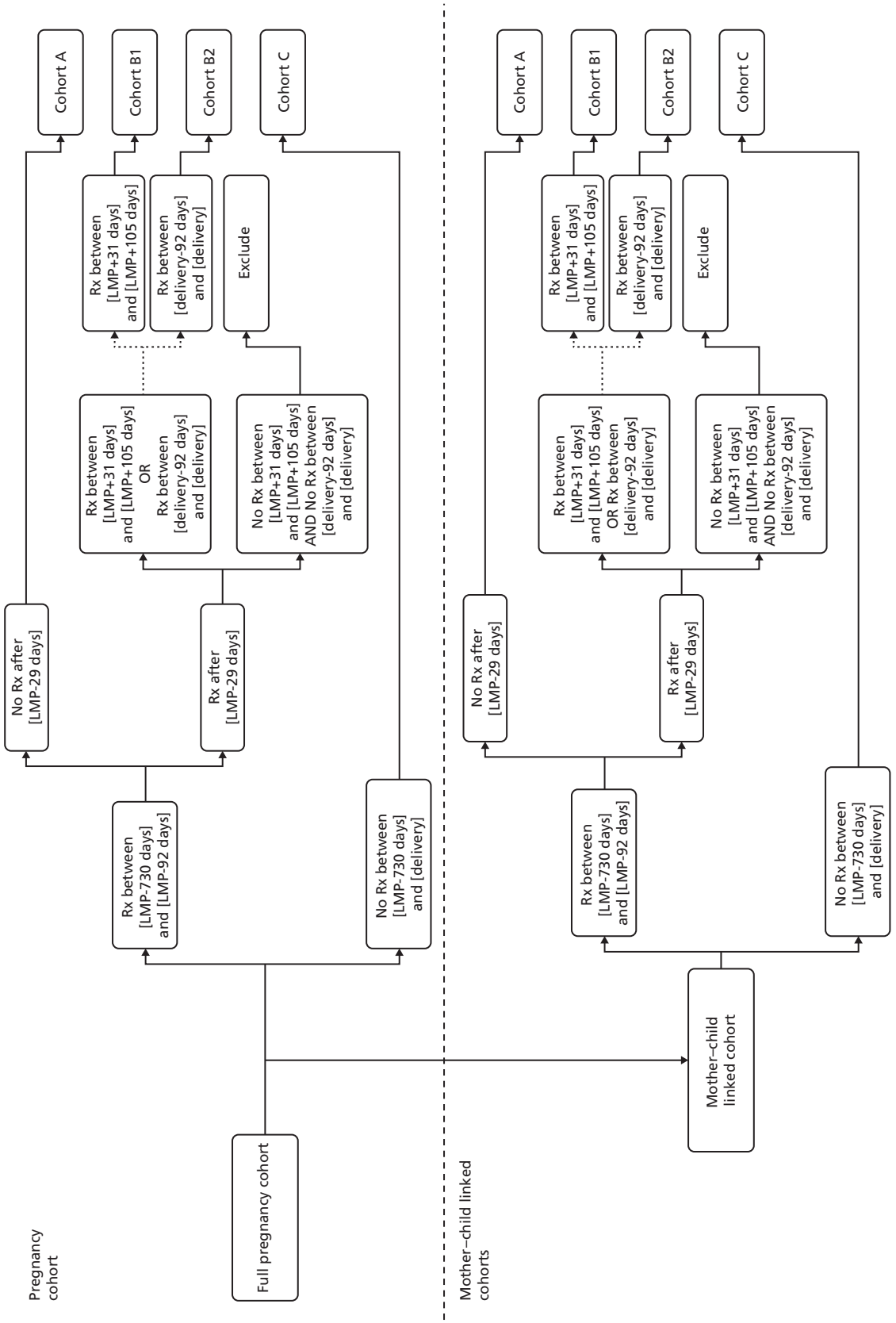


FIGURE 13 Schematic describing the derivation of the four exposure cohorts in the pregnancy and mother-child linked cohorts. Rx, prescription.

Characteristics of the women and information on prescribed medication

We extracted information from the women's electronic primary care health records in order to include the following information in the analyses: age at delivery, social deprivation (Townsend scores), calendar year of delivery, body mass index (BMI), illicit drug use, alcohol problem, smoking status, ethnicity, pre-existing medical conditions (depression, epilepsy, psychosis, hypertension, diabetes), prescriptions from medication listed in the BNF chapter 4, including antidepressants, anxiolytics, hypnotics, anticonvulsant mood stabilisers, antipsychotics and lithium.

Details on how the characteristics and information on prescribed medications were defined and relevant Read codes and drug codes are provided in *Appendix 1*.

Outcomes

We separated the outcomes into maternal and child outcomes. Below we describe these in further detail.

Maternal outcomes

Our outcomes were pre-eclampsia, gestational hypertension, gestational diabetes, perinatal death and caesarean section. These are all outcomes that have previously been examined in association with exposure to psychotropic medication in pregnancy.[19,48]

Further details on how each of these outcomes were defined and relevant Read codes are provided in *Appendix 1*.

Child outcomes

First we considered major congenital malformations. Further, we considered the following outcomes: prematurity, low Apgar score (< 7), low birthweight, small for gestation age (SGA), tremor, agitation, any breathing problems and problems with the infants' muscle tone. We combined prematurity, low Apgar score, low birthweight and SGA into one composite outcome, which we refer to as poor birth outcomes, and tremor, agitation, breathing and muscle tone problems into a second composite outcome, which we refer to as transient poor birth outcomes. This was done for several reasons. First, from a mother's (and health professionals) perspective these outcomes are all signs of poor pregnancy outcomes and as they are all equally relevant, there is no obvious choice of one over the other as a primary outcome. Further, the clinical decision to stop psychotropic medication in pregnancy is often based on a general uncertainty about adverse effects rather than the risks of specific adverse outcomes.[72] Second, the use of composite outcomes reduces the number of statistical tests and improves the statistical power of the study, albeit with the potential disadvantage that results relate to a cluster of outcomes that make up the composite outcome, and cannot be extrapolated to the individual components.[73]

Finally, we included an outcome, which we refer to as neurodevelopmental and behavioural outcomes. This outcome includes a broad range of Read codes describing developmental delay as well as behavioural problems recorded within the first 5 years of life.

Further details on how each of these outcomes were defined and relevant Read codes are provided in *Appendix 1*.

Data analysis

For each class of psychotropic medications, characteristics of the women and the maternal and child outcomes were tabulated for cohort A, B1 and C. For continuous variables, the means and standard deviations (SDs) were estimated and for categorical variables, the numbers of individuals in each category and percentage were estimated. As there was an overlap between the individuals in cohort B1 and B2, and as cohort B2 was only used for a few specific sets of analyses the characteristics of these cohorts are described in *Appendix 1*.

For each outcome we first estimated and tabulated the number and percentage of events as well as risk difference with 95% CIs where there were more than five events. We then estimated RRRs using Poisson regression. Comparisons were made between cohort B1 (women who had continued psychotropic medication in the first part of pregnancy) and cohort A (women who had discontinued treatment before pregnancy) using the latter as a reference category. Likewise, comparisons were made between cohort B1 (women who had continued psychotropic medication in the first part of pregnancy) and cohort C (women who had not been treated with psychotropic medication) using cohort C as a reference category.

For transient poor birth outcomes (tremor, agitation, breathing and muscle tone problems) the comparisons were made between cohort B2 (women who had received psychotropic medication in the later part of pregnancy) and cohort A, as well as between cohort B2 and cohort C. Specifically for anticonvulsant mood stabilisers we compared outcomes between women in cohort B1 who were prescribed valproate against women in cohort A and C as well as women in cohort B1 who were prescribed other anticonvulsant mood stabilisers.

Poisson regression models were developed, thus providing RRRs with 95% CIs. For all analyses we adopted the following sequence of analysis: model (a): examining crude associations, that is, with no adjustment; model (b): examining associations with adjustment for maternal age; model (c): examining associations with adjustment for 'health and lifestyle' factors, that is, adjustment for smoking, obesity, records of alcohol and illicit drug problems; model (d): examining associations with adjustment for concomitant prescriptions issued in the same time window as for cohort B1. For example, for the analyses on antipsychotics we accounted for prescription of antidepressants and anticonvulsant mood stabilisers; and model (e): examining associations with adjustment for all covariates. The results of model (a) and model (e) were tabulated. Further, we tabulated the associations between the health, lifestyle factors, concomitant medication and the outcomes from model (e). These are reported in *Appendix 1*.

We only report results from analyses where there were more than five events in each exposure group.

Changes to the project protocol

Although we have maintained the same cohorts as planned in our original proposal, A, B1 and B2 (originally called C), we decided to also include a cohort of women not treated with psychotropic medication (cohort C) in our comparisons. We then made the comparisons between B1 (and B2 for specific outcomes) and A as well as B1 and C. This allowed us to compare our results with other studies where similar comparisons were made. In general we did not conduct analyses on specific drugs as the sample sizes became small. However, we did perform specific analyses to examine child outcomes in women prescribed valproate in pregnancy (cohort B1) in contrast to other anticonvulsant mood stabilisers prescribed in pregnancy (cohort B1) as well as cohorts A and C.

We decided to use standard regression analyses methods rather than propensity score-matched methods in order to have direct estimates available for the covariates. In terms of the outcomes we still use composite outcomes, but have changed our groupings from the original proposal to form three groups of composite child outcomes: (1) poor birth outcome, (2) transient poor birth outcome and (3) neurodevelopmental and behavioural outcomes as described further in *Chapter 4, Child outcomes*. We were unable to identify child and maternal renal problems in a coherent way and decided to drop this as an outcome.

Results

In the case of antipsychotics there were 670 women who discontinued treatment before pregnancy (cohort A), 416 who received treatment in the beginning of pregnancy (cohort B1), 322 who received treatment towards the end of pregnancy (cohort B2) and 318,434 who did not receive antipsychotic treatment between 24 months before pregnancy and up to delivery (cohort C) (*Table 16*).

For the studies on lithium there were 84 women in cohort A, 35 in cohort B1, 20 in cohort B2 and 320,853 in cohort C (*Table 17*).

TABLE 16 Characteristics of women prescribed antipsychotics in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	670 (100)	416 (100)	318,434 (100)
Age (years)			
Mean (SD)	30 (5.9)	32 (5.8)	30 (5.9)
12–19	21 (3.1)	0 (0)	14,004 (4.4)
20–29	291 (43.4)	136 (32.7)	123,704 (38.8)
30–39	326 (48.7)	238 (57.2)	165,353 (51.9)
40–49	32 (4.8)	42 (10.1)	15,373 (4.8)
Year			
1995–9	42 (6.3)	14 (3.4)	46,548 (14.6)
2000–4	184 (27.5)	63 (15.1)	80,542 (25.3)
2005–9	232 (34.6)	120 (28.8)	99,765 (31.3)
2010–12	212 (31.6)	219 (52.6)	91,579 (28.8)
Lifestyle variables			
Smoker	254 (37.9)	195 (46.9)	62,746 (19.7)
Illicit drug use	56 (8.4)	56 (13.5)	2002 (0.6)
Alcohol problems	37 (5.5)	29 (7)	1624 (0.5)
Obesity	77 (11.5)	72 (17.3)	20,554(6.5)
BMI (kg/m^2)			
Mean (SD)	27 (6.8)	28 (6.5)	26 (6.3)
Missing	443 (66.1)	241 (57.9)	232,039 (72.9)
Townsend score			
1	24 (13.1)	5 (5.7)	71,024 (23.4)
2	23 (12.6)	13 (14.9)	60,407 (19.9)
3	37 (20.2)	15 (17.2)	64,868 (21.4)
4	48 (26.2)	29 (33.3)	61,191 (20.2)
5	51 (27.9)	25 (28.7)	45,942 (15.1)
Missing	487 (72.7)	329 (79.1)	15,002 (4.7)

TABLE 16 Characteristics of women prescribed antipsychotics in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Ethnicity			
White	320 (47.8)	212 (51)	133,856 (42)
Mixed	2 (0.3)	0 (0)	1786 (0.6)
Asian	8 (1.2)	12 (2.9)	9937 (3.1)
Black	7 (1)	16 (3.8)	4615 (1.4)
Other	2 (0.3)	3 (0.7)	1803 (0.6)
Missing	331 (49.4)	173 (41.6)	166,437 (52.3)
Use of psychiatric drugs during exposure period B1			
Anticonvulsant mood stabilisers	15 (2.2)	44 (10.6)	1305 (0.4)
Lithium	4 (0.6)	13 (3.1)	11 (0)
Antipsychotics	0 (0)	416 (100)	0 (0)
Antidepressants	150 (22.4)	238 (57.2)	5942 (1.9)
Anxiolytics	33 (4.9)	48 (11.5)	805 (0.3)
Hypnotics	32 (4.8)	63 (15.1)	598 (0.2)
Pre-existing medical conditions			
Depression	217 (32.4)	105 (25.2)	20,374 (6.4)
Epilepsy	30 (4.5)	31 (7.5)	4846 (1.5)
SMI	204 (30.4)	250 (60.1)	1480 (0.5)
Pre-existing hypertension	66 (9.9)	57 (13.7)	26,232 (8.2)
Pre-existing diabetes	9 (1.3)	9 (2.2)	2762 (0.9)

SMI, severe mental illness.

Notes

Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

TABLE 17 Characteristics of women prescribed lithium in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed lithium (cohort C)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	84 (100)	35 (100)	320,853 (100)
Age (years)			
Mean (SD)	33 (5.3)	35 (5.4)	30 (5.9)
12–19	1 (1.2)	0 (0)	14,034 (4.4)
20–29	22 (26.2)	6 (17.1)	124,982 (39)
30–39	53 (63.1)	21 (60)	166,294 (51.8)
40–49	8 (9.5)	8 (22.9)	15,543 (4.8)
Year			
1995–99	13 (15.5)	3 (8.6)	46,855 (14.6)
2000–4	26 (31)	8 (22.9)	81,190 (25.3)
2005–9	29 (34.5)	11 (31.4)	100,574 (31.3)
2010–12	16 (19)	13 (37.1)	92,234 (28.7)
Lifestyle variables			
Smoker	24 (28.6)	13 (37.1)	63,778 (19.9)
Illicit drug use	6 (7.1)	1 (2.9)	2167 (0.7)
Alcohol problems	4 (4.8)	3 (8.6)	1718 (0.5)
Obesity	9 (10.7)	7 (20)	20,870 (6.5)
BMI (kg/m^2)			
Mean (SD)	27 (5.5)	29 (4.5)	26 (6.3)
Missing	56 (66.7)	22 (62.9)	233,534 (72.8)
Townsend score			
1	3 (17.6)	1 (16.7)	71,307 (23.3)
2	3 (17.6)	0 (0)	60,753 (19.9)
3	4 (23.5)	3 (50)	65,291 (21.4)
4	5 (29.4)	1 (16.7)	61,850 (20.2)
5	2 (11.8)	1 (16.7)	46,548 (15.2)
Missing	67 (79.8)	29 (82.9)	15,104 (4.7)
Ethnicity			
White	35 (41.7)	19 (54.3)	134,809 (42)
Mixed	0 (0)	0 (0)	1788 (0.6)
Asian	1 (1.2)	1 (2.9)	9978 (3.1)
Black	1 (1.2)	0 (0)	4641 (1.4)
Other	0 (0)	0 (0)	1822 (0.6)
Missing	47 (56)	15 (42.9)	167,815 (52.3)

TABLE 17 Characteristics of women prescribed lithium in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed lithium (cohort C) (*continued*)

Characteristics	Exposure cohort		
	A	B1	C
	n (% or SD)	*n* (% or SD)	*n* (% or SD)
Use of psychiatric drugs during exposure period B1			
Anticonvulsant mood stabilisers	7 (8.3)	2 (5.7)	1355 (0.4)
Lithium	0 (0)	35 (100)	0 (0)
Antipsychotics	17 (20.2)	15 (42.9)	457 (0.1)
Antidepressants	24 (28.6)	17 (48.6)	6455 (2)
Anxiolytics	4 (4.8)	5 (14.3)	907 (0.3)
Hypnotics	5 (6)	4 (11.4)	690 (0.2)
Pre-existing medical conditions			
Depression	23 (27.4)	9 (25.7)	21,084 (6.6)
Epilepsy	3 (3.6)	3 (8.6)	4925 (1.5)
SMI	57 (67.9)	31 (88.6)	1945 (0.6)
Pre-existing hypertension	8 (9.5)	4 (11.4)	26,362 (8.2)
Pre-existing diabetes	3 (3.6)	2 (5.7)	2803 (0.9)

SMI, severe mental illness.
Notes
Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

For the studies of anticonvulsant mood stabilisers without restriction of the indication, there were 558 in cohort A, 1539 in cohort B1, 1375 in cohort B2 and 318,612 in cohort C (*Table 18*). For the study of valproate there were 558 women in cohort A, 398 women receiving valproate in pregnancy (cohort B1) and 1141 receiving other anticonvulsant mood stabilisers in pregnancy (*Table 19*). Finally, limited to women with a diagnosis of psychoses or depression there were 131 women in cohort A, 61 in cohort B1, 22 in cohort B2 and 318,612 in cohort C (*Table 20*).

Characteristics of the women in the pregnancy cohort

The characteristics of the women in cohort A, B1 and C are detailed in *Tables 16–20*. There was a substantial overlap between the women in cohort B1 and B2 (i.e. many of the women who received treatment in the beginning of pregnancy also received treatment towards the end). The details of the characteristics of women in cohort B2 can be found in *Appendix 1*.

Women who were prescribed antipsychotics, lithium or anticonvulsant mood stabilisers (with a record of psychosis or depression) in pregnancy were older {mean ages between 32 years (SD 5.6 years) and 35 years (SD 5.4 years) than women not prescribed psychotropic medication (cohort C) [mean age 30 years (SD 5.9 years)]}. Likewise, women who were prescribed antipsychotics and lithium in pregnancy were older than women who discontinued before pregnancy (cohort A). A large proportion of the women prescribed psychotropic medication in pregnancy were obese. For example, 72 out of 416 (17%) of the women who were prescribed antipsychotics were obese in contrast to 77 out of 670 (12%) in those who discontinued antipsychotics (cohort A) and 20,554 out of 318,434 (6.5%) in those not prescribed antipsychotics (cohort C) (see *Table 16*). Illicit drug use and alcohol problems were commonly recorded among women who continued psychotropic medication in pregnancy as well as those who discontinued. Hence, illicit drug use was recorded in 56 out of 416 (13.5%) of women who continued antipsychotics in pregnancy (see *Table 16*)

TABLE 18 Characteristics of women prescribed anticonvulsant mood stabilisers irrespectively of diagnosis (cohort B1) vs. women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	558 (100)	1539 (100)	318,612 (100)
Age (years)			
Mean (SD)	30 (5.8)	30 (5.6)	30 (5.9)
12–19	24 (4.3)	56 (3.6)	14,008 (4.4)
20–29	237 (42.5)	645 (41.9)	123,740 (38.8)
30–39	276 (49.5)	768 (49.9)	165,396 (51.9)
40–49	21 (3.8)	70 (4.5)	15,468 (4.9)
Year			
1995–9	41 (7.3)	190 (12.3)	46,638 (14.6)
2000–4	114 (20.4)	349 (22.7)	80,466 (25.3)
2005–9	218 (39.1)	542 (35.2)	100,009 (31.4)
2010–12	185 (33.2)	458 (29.8)	91,499 (28.7)
Lifestyle variables			
Smoker	185 (33.2)	378 (24.6)	63,085 (19.8)
Illicit drug use	17 (3)	28 (1.8)	2,110 (0.7)
Alcohol problems	12 (2.2)	22 (1.4)	1653 (0.5)
Obesity	***47 (8.4)***	***128 (8.3)***	***18,018 (5.7)***
BMI (kg/m^2)			
Mean (SD)	27 (6.8)	27 (6.3)	26 (6.3)
Missing	385 (69)	1091 (70.9)	234,733 (73.7)
Townsend score			
1	19 (18.8)	44 (17.1)	70,879 (23.3)
2	19 (18.8)	37 (14.4)	60,417 (19.9)
3	16 (15.8)	53 (20.6)	64,877 (21.4)
4	23 (22.8)	62 (24.1)	61,357 (20.2)
5	24 (23.8)	61 (23.7)	46,074 (15.2)
Missing	457 (81.9)	1282 (83.3)	15,008 (4.7)
Ethnicity			
White	222 (39.8)	604 (39.2)	133,929 (42)
Mixed	2 (0.4)	13 (0.8)	1772 (0.6)
Asian	9 (1.6)	25 (1.6)	9943 (3.1)
Black	51 (9.1)	116 (7.5)	4619 (1.4)
Other	2 (0.4)	13 (0.8)	1827 (0.6)
Missing	272 (48.7)	768 (49.9)	166,522 (52.3)

TABLE 18 Characteristics of women prescribed anticonvulsant mood stabilisers irrespectively of diagnosis (cohort B1) vs. women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C) (*continued*)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Use of psychiatric drugs during exposure period B1			
Anticonvulsant mood stabilisers	42 (7.5)	1539 (100)	170 (0.1)
Lithium	4 (0.7)	2 (0.1)	22 (0)
Antipsychotics	26 (4.7)	46 (3)	423 (0.1)
Antidepressants	68 (12.2)	122 (7.9)	6308 (2)
Anxiolytics	12 (2.2)	33 (2.1)	859 (0.3)
Hypnotics	19 (3.4)	38 (2.5)	670 (0.2)
Pre-existing medical conditions			
Depression	87 (15.6)	138 (9)	20,722 (6.5)
Epilepsy	249 (44.6)	1441 (93.6)	3268 (1)
SMI	97 (17.4)	79 (5.1)	1840 (0.6)
Pre-existing hypertension	69 (12.4)	155 (10.1)	26,228 (8.2)
Pre-existing diabetes	4 (0.7)	24 (1.6)	2767 (0.9)

SMI, severe mental illness.
Notes
Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

TABLE 19 Characteristics of women prescribed valproate vs. other anticonvulsant mood stabilisers, women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C). Women included irrespective of psychoses or depression in pregnancy

	Exposure cohort			
	A	Valproate	Other ACMS	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	558 (100)	398 (100)	1141 (100)	318,612 (100)
Age (years)				
Mean (SD)	30 (5.8)	30 (5.7)	30 (5.6)	30 (5.9)
12–19	24 (4.3)	19 (4.8)	37 (3.2)	14,008 (4.4)
20–29	237 (42.5)	168 (42.2)	477 (41.8)	123,740 (38.8)
30–39	276 (49.5)	195 (49)	573 (50.2)	165,396 (51.9)
40–49	21 (3.8)	16 (4)	54 (4.7)	15,468 (4.9)
Year				
1995–9	41 (7.3)	78 (19.6)	112 (9.8)	46,638 (14.6)
2000–4	114 (20.4)	119 (29.9)	230 (20.2)	80,466 (25.3)
2005–9	218 (39.1)	123 (30.9)	419 (36.7)	100,009 (31.4)
2010–12	185 (33.2)	78 (19.6)	380 (33.3)	91,499 (28.7)

continued

TABLE 19 Characteristics of women prescribed valproate vs. other anticonvulsant mood stabilisers, women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C). Women included irrespective of psychoses or depression in pregnancy (*continued*)

	Exposure cohort			
	A	Valproate	Other ACMS	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Lifestyle variables				
Obesity	45 (8.1)	32 (8)	93 (8.2)	17,058 (5.4)
Illicit drug use	17 (3)	13 (3.3)	15 (1.3)	2110 (0.7)
Alcohol problems	12 (2.2)	5 (1.3)	17 (1.5)	1653 (0.5)
Smoker	185 (33.2)	120 (30.2)	258 (22.6)	63,085 (19.8)
BMI (kg/m²)				
Mean (SD)	27 (6.8)	27 (6.7)	27 (6.2)	26 (6.3)
Missing	385 (69)	288 (72.4)	803 (70.4)	234,733 (73.7)
Townsend score				
1	19 (18.8)	6 (11.5)	38 (18.5)	70,879 (23.3)
2	19 (18.8)	4 (7.7)	33 (16.1)	60,417 (19.9)
3	16 (15.8)	4 (7.7)	49 (23.9)	64,877 (21.4)
4	23 (22.8)	19 (36.5)	43 (21)	61,357 (20.2)
5	24 (23.8)	19 (36.5)	42 (20.5)	46,074 (15.2)
Missing	457 (81.9)	346 (86.9)	936 (82)	15,008 (4.7)
Ethnicity				
White	222 (39.8)	131 (32.9)	473 (41.5)	133,929 (42)
Mixed	2 (0.4)	3 (0.8)	10 (0.9)	1772 (0.6)
Asian	9 (1.6)	9 (2.3)	16 (1.4)	9943 (3.1)
Black	51 (9.1)	21 (5.3)	95 (8.3)	4619 (1.4)
Other	2 (0.4)	3 (0.8)	10 (0.9)	1827 (0.6)
Missing	272 (48.7)	231 (58)	537 (47.1)	166,522 (52.3)
Use of psychiatric drugs during exposure period B1				
Anticonvulsant mood stabilisers	42 (7.5)	398 (100)	1141 (100)	170 (0.1)
Lithium	4 (0.7)	0 (0)	2 (0.2)	22 (0)
Antipsychotics	26 (4.7)	13 (3.3)	33 (2.9)	423 (0.1)
Antidepressants	68 (12.2)	27 (6.8)	95 (8.3)	6308 (2)
Anxiolytics	12 (2.2)	10 (2.5)	23 (2)	859 (0.3)
Pre-existing medical conditions				
Hypnotics	8 (1.4)	8 (2)	17 (1.5)	693 (0.2)
Depression	87 (15.6)	38 (9.5)	100 (8.8)	20,722 (6.5)
Epilepsy	249 (44.6)	372 (93.5)	1069 (93.7)	3268 (1)
SMI	97 (17.4)	26 (6.5)	53 (4.6)	1840 (0.6)
Pre-existing hypertension	69 (12.4)	29 (7.3)	126 (11)	26,228 (8.2)
Pre-existing diabetes	4 (0.7)	5 (1.3)	19 (1.7)	2767 (0.9)

ACMS, anticonvulsant mood stabiliser; SMI, severe mental illness.

Notes

Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

TABLE 20 Characteristics of women prescribed anticonvulsant mood stabilisers with a record of psychoses or depression in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	131 (100)	61 (100)	318,612 (100)
Age (years)			
Mean (SD)	32 (5.5)	32 (5.4)	30 (5.9)
12–19	2 (1.5)	1 (1.6)	14,008 (4.4)
20–29	43 (32.8)	20 (32.8)	123,740 (38.8)
30–39	77 (58.8)	36 (59)	165,396 (51.9)
40–49	9 (6.9)	4 (6.6)	15,468 (4.9)
Year			
1995–9	3 (2.3)	3 (4.9)	46,638 (14.6)
2000–4	17 (13)	10 (16.4)	80,466 (25.3)
2005–9	54 (41.2)	24 (39.3)	100,009 (31.4)
2010–12	57 (43.5)	24 (39.3)	91,499 (28.7)
Lifestyle variables			
Smoker	49 (37.4)	29 (47.5)	63,085 (19.8)
Illicit drug use	8 (6.1)	4 (6.6)	2110 (0.7)
Alcohol problems	7 (5.3)	5 (8.2)	1653 (0.5)
Obesity	14 (10.7)	11 (18)	18,018 (5.7)
BMI (kg/m²)			
Mean (SD)	27 (5.5)	28 (7.9)	26 (6.3)
Missing	77 (58.8)	38 (62.3)	234,733 (73.7)
Townsend score			
1	5 (20)	0 (0)	70,879 (23.3)
2	2 (8)	4 (28.6)	60,417 (19.9)
3	5 (20)	2 (14.3)	64,877 (21.4)
4	9 (36)	5 (35.7)	61,357 (20.2)
5	4 (16)	3 (21.4)	46,074 (15.2)
Missing	106 (80.9)	47 (77)	15,008 (4.7)
Ethnicity			
White	50 (38.2)	21 (34.4)	133,929 (42)
Mixed	2 (1.5)	1 (1.6)	1772 (0.6)
Asian	4 (3.1)	2 (3.3)	9943 (3.1)
Black	14 (10.7)	3 (4.9)	4619 (1.4)
Other	1 (0.8)	0 (0)	1827 (0.6)
Missing	60 (45.8)	34 (55.7)	166,522 (52.3)

continued

TABLE 20 Characteristics of women prescribed anticonvulsant mood stabilisers with a record of psychoses or depression in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C) (*continued*)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Use of psychiatric drugs during exposure period B1			
Anticonvulsant mood stabilisers	0 (0)	61 (100)	170 (0.1)
Lithium	4 (3.1)	2 (3.3)	22 (0)
Antipsychotics	19 (14.5)	29 (47.5)	423 (0.1)
Antidepressants	29 (22.1)	33 (54.1)	6308 (2)
Anxiolytics	7 (5.3)	5 (8.2)	859 (0.3)
Hypnotics	6 (4.6)	8 (13.1)	670 (0.2)
Pre-existing medical condition			
Depression	61 (46.6)	20 (32.8)	20,722 (6.5)
Epilepsy	0 (0)	0 (0)	3268 (1)
SMI	88 (67.2)	57 (93.4)	1840 (0.6)
Pre-existing hypertension	16 (12.2)	8 (13.1)	26,228 (8.2)
Pre-existing diabetes	2 (1.5)	4 (6.6)	2767 (0.9)

SMI, severe mental illness.
Notes
Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

and in 2–3% of women who continued anticonvulsant mood stabilisers and lithium. Less than 1% of the women not prescribed psychotropic medication had a record of illicit drug use or alcohol problems. More than 45% of women prescribed antipsychotics and anticonvulsant mood stabilisers in pregnancy (cohort B1) (with a record of psychosis or depression) were smokers. In women prescribed lithium in pregnancy (cohort B1) it was 37% and in the cohorts of women not prescribed psychotropic medication it was just under 20% (cohort C). Despite the fact that a large number of data on ethnicity was missing it appears that a relatively large proportion of women prescribed antipsychotics in pregnancy were black. Many women who continued antipsychotics, lithium or anticonvulsant mood stabilisers in pregnancy were also prescribed other medication listed in BNF chapter 4. For example, 238 out of 416 (57%) women who received antipsychotic treatment in pregnancy (cohort B1) also received antidepressant treatment in contrast to < 2% (5942/318,434) of the women in cohort C. Likewise, many received anticonvulsant mood stabilisers in the cohort of women receiving antipsychotics in pregnancy and vice versa.

Including all women, irrespective of indication, in anticonvulsant mood stabilisers cohorts slightly changed the characteristics of cohorts (see *Table 18*). In these cohorts the proportion of individuals with a record of obesity, alcohol problems and smoking was larger in those who discontinued treatment before pregnancy (cohort A) than in those who continued treatment (cohort B1).

Characteristics of the women in the mother–child cohorts

The mother–child cohorts were a subset of the pregnancy cohorts and included between 65% and 75% of the pregnancy cohorts. The characteristics of women in the mother–child cohorts varied slightly from the distribution in the pregnancy cohorts, but cohorts were overall similar for each class of psychotropic medication (*Tables 21–25*).

TABLE 21 Characteristics of women in the mother–child cohort prescribed antipsychotics in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	492 (100)	290 (100)	210,966 (100)
Age (years)			
Mean (SD)	30 (5.7)	32 (5.6)	30 (5.9)
12–19	12 (2.4)	0 (0)	8955 (4.2)
20–29	222 (45.1)	92 (31.7)	80,491 (38.2)
30–39	236 (48)	166 (57.2)	110,839 (52.5)
40–49	22 (4.5)	32 (11)	10,681 (5.1)
Year			
1995–9	25 (5.1)	9 (3.1)	13,339 (6.3)
2000–4	134 (27.2)	40 (13.8)	46,707 (22.1)
2005–9	173 (35.2)	82 (28.3)	77,626 (36.8)
2010–12	160 (32.5)	159 (54.8)	73,294 (34.7)
Lifestyle variables			
Smoker	183 (37.2)	139 (47.9)	42,502 (20.1)
Illicit drug use	40 (8.1)	37 (12.8)	1354 (0.6)
Alcohol problems	28 (5.7)	23 (7.9)	1124 (0.5)
Obesity	62 (12.6)	53 (18.3)	15,363 (7.3)
BMI (kg/m^2)			
Mean (SD)	27 (6.8)	28 (6.7)	26 (6.4)
Missing	315 (64)	164 (56.6)	148,897 (70.6)
Townsend score			
1	16 (14.5)	3 (5.9)	47,381 (23.5)
2	21 (19.1)	10 (19.6)	40,309 (20)
3	19 (17.3)	9 (17.6)	43,152 (21.4)
4	25 (22.7)	11 (21.6)	40,915 (20.3)
5	29 (26.4)	18 (35.3)	30,120 (14.9)
Missing	382 (77.6)	239 (82.4)	9089 (4.3)
Ethnicity			
White	256 (52)	172 (59.3)	104,928 (49.7)
Mixed	2 (0.4)	0 (0)	1504 (0.7)
Asian	7 (1.4)	10 (3.4)	7461 (3.5)
Black	3 (0.6)	11 (3.8)	3446 (1.6)
Other	2 (0.4)	2 (0.7)	1350 (0.6)
Missing	222 (45.1)	95 (32.8)	92,277 (43.7)

continued

TABLE 21 Characteristics of women in the mother–child cohort prescribed antipsychotics in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Use of psychiatric drugs during exposure period B1			
Anticonvulsant mood stabilisers	14 (2.8)	27 (9.3)	887 (0.4)
Lithium	2 (0.4)	11 (3.8)	7 (0)
Antipsychotics	0 (0)	290 (100)	0 (0)
Antidepressants	124 (25.2)	169 (58.3)	4351 (2.1)
Anxiolytics	24 (4.9)	31 (10.7)	523 (0.2)
Hypnotics	28 (5.7)	41 (14.1)	423 (0.2)
Pre-existing medical conditions			
Depression	152 (30.9)	79 (27.2)	14,626 (6.9)
Epilepsy	22 (4.5)	17 (5.9)	3254 (1.5)
SMI	144 (29.3)	180 (62.1)	882 (0.4)
Pre-existing hypertension	47 (9.6)	42 (14.5)	19,570 (9.3)
Pre-existing diabetes	6 (1.2)	7 (2.4)	2005 (1)

SMI, severe mental illness.
Notes
Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

TABLE 22 Characteristics of women in the mother–child cohort prescribed lithium in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	57 (100)	28 (100)	212,531 (100)
Age (years)			
Mean (SD)	34 (5.1)	36 (5.6)	30 (5.9)
12–19	0 (0)	0 (0)	8975 (4.2)
20–29	14 (24.6)	5 (17.9)	81,287 (38.2)
30–39	37 (64.9)	15 (53.6)	111,496 (52.5)
40–49	6 (10.5)	8 (28.6)	10,773 (5.1)
Year			
1995–9	7 (12.3)	1 (3.6)	13,427 (6.3)
2000–4	17 (29.8)	6 (21.4)	47,128 (22.2)
2005–9	20 (35.1)	11 (39.3)	78,169 (36.8)
2010–12	13 (22.8)	10 (35.7)	73,807 (34.7)

TABLE 22 Characteristics of women in the mother–child cohort prescribed lithium in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Lifestyle variables			
Smoker	15 (26.3)	10 (35.7)	43,146 (20.3)
Illicit drug use	2 (3.5)	1 (3.6)	1453 (0.7)
Alcohol problems	3 (5.3)	3 (10.7)	1188 (0.6)
Obesity	8 (14)	7 (25)	15,619 (7.3)
BMI (kg/m²)			
Mean, SD	27 (6.1)	30 (4.3)	26 (6.4)
Missing	36 (63.2)	16 (57.1)	149,792 (70.5)
Townsend score			
1	1 (8.3)	0 (0)	47,623 (23.4)
2	3 (25)	0 (0)	40,530 (19.9)
3	3 (25)	3 (75)	43,385 (21.3)
4	3 (25)	1 (25)	41,380 (20.3)
5	2 (16.7)	0 (0)	30,492 (15)
Missing	45 (78.9)	24 (85.7)	9121 (4.3)
Ethnicity			
White	26 (45.6)	17 (60.7)	105,638 (49.7)
Mixed	0 (0)	0 (0)	1505 (0.7)
Asian	1 (1.8)	1 (3.6)	7476 (3.5)
Black	1 (1.8)	0 (0)	3455 (1.6)
Other	0 (0)	0 (0)	1360 (0.6)
Missing	29 (50.9)	10 (35.7)	93,097 (43.8)
Use of psychiatric drugs during exposure period B1			
Anticonvulsant mood stabilisers	4 (7)	2 (7.1)	916 (0.4)
Lithium	0 (0)	28 (100)	0 (0)
Antipsychotics	10 (17.5)	14 (50)	301 (0.1)
Antidepressants	16 (28.1)	17 (60.7)	4694 (2.2)
Anxiolytics	2 (3.5)	4 (14.3)	582 (0.3)
Hypnotics	3 (5.3)	4 (14.3)	472 (0.2)
Pre-existing medical conditions			
Depression	17 (29.8)	8 (28.6)	15,100 (7.1)
Epilepsy	2 (3.5)	3 (10.7)	3296 (1.6)
SMI	40 (70.2)	25 (89.3)	1168 (0.5)
Pre-existing hypertension	6 (10.5)	4 (14.3)	19,634 (9.2)
Pre-existing diabetes	3 (5.3)	2 (7.1)	2022 (1)

SMI, severe mental illness.

Notes

Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

TABLE 23 Characteristics of women in the mother–child cohort prescribed anticonvulsant mood stabilisers including all women irrespective of indication in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	429 (100)	1108 (100)	211,112 (100)
Age (years)			
Mean (SD)	30 (5.7)	30 (5.5)	30 (5.9)
12–19	19 (4.4)	41 (3.7)	8951 (4.2)
20–29	181 (42.2)	454 (41)	80,581 (38.2)
30–39	217 (50.6)	567 (51.2)	110,873 (52.5)
40–49	12 (2.8)	46 (4.2)	10,707 (5.1)
Year			
1995–9	24 (5.6)	116 (10.5)	13,389 (6.3)
2000–4	83 (19.3)	237 (21.4)	46,601 (22.1)
2005–9	168 (39.2)	398 (35.9)	77,886 (36.9)
2010–12	154 (35.9)	357 (32.2)	73,236 (34.7)
Lifestyle variables			
Smoker	139 (32.4)	264 (23.8)	42,707 (20.2)
Illicit drug use	10 (2.3)	18 (1.6)	1419 (0.7)
Alcohol problems	9 (2.1)	14 (1.3)	1125 (0.5)
Obesity	39 (9.1)	104 (9.4)	13,596 (6.4)
BMI (kg/m^2)			
Mean (SD)	27 (6.7)	27 (6.4)	26 (6.4)
Missing	296 (69)	764 (69)	150,820 (71.4)
Townsend score			
1	11 (16.7)	22 (13.3)	47,305 (23.4)
2	16 (24.2)	22 (13.3)	40,308 (20)
3	10 (15.2)	35 (21.2)	43,152 (21.4)
4	17 (25.8)	43 (26.1)	41,067 (20.3)
5	12 (18.2)	43 (26.1)	30,207 (15)
Missing	363 (84.6)	943 (85.1)	9073 (4.3)
Ethnicity			
White	196 (45.7)	471 (42.5)	104,998 (49.7)
Mixed	2 (0.5)	13 (1.2)	1489 (0.7)
Asian	7 (1.6)	18 (1.6)	7468 (3.5)
Black	36 (8.4)	95 (8.6)	3434 (1.6)
Other	2 (0.5)	7 (0.6)	1375 (0.7)
Missing	186 (43.4)	504 (45.5)	92,348 (43.7)

TABLE 23 Characteristics of women in the mother–child cohort prescribed anticonvulsant mood stabilisers including all women irrespective of indication in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C) (*continued*)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Use of psychiatric drugs during exposure period B1			
Anticonvulsant mood stabilisers	31 (7.2)	1108 (100)	116 (0.1)
Lithium	2 (0.5)	2 (0.2)	13 (0)
Antipsychotics	22 (5.1)	31 (2.8)	268 (0.1)
Antidepressants	49 (11.4)	94 (8.5)	4582 (2.2)
Anxiolytics	9 (2.1)	25 (2.3)	551 (0.3)
Hypnotics	13 (3)	31 (2.8)	454 (0.2)
Pre-existing medical conditions			
Depression	68 (15.9)	104 (9.4)	14,879 (7)
Epilepsy	192 (44.8)	1039 (93.8)	2186 (1)
SMI	78 (18.2)	60 (5.4)	1093 (0.5)
Pre-existing hypertension	54 (12.6)	120 (10.8)	19,570 (9.3)
Pre-existing diabetes	2 (0.5)	19 (1.7)	1998 (0.9)

SMI, severe mental illness.
Notes
Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

TABLE 24 Characteristics of women in the mother-child cohort prescribed valproate vs. other anticonvulsant mood stabilisers, women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C). Women included irrespective of psychoses or depression in pregnancy

	Exposure cohort			
	A	Valproate	Other ACMS	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	429 (100)	273 (100)	835 (100)	211,112 (100)
Age (years)				
Mean SD	30 (5.7)	30 (5.5)	30 (5.6)	30 (5.9)
12–19	19 (4.4)	13 (4.8)	28 (3.4)	8951 (4.2)
20–29	181 (42.2)	109 (39.9)	345 (41.3)	80,581 (38.2)
30–39	217 (50.6)	141 (51.6)	426 (51)	110,873 (52.5)
40–49	12 (2.8)	10 (3.7)	36 (4.3)	10,707 (5.1)
Year				
1995–9	24 (5.6)	50 (18.3)	66 (7.9)	13,389 (6.3)
2000–4	83 (19.3)	75 (27.5)	162 (19.4)	46,601 (22.1)
2005–9	168 (39.2)	86 (31.5)	312 (37.4)	77,886 (36.9)
2010–12	154 (35.9)	62 (22.7)	295 (35.3)	73,236 (34.7)

continued

TABLE 24 Characteristics of women in the mother-child cohort prescribed valproate vs. other anticonvulsant mood stabilisers, women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C). Women included irrespective of psychoses or depression in pregnancy (*continued*)

	Exposure cohort			
	A	Valproate	Other ACMS	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Lifestyle variables				
Obesity	38 (8.9)	26 (9.5)	75 (9)	12,831 (6.1)
Illicit drug use	10 (2.3)	7 (2.6)	11 (1.3)	1419 (0.7)
Alcohol problems	9 (2.1)	4 (1.5)	10 (1.2)	1125 (0.5)
Smoker	139 (32.4)	78 (28.6)	186 (22.3)	42,707 (20.2)
BMI (kg/m²)				
Mean, SD	27 (6.7)	27 (7.2)	27 (6.2)	26 (6.4)
Missing	296 (69)	193 (70.7)	571 (68.4)	150,820 (71.4)
Townsend score				
1	11 (16.7)	3 (9.7)	19 (14.2)	47,305 (23.4)
2	16 (24.2)	2 (6.5)	20 (14.9)	40,308 (20)
3	10 (15.2)	4 (12.9)	31 (23.1)	43,152 (21.4)
4	17 (25.8)	11 (35.5)	32 (23.9)	41,067 (20.3)
5	12 (18.2)	11 (35.5)	32 (23.9)	30,207 (15)
Missing	363 (84.6)	242 (88.6)	701 (84)	9,073 (4.3)
Ethnicity				
White	196 (45.7)	88 (32.2)	383 (45.9)	104,998 (49.7)
Mixed	2 (0.5)	3 (1.1)	10 (1.2)	1489 (0.7)
Asian	7 (1.6)	7 (2.6)	11 (1.3)	7468 (3.5)
Black	36 (8.4)	16 (5.9)	79 (9.5)	3434 (1.6)
Other	2 (0.5)	3 (1.1)	4 (0.5)	1375 (0.7)
Missing	186 (43.4)	156 (57.1)	348 (41.7)	92,348 (43.7)
Use of psychiatric drugs during exposure period B1				
Anticonvulsant mood stabilisers	31 (7.2)	273 (100)	835 (100)	116 (0.1)
Lithium	2 (0.5)	0 (0)	2 (0.2)	13 (0)
Antipsychotics	22 (5.1)	8 (2.9)	23 (2.8)	268 (0.1)
Antidepressants	49 (11.4)	17 (6.2)	77 (9.2)	4582 (2.2)
Anxiolytics	9 (2.1)	6 (2.2)	19 (2.3)	551 (0.3)
Hypnotics	5 (1.2)	6 (2.2)	14 (1.7)	387 (0.2)
Pre-existing medical conditions				
Depression	68 (15.9)	28 (10.3)	76 (9.1)	14,879 (7)
Epilepsy	192 (44.8)	253 (92.7)	786 (94.1)	2186 (1)
SMI	78 (18.2)	19 (7)	41 (4.9)	1093 (0.5)
Pre-existing hypertension	54 (12.6)	21 (7.7)	99 (11.9)	19,570 (9.3)
Pre-existing diabetes	2 (0.5)	4 (1.5)	15 (1.8)	1998 (0.9)

ACMS, anticonvulsant mood stabiliser; SMI, severe mental illness.

Notes

Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

TABLE 25 Characteristics of women in the mother–child cohort with a record of psychoses or depression prescribed anticonvulsant mood stabilisers in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	103 (100)	45 (100)	211,112 (100)
Age (years)			
Mean (SD)	31 (5.3)	31 (5.2)	30 (5.9)
12–19	2 (1.9)	0 (0)	8951 (4.2)
20–29	35 (34)	16 (35.6)	80,581 (38.2)
30–39	61 (59.2)	27 (60)	110,873 (52.5)
40–49	5 (4.9)	2 (4.4)	10,707 (5.1)
Year			
1995–9	2 (1.9)	1 (2.2)	13,389 (6.3)
2000–4	13 (12.6)	8 (17.8)	46,601 (22.1)
2005–9	39 (37.9)	16 (35.6)	77,886 (36.9)
2010–12	49 (47.6)	20 (44.4)	73,236 (34.7)
Lifestyle variables			
Smoker	39 (37.9)	23 (51.1)	42,707 (20.2)
Illicit drug use	6 (5.8)	3 (6.7)	1419 (0.7)
Alcohol problems	4 (3.9)	4 (8.9)	1125 (0.5)
Obesity	12 (11.7)	9 (20)	13,596 (6.4)
BMI (kg/m^2)			
Mean (SD)	28 (5.7)	29 (8.1)	26 (6.4)
Missing	58 (56.3)	26 (57.8)	150,820 (71.4)
Townsend score			
1	5 (22.7)	0 (0)	47,305 (23.4)
2	2 (9.1)	4 (40)	40,308 (20)
3	4 (18.2)	1 (10)	43,152 (21.4)
4	8 (36.4)	3 (30)	41,067 (20.3)
5	3 (13.6)	2 (20)	30,207 (15)
Missing	81 (78.6)	35 (77.8)	9073 (4.3)
Ethnicity			
White	48 (46.6)	17 (37.8)	104,998 (49.7)
Mixed	2 (1.9)	1 (2.2)	1489 (0.7)
Asian	3 (2.9)	1 (2.2)	7468 (3.5)
Black	10 (9.7)	3 (6.7)	3434 (1.6)
Other	1 (1)	0 (0)	1375 (0.7)
Missing	39 (37.9)	23 (51.1)	92,348 (43.7)

continued

TABLE 25 Characteristics of women in the mother–child cohort with a record of psychoses or depression prescribed anticonvulsant mood stabilisers in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed anticonvulsant mood stabilisers (cohort C) (*continued*)

	Exposure cohort		
	A	B1	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Use of psychiatric drugs during exposure period B1			
Anticonvulsant mood stabilisers	0 (0)	45 (100)	116 (0.1)
Lithium	2 (1.9)	2 (4.4)	13 (0)
Antipsychotics	16 (15.5)	21 (46.7)	268 (0.1)
Antidepressants	22 (21.4)	28 (62.2)	4582 (2.2)
Anxiolytics	6 (5.8)	3 (6.7)	551 (0.3)
Hypnotics	5 (4.9)	7 (15.6)	454 (0.2)
Pre-existing medical conditions			
Depression	46 (44.7)	17 (37.8)	14,879 (7)
Epilepsy	0 (0)	0 (0)	2186 (1)
SMI	71 (68.9)	42 (93.3)	1093 (0.5)
Pre-existing hypertension	12 (11.7)	6 (13.3)	19,570 (9.3)
Pre-existing diabetes	1 (1)	3 (6.7)	1998 (0.9)

SMI, severe mental illness.
Notes
Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

Characteristics of children in the mother–child study cohorts

The characteristics of the children in the mother–child cohorts are detailed in *Table 26*. The median days of follow-up varied within and between drug exposures from 657 days [interquartile range (IQR) 286–1351 days] in children of women who were prescribed antipsychotics in pregnancy (cohort B1) to 1197 days (IQR 396–1671 days) in children of women who were prescribed lithium in pregnancy (cohort B1). The median follow-up for children of women not prescribed psychotropic medications (cohort C) was around 740 days depending on the comparison cohorts. The male-to-female ratio varied between cohorts. For example, more females (55%) than males (45%) were born to women who continued antipsychotic treatment in pregnancy (cohort B1) (see *Table 26*). Major congenital malformations were recorded relatively soon after birth and most records of neurodevelopmental/behavioural disorders were made around the age of 2–3 years (see *Table 26*).

TABLE 26 Characteristics of children in the mother–child cohorts of women who were prescribed psychotropic medication in pregnancy (cohort B1) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

Characteristics	A	B1	C
Antipsychotic cohorts			
Total number of children, *N* (%)	492 (100)	290 (100)	210,966 (100)
Sex, *n* (%)			
Male	253 (51.4)	132 (45.5)	107,979 (51.2)
Female	239 (48.6)	158 (54.5)	102,987 (48.8)
Time to event (days), median (IQR)			
Child follow-up	834 (352.5–1758)	657 (286–1351)	738 (349–1416)
Major congenital malformation	136 (33–1167)	85 (21–110)	50 (10–120)
NDBD	1048 (710–1361)	947 (778–1252)	930 (619–1274)
Lithium cohorts			
Total number of children, *N* (%)	57 (100)	28 (100)	212,531 (100)
Sex, *n* (%)			
Males	24 (42.1)	12 (42.9)	108,797 (51.2)
Females	33 (57.9)	16 (57.1)	103,734 (48.8)
Time to event (days), median (IQR)			
Child follow-up	879 (285–1595)	1197 (396–1671)	741 (350–1420)
Major congenital malformation	242 (6–477)	60 (22–97)	50 (10–123)
NDBD	1318 (805–1500)	1252 (622–1642)	937 (622–1280)
Limited anticonvulsant cohort			
Total number of children, *N* (%)	103 (100)	45 (100)	211,112 (100)
Sex, *n* (%)			
Males	49 (47.6)	25 (55.6)	108,015 (51.2)
Females	54 (52.4)	20 (44.4)	103,097 (48.8)
Time to event (days), median (IQR)			
Child follow-up	667 (229–1265)	957 (192.5–1692)	738 (350–1420)
Major congenital malformation	1047 (477–3961)	22 (22–22)	49 (10–120)
NDBD	1360 (1051.5–1418)	1087 (812–1361)	934 (623–1270)
Anticonvulsant mood stabilisers cohort			
Total number of children, *N* (%)	429 (100)	1108 (100)	211,112 (100)
Sex, *n* (%)			
Males	207 (48.3)	566 (51.1)	108,015 (51.2)
Females	222 (51.7)	542 (48.9)	103,097 (48.8)
Time to event (days), median (IQR)			
Child follow-up	740 (297–1465)	924 (349–1741)	738 (350–1420)
Major congenital malformation	7 (1–477)	65 (25–371)	49 (10–120)
NDBD	982 (666–1398)	1042 (594–1370)	934 (623–1270)

NDBD, neurodevelopment disorders and behavioural disorder.

Maternal outcomes

Antipsychotics

Absolute number of events, absolute risks (%) and risk differences with 95% CIs for the outcomes for each of the cohorts are listed in *Table 27*. The relative risk estimates with 95% CIs are listed in *Table 28*.

TABLE 27 Absolute risks and risk differences of adverse maternal and child outcomes associated with antipsychotic treatment in pregnancy. Cohort B1: women prescribed antipsychotics in pregnancy. Cohort A: women who discontinued antipsychotics and cohort C, women not prescribed antipsychotics

	Number of events and absolute risks (%)			Risk difference (95% CI)	
Outcomes	A	B1	C	B1 vs. A	B1 vs. C
Maternal outcomes					
Pre-eclampsia	28 (4.2)	18 (4.3)	9355 (2.9)	0.1 (–2.3 to 2.6)	1.4 (–0.6 to 3.3)
Gestational diabetes	18 (2.7)	11 (2.6)	5227 (1.6)	0 (–2 to 1.9)	1 (–0.5 to 2.5)
Caesarean section	145 (21.6)	104 25)	58,532 (18.4)	3.4 (–1.8 to 8.6)	**6.6 (2.5 to 10.8)**
Perinatal death	< 5	< 5	931 (0.3)	–	–
Child outcomes					
MCM	11 (2.2)	10 (3.4)	4162 (2)	1.2 (–1.3 to 3.7)	1.5 (–0.6 to 3.6)
PBO	24 (4.9)	31 (10.7)	9244 (4.4)	**5.8 (1.8 to 9.8)**	**6.3 (2.8 to 9.9)**
Transient PBO	20 (4.1)	15 (5.2)	4482 (2.1)	1.1 (–2 to 4.2)	**3 (0.5 to 5.6)**
NDBD	50 (10.2)	22 (7.6)	10,107 (4.8)	–2.6 (–6.6 to 1.5)	2.8 (–0.3 to 5.8)

MCM, major congenital malformation; NDBD, neurodevelopment disorders and behavioural disorder; PBO, poor birth outcome.
Bold indicates statistical significance.

TABLE 28 Relative risks of adverse pregnancy outcomes associated with antipsychotic treatment in pregnancy. Results from crude and adjusted Poisson regression models. Cohort B: women prescribed antipsychotics in pregnancy; cohort A: women who discontinued antipsychotics; and cohort C, women not prescribed antipsychotics

	RRR (95% CI)	*p*-value	RRR (95% CI)	*p*-value
Cohort comparisons	B vs. A		B vs. C	
Pre-eclampsia	1.03 (0.57 to 1.87)	0.908	1.47 (0.92 to 2.33)	0.100
Pre-eclampsia (adjusted)[a]	0.69 (0.37 to 1.29)	0.248	1.24 (0.79 to 1.96)	0.342
Gestational diabetes	0.98 (0.46 to 2.08)	0.966	1.61 (0.89 to 2.91)	0.114
Gestational diabetes (adjusted)[a]	**0.43 (0.20 to 0.93)**	**0.032**	0.95 (0.53 to 1.69)	0.867
Caesarean section	1.15 (0.89 to 1.48)	0.261	**1.36 (1.12 to 1.64)**	**0.001**
Caesarean section (adjusted)[a]	1.05 (0.82 to 1.34)	0.671	1.09 (0.92 to 1.30)	0.278
Perinatal death	–	–	–	–
Perinatal death (adjusted)[a]	–	–	–	–

a The adjusted models include adjustments for age, obesity, alcohol problems, smoking, illicit drug use, and antidepressant prescribing and anticonvulsant mood stabilisers. The full results of the adjusted models can be found in *Appendix 1*.

Notes
En rules represent when no analysis was performed, as there were fewer than five events for one or both of the exposure cohorts.
Bold indicates statistical significance.

Of the women who received antipsychotic treatment in pregnancy (cohort B1) 18 out of 416 (4.3%) developed pre-eclampsia/gestational hypertension and 11 out of 416 (2.6%) developed gestational diabetes. The proportions were similar for women who discontinued antipsychotics before pregnancy (cohort A) (see *Table 27*). After adjustment for concomitant medications, health and lifestyle characteristics, women who continued antipsychotic treatment in pregnancy were at lower risks of developing gestational diabetes than women who discontinued treatment [adjusted relative risk ratio (RRR_{adj}) 0.43 (95% CI 0.20 to 0.93)] (see *Table 28*). Notably, obesity was strongly associated with gestational diabetes in this analysis [obesity RRR_{adj} 5.49 (95% CI 2.67 to 11.2)]. Comparing women treated in pregnancy (cohort B1) to women not treated with antipsychotics (cohort C) there were small differences for pre-eclampsia/gestational hypertension and gestational diabetes in the treated group (cohort B1) (see *Table 27*). After adjustments for concomitant medications, health and lifestyle characteristics, the effects attenuated and the associations were not statistically significant [pre-eclampsia/gestational hypertension RRR_{adj} 1.24 (95% CI 0.79 to 1.96) and gestational diabetes RRR_{adj} 0.95 (95% CI 0.53 to 1.69)] (see *Table 28*). Notably there was an independent and strong association with obesity, antidepressant treatment and pre-eclampsia as well as gestational diabetes in the adjusted analyses (see *Appendix 1*).

Of the women who continued antipsychotics in pregnancy (cohort B1), 104 out of 416 (25%) had a caesarean section compared with 145 out of 670 (21.6%) of the women who discontinued treatment (cohort A), the figures for women not treated with antipsychotics were 58,532 out of 318,434 (18.4%) (see *Table 27*). After adjustments for concomitant prescriptions, health and lifestyle characteristics of the women, those who continued antipsychotic treatments in pregnancy were no longer at higher risk of having a caesarean section than women not treated [RRR_{adj} 1.09 (95% CI 0.92 to 1.30)] or than women who discontinued treatment (cohort A) [RRR_{adj} 1.05 (95% CI 0.82 to 1.34)] (see *Table 28*).

Of the women who continued antipsychotic treatment in pregnancy (cohort B1) and those who discontinued treatment before (cohort A) fewer than five women in each of the cohorts experienced a perinatal death and hence no further analyses were carried out.

Lithium

There were 8 out of 35 (23%) women who had a caesarean section among the women who continued lithium in pregnancy (cohort B1) in contrast to 11 out of 84 (13%) in those who discontinued treatment (cohort A) and 59,080 out of 320,853 (18%) among those not treated (cohort C). However, the RRR_{adj} were not statistically significant [B1 vs. A: RRR_{adj} 1.40 (95% CI 0.57 to 3.44)], [B1 vs. C: RRR_{adj} 0.83 (95% CI 0.44 to 1.56)]. Of the cohort of women who received lithium in pregnancy (cohort B1) and the cohort of women who discontinued lithium treatment before pregnancy (cohort A) there were fewer than five individuals who experienced pre-eclampsia/gestational hypertension, gestational diabetes and perinatal death. Therefore, no further analyses were carried out for these outcomes.

Anticonvulsant mood stabilisers

Absolute numbers of events, absolute risks (%) and risk differences with 95% CIs for the outcomes for each of the cohorts are listed in *Tables 29–31*. The relative risk estimates with 95% CIs are listed in *Tables 32–34*.

Comparing women who continued anticonvulsant mood stabilisers in pregnancy, irrespective of whether or not they had a record of psychosis or depression (cohort B1) to women who were not prescribed anticonvulsant mood stabilisers (cohort C), there were small differences (< 1%) in the proportions of women experiencing pre-eclampsia/gestational hypertension, gestational diabetes and perinatal death (see *Table 29*). However, women who continued prescribing in pregnancy (cohort B) were more likely to have a caesarean section than women not treated (cohort C), but there were no statistically significant differences between women who discontinued and women who continued treatment after accounting for health and lifestyle factors (see *Table 32*). Likewise, when contrasting women prescribed valproate to other anticonvulsant mood stabilisers and when restricting the cohort to women with a record of psychosis or recent depression there were no significant associations with maternal outcomes (see *Tables 30* and *31*).

TABLE 29 Absolute risks and risk differences of adverse maternal and child outcomes associated with anticonvulsant mood stabilisers treatment in pregnancy. Cohort B1: women prescribed anticonvulsant mood stabilisers in pregnancy; cohort A: women who discontinued anticonvulsant mood stabilisers; and cohort C: women not prescribed anticonvulsant mood stabilisers

	Absolute risk (%)			Risk difference (95% CI)	
Outcome	A	B1	C	B1 vs. A	B1 vs. C
Maternal outcome					
Pre-eclampsia	15 (2.7)	57 (3.7)	9381 (2.9)	1 (–0.6 to 2.7)	0.8 (–0.2 to 1.7)
Gestational diabetes	6 (1.1)	34 (2.2)	5200 (1.6)	**1.1 (0 to 2.3)**	0.6 (–0.2 to 1.3)
Caesarean section	111 (19.9)	329 (21.4)	58456 (18.3)	1.5 (–2.4 to 5.4)	**3 (1.0 to 5.1)**
Perinatal death	4 (0.7)	7 (0.5)	947 (0.3)	–0.3 (–1 to 0.5)	0.2 (–0.2 to 0.5)
Child outcomes					
MCM	9 (2.1)	45 (4.1)	4119 (2.0)	**2 (0.2 to 3.7)**	**2.1 (0.9 to 3.3)**
PBO	23 (5.4)	69 (6.2)	9186 (4.4)	0.9 (–1.7 to 3.4)	**1.9 (0.5 to 3.3)**
Transient PBO	15 (3.5)	44 (4.0)	4543 (2.2)	0.5 (–1.6 to 2.6)	**1.8 (0.7 to 3.0)**
NDBD	33 (7.7)	96 (8.7)	10217 (4.8)	1 (–2.0 to 4.0)	**3.8 (2.2 to 5.5)**

MCM, major congenital malformation; NDBD, neurodevelopment disorders and behavioural disorder; PBO, poor birth outcome.
Notes
Bold indicates statistical significance.

TABLE 30 Absolute risks and risk differences of adverse maternal and child outcomes associated with valproate treatment in pregnancy. Cohort B1: women prescribed valproate in pregnancy; cohort A: women who discontinued valproate; and cohort C: women not prescribed valproate

	Absolute risk (%)				Risk difference (95% CI)		
Outcome	A	Valproate (B1)	Other ACMS (B1)	C	Valproate (B1) vs. Other ACMS (B1)	Valproate (B1) vs. A	Valproate (B1) vs. C
Maternal outcomes							
Pre-eclampsia	15 (2.7)	13 (3.3)	44 (3.9)	9381 (2.9)	–0.6 (–2.7 to 1.5)	0.6 (–1.6 to 2.8)	0.3 (–1.4 to 2.1)
Gestational diabetes	6 (1.1)	9 (2.3)	25 (2.2)	5200 (1.6)	0.1 (–1.6 to 1.8)	1.2 (–0.5 to 2.9)	0.6 (–0.8 to 2.1)
Caesarean section	111 (19.9)	81 (20.4)	248 (21.7)	58,456 (18.3)	–1.4 (–6 to 3.2)	0.5 (–4.7 to 5.6)	2 (–2.0 to 6.0)
Perinatal death	4 (0.7)	3 (0.8)	4 (0.4)	947 (0.3)	0.4 (–0.5 to 1.3)	0 (–1.1 to 1.1)	0.5 (–0.4 to 1.3)
Child outcomes							
MCM	9 (2.1)	17 (6.2)	28 (3.4)	4119 (2)	2.9 (–0.2 to 6)	**4.1 (1.0 to 7.3)**	**4.3 (1.4 to 7.1)**
PBO	23 (5.4)	15 (5.5)	54 (6.5)	9186 (4.4)	–1 (–4.1 to 2.2)	0.1 (–3.3 to 3.6)	1.1 (–1.6 to 3.8)
Transient PBO	15 (3.5)	16 (5.9)	28 (3.4)	4543 (2.2)	2.5 (–0.5 to 5.5)	2.4 (–0.9 to 5.6)	**3.7 (0.9 to 6.5)**
NDBD	33 (7.7)	39 (14.3)	57 (6.8)	10,217 (4.8)	**7.5 (3.0 to 11.9)**	**6.6 (1.7 to 11.5)**	**9.4 (5.3 to 13.6)**

ACMS, anticonvulsant mood stabilisers; MCM, major congenital malformation; NDBD, neurodevelopment disorders and behavioural disorder; PBO, poor birth outcome.
Notes
Bold indicates statistical significance.

TABLE 31 Absolute risks and risk differences of adverse maternal and child outcomes associated with anticonvulsant mood stabilisers treatment in pregnancy limited to women with a record of psychosis or depression. Cohort B1: women prescribed anticonvulsant mood stabilisers in pregnancy; cohort A: women who discontinued anticonvulsant mood stabilisers; and cohort C: women not prescribed anticonvulsant mood stabilisers

	Absolute risk (%)			Risk difference (95% CI)	
Outcome	A	B1	C	B1 vs. A	B1 vs. C
Maternal outcomes					
Pre-eclampsia	6 (4.6)	< 5	9381 (2.9)		
Gestational diabetes	2 (1.5)	< 5	5200 (1.6)		
Caesarean section	22 (16.8)	13 (21.3)	58,456 (18.3)	4.5 (–7.6 to 16.6)	3 (–7.3 to 13.2)
Perinatal death	< 5	< 5	947 (0.3)		
Child outcomes					
MCM	3 (2.9)	< 5	4119 (2.0)		
PBO	5 (4.9)	8 (17.8)	9186 (4.4)	**12.9 (1.0 to 24.8)**	**13.4 (2.3 to 24.6)**
Transient PBO	4 (3.9)	< 5	4543 (2.2)		
NDBD	4 (3.9)	< 5	10,217 (4.8)		

MCM, major congenital malformation; NDBD, neurodevelopment disorders and behavioural disorder; PBO, poor birth outcome.

Notes

Bold indicates statistical significance.

TABLE 32 Relative risks of adverse pregnancy outcomes associated with anticonvulsant mood stabilisers treatment in pregnancy. Results from crude and adjusted Poisson regression models. Cohort B: women prescribed anticonvulsant mood stabilisers in pregnancy; cohort A: women who discontinued anticonvulsant mood stabilisers; and cohort C: women not prescribed anticonvulsant mood stabilisers

	RRR (95% CI)	*p*-value	RRR (95% CI)	*p*-value
Cohort comparisons	B vs. A		B vs. C	
Pre-eclampsia	1.37 (0.78 to 2.43)	0.269	1.25 (0.96 to 1.63)	0.084
Pre-eclampsia (adjusted)[a]	1.34 (0.76 to 2.36)	0.299	1.22 (0.95 to 1.58)	0.112
Gestational diabetes	2.05 (0.86 to 4.89)	0.103	1.35 (0.96 to 1.89)	0.078
Gestational diabetes (adjusted)[a]	2.17 (0.93 to 5.10)	0.072	1.26 (0.90 to 1.76)	0.165
Caesarean section	1.07 (0.86 to 1.33)	0.511	**1.16 (1.04 to 1.29)**	**0.005**
Caesarean section (adjusted)[a]	1.07 (0.88 to 1.30)	0.450	**1.14 (1.04 to 1.26)**	**0.004**
Perinatal death	–	–	1.53 (0.72 to 3.21)	0.262
Perinatal death (adjusted)[a]	–	–	1.42 (0.67 to 2.99)	0.356

a The adjusted models include adjustments for age, obesity, alcohol problems, smoking, illicit drug use, antidepressant treatment and anticonvulsant mood stabilisers. The full results of the adjusted models can be found in *Appendix 1*.

Notes

En rules represent when no analysis was performed, as there were fewer than five events for one or both of the exposure cohorts.

Bold indicates statistical significance.

TABLE 33 Relative risks of adverse pregnancy outcomes associated with valproate treatment in pregnancy. Results from crude and adjusted Poisson regression models. Cohort B1: women prescribed valproate in pregnancy; cohort A: women who discontinued valproate and cohort C: women not prescribed valproate

	Valproate (B1) vs. other ACMS (B1)		Valproate (B1) vs. A		Valproate (B1) vs. C
Cohort comparisons	RRR (95% CI)	*p*-value	RRR (95% CI)	*p*-value	RRR (95% CI)
Pre-eclampsia	0.84 (0.45 to 1.57)	0.598	1.21 (0.57 to 2.55)	0.607	1.10 (0.64 to 1.91)
Pre-eclampsia (adjusted)[a]	0.85 (0.46 to 1.56)	0.600	1.30 (0.62 to 2.70)	0.477	1.10 (0.64 to 1.87)
Gestational diabetes	1.03 (0.48 to 2.21)	0.935	2.10 (0.74 to 5.90)	0.158	1.38 (0.72 to 2.66)
Gestational diabetes (adjusted)[a]	1.17 (0.54 to 2.52)	0.683	2.73 (0.98 to 7.63)	0.054	1.34 (0.70 to 2.56)
Caesarean section	0.93 (0.72 to 1.20)	0.607	1.02 (0.76 to 1.36)	0.875	1.10 (0.89 to 1.37)
Caesarean section (adjusted)[a]	0.96 (0.77 to 1.20)	0.770	1.03 (0.80 to 1.33)	0.782	1.11 (0.91 to 1.34)
Perinatal death	–	–	–	–	2.53 (0.81 to 7.87)
Perinatal death (adjusted)[a]	–	–	–	–	2.30 (0.74 to 7.17)

ACMS, anticonvulsant mood stabilisers.

a The adjusted models include adjustments for age, obesity, alcohol problems, smoking, illicit drug use, antidepressant treatment and anticonvulsant mood stabilisers. The full results of the adjusted models can be found in *Appendix 1*.

Notes

En rules represent when no analysis was performed, as there were fewer than five events for one or both of the exposure cohorts.

TABLE 34 Relative risks of adverse pregnancy outcomes associated with anticonvulsant mood stabilisers treatment in pregnancy limited to women with a record of psychosis or depression. Results from crude and adjusted Poisson regression models. Cohort B1: women prescribed anticonvulsant mood stabilisers in pregnancy, Cohort A: women who discontinued anticonvulsant mood stabilisers and cohort C: women not prescribed anticonvulsant mood stabilisers

	RRR (95% CI)	*p*-value	RRR (95% CI)	*p*-value
Cohort comparisons	B vs. A		B vs. C	
Pre-eclampsia	–	–	–	–
Pre-eclampsia (adjusted)[a]	–	–	–	–
Gestational diabetes	–	–	–	–
Gestational diabetes (adjusted)[a]	–	–	–	–
Caesarean section	1.26 (0.63 to 2.51)	0.495	1.16 (0.67 to 2.00)	0.589
Caesarean section (adjusted)[a]	0.80 (0.44 to 1.45)	0.464	0.92 (0.58 to 1.45)	0.732
Perinatal death	–	–	–	–
Perinatal death (adjusted)[a]	–	–	–	–

a The adjusted models include adjustments for age, obesity, alcohol problems, smoking, illicit drug use and antidepressant, antipsychotic and lithium prescribing. The full results of the adjusted models can be found in *Appendix 1*.

Notes

En rules represent when no analysis was performed, as there were fewer than five events for one or both of the exposure cohorts.

Child outcomes

Antipsychotics

Absolute number of events, absolute risks (%) and risk differences with 95% CIs for the outcomes for each of the cohorts are listed in *Table 27*. The relative risk estimates with 95% CIs are listed in *Table 35*.

Out of 290 women prescribed antipsychotics in pregnancy (cohort B1), 10 (3.4%) gave birth to a child with a major congenital malformation in comparison to 11 out of 492 (2.2%) in the cohort of women who discontinued treatment before pregnancy (cohort A), and 4162 out of 210,966 (2.0%) in the cohort of women not treated with antipsychotics (cohort C) (see *Table 27*). Thus, the risk differences and RRRs were non-significant both before and after adjustments for concomitant medications, health and lifestyle characteristics (see *Tables 27* and *35*).

The proportion of women that were prescribed antipsychotics in pregnancy (cohort B1) who gave birth to a child with poor birth outcomes was 31 out of 290 (10.7%), double the proportion [24/492 (4.9%)] in women who discontinued treatment (cohort A) and nearly triple the proportion [9244/210,966 (4.4%)] in women who were not treated with antipsychotics (see *Table 35*). After adjustment for concomitant medication and health and lifestyle factors the relative risks remained elevated in comparison with cohort A (RRR_{adj} 1.83, 95% CI 1.05 to 3.20), but not in comparison with cohort C (RRR_{adj} 1.39, 95% CI 0.98 to 1.97) (see *Table 35*). Notably, obesity, smoking, alcohol problems and illicit drug use, as well as concomitant medications, all remained independently associated with poor birth outcomes in the comparison between cohort B1 and cohort C (see *Appendix 1*).

TABLE 35 Relative risks of adverse child outcomes associated with antipsychotic treatment in pregnancy. Results from crude and adjusted Poisson regression models. Cohort B1: women prescribed antipsychotics in pregnancy; cohort A: women who discontinued antipsychotics; and cohort C, women not prescribed antipsychotics

	RRR (95% CI)	*p*-value	RRR (95% CI)	*p*-value
Cohort comparisons	**B vs. A**		**B vs. C**	
MCM	1.54 (0.65 to 3.63)	0.321	1.74 (0.93 to 3.25)	0.077
MCM (adjusted)[a]	1.79 (0.72 to 4.47)	0.207	1.59 (0.84 to 3.00)	0.148
PBO	**2.19 (1.28 to 3.73)**	**0.003**	**2.44 (1.71 to 3.47)**	**< 0.001**
PBO (adjusted)[a]	**1.83 (1.05 to 3.20)**	**0.031**	1.39 (0.98 to 1.97)	0.061
Transient PBO[b]	1.37 (0.68 to 2.75)	0.374	**2.62 (1.52 to 4.52)**	**< 0.001**
Transient PBO (adjusted)[a,b]	1.20 (0.57 to 2.53)	0.625	1.59 (0.92 to 2.74)	0.091
NDBD	0.74 (0.45 to 1.23)	0.253	**1.58 (1.04 to 2.40)**	**0.031**
NDBD (adjusted)[a]	0.83 (0.49 to 1.39)	0.487	1.22 (0.80 to 1.84)	0.344

MCM, major congenital malformation; NDBD, neurodevelopment disorders and behavioural disorder; PBO, poor birth outcome.

a The adjusted models include adjustments for age, obesity, alcohol problems, smoking, illicit drug use, antidepressant treatment and anticonvulsant mood stabilisers. The full results of the adjusted models can be found in *Appendix 1*.

b Comparisons were made between women who received treatment towards the end of pregnancy (cohort B2).

Notes

Bold indicates statistical significance.

The proportion of women who were prescribed antipsychotics in the later stages of pregnancy (cohort B2) who gave birth to a child with transient poor birth outcomes was 13 out of 233 (5.6%) compared with 20 out of 492 (4.1%) in women who discontinued treatment before pregnancy (cohort A) and 4482 out of 210,966 (2.1%) in women not treated with antipsychotics (cohort C). However, after adjustments, relative risk estimates were not statistically significant [cohort B2 vs. cohort A: RRR_{adj} 1.20 (95% CI 0.57 to 2.53) and cohort B2 vs. cohort C: RRR_{adj} 1.59 (95% CI 0.92 to 2.74)] (see *Table 35*). Age, obesity, smoking, illicit drug and concomitant medications, however, all remained independently associated with transient poor pregnancy outcomes in the comparison between cohort B1 and cohort C.

Finally, we observed a similar pattern for neurodevelopmental and behavioural disorders. Thus, in the unadjusted analysis the association was significant, but after adjustment the relative risk estimates attenuated and were no longer statistically significant (see *Table 35*).

Lithium

For all child outcomes there were fewer than five women prescribed lithium in pregnancy (cohort B1) who experienced the outcomes and therefore no further analyses were carried out.

Anticonvulsant mood stabilisers

Absolute number of events, absolute risk (%) and risk differences with 95% CIs for the outcomes for each of the cohorts are listed in *Tables 29–31*.

When including all women, irrespective of indication, 45 out of 1108 (4.1%) women prescribed anticonvulsant mood stabilisers in pregnancy (cohort B1) gave birth to a child with major congenital malformations (see *Table 29*). In contrast, 4119 out of 211,112 (2%) women not treated (cohort C) gave birth to a child with major congenital malformations. Thus, relative risks more than doubled when comparing cohort B1 and cohort C (RRR_{adj} 2.05, 95% CI 1.53 to 2.74) (*Table 36*). There was no significant difference in the proportions with major congenital malformations between women who discontinued treatment before pregnancy (cohort A) and those who continued treatment in pregnancy (cohort B1) (see *Tables 29* and *36*).

TABLE 36 Relative risks of adverse child outcomes associated with anticonvulsant mood stabiliser treatment in pregnancy. Results from crude and adjusted Poisson regression models. Cohort B1: women prescribed anticonvulsant mood stabilisers in pregnancy, cohort A: women who discontinued anticonvulsant mood stabilisers; and cohort C: women not prescribed anticonvulsant mood stabilisers

Cohort comparisons	RRR (95% CI) B vs. A	*p*-value	RRR (95% CI) B vs. C	*p*-value
MCM	1.93 (0.94 to 3.96)	0.070	**2.08 (1.55 to 2.79)**	**< 0.001**
MCM (adjusted)[a]	1.89 (0.93 to 3.85)	0.077	**2.05 (1.53 to 2.74)**	**< 0.001**
PBO	1.16 (0.72 to 1.86)	0.533	**1.43 (1.12 to 1.81)**	**0.003**
PBO (adjusted)[a]	1.25 (0.78 to 2.01)	0.340	**1.33 (1.06 to 1.67)**	**0.013**
Transient PBO[b]	1.14 (0.63 to 2.07)	0.654	**1.86 (1.36 to 2.54)**	**< 0.001**
Transient PBO (adjusted)[a,b]	1.41 (0.78 to 2.53)	0.250	**1.76 (1.30 to 2.38)**	**< 0.001**
NDBD	1.12 (0.75 to 1.67)	0.555	**1.79 (1.46 to 2.18)**	**< 0.001**
NDBD (adjusted)[a]	1.10 (0.75 to 1.61)	0.604	**1.73 (1.42 to 2.09)**	**< 0.001**

MCM, major congenital malformation; NDBD, neurodevelopment disorders and behavioural disorder; PBO, poor birth outcome.

a The adjusted models include adjustments for age, obesity, alcohol problems, smoking, illicit drug use, antidepressant treatment and anticonvulsant mood stabilisers. The full results of the adjusted models can be found in *Appendix 1*.

b Comparisons were made between women who received treatment towards the end of pregnancy (cohort B2).

Notes

Bold indicates statistical significance.

When we compared women in cohort B1 who were prescribed valproate with women who were prescribed other anticonvulsant mood stabilisers (lamotrigine and carbamazepine) the relative risk of giving birth to a child with major congenital malformations nearly doubled (RRR_{adj} 1.85, 95% CI 1.02 to 3.36) (*Table 37*). It was further elevated when comparing women prescribed valproate in pregnancy (B1) with women who discontinued treatment before pregnancy (cohort A) and more than a threefold increase was observed when comparing with women not prescribed anticonvulsant mood stabilisers (cohort C) [RRR_{adj} 3.15 (95% CI 1.98 to 5.00)] (see *Table 37*).

Fewer than five women with a record of psychoses or depression and prescribed anticonvulsant mood stabilisers in pregnancy (cohort B1) gave birth to a child with major congenital malformations and therefore no further analyses were carried out.

The risks of giving birth to a child with poor birth outcomes were elevated for all women who were prescribed anticonvulsant mood stabilisers in pregnancy [69/1108 (6.2%)] compared with women who were not prescribed anticonvulsant mood stabilisers (cohort C) [9186/211,112 (4.4%)] (see *Table 29*). This remained significant after adjustments for health and lifestyle factors and concomitant medications for cohort B vs. C (RRR_{adj} 1.33, 95% CI 1.06 to 1.67) (see *Table 36*). Notably, obesity, smoking and illicit drug use as well as concomitant medications were all independently associated with poor pregnancy outcomes in the comparison between cohort B1 and cohort C (see *Appendix 1*). There were no significant differences when the comparisons were made between cohort B and cohort A (see *Tables 29* and *36*). Very similar patterns were observed for transient poor birth outcomes and neurodevelopmental and

TABLE 37 Relative risks of adverse child outcomes associated with valproate treatment in pregnancy. Results from crude and adjusted Poisson regression models. Cohort B1: women prescribed valproate in pregnancy, cohort A: women who discontinued valproate; and cohort C: women not prescribed valproate

Cohort comparisons	RRR (95% CI) Valproate (B1) vs. other ACMS (B1)	*p*-value	RRR (95% CI) Valproate (B1) vs. A	*p*-value	RRR (95% CI) Valproate (B1) vs. C	*p*-value
MCM	**1.85 (1.01 to 3.39)**	**0.044**	**2.96 (1.32 to 6.65)**	**0.008**	**3.19 (1.98 to 5.13)**	**< 0.001**
MCM (adjusted)[a]	**1.85 (1.02 to 3.36)**	**0.040**	**2.93 (1.36 to 6.34)**	**0.006**	**3.15 (1.98 to 5.00)**	**< 0.001**
Poor birth outcome	0.85 (0.47 to 1.50)	0.576	1.02 (0.53 to 1.96)	0.941	1.38 (0.72 to 2.66)	0.328
Poor birth outcome (adjusted)[a]	0.82 (0.47 to 1.44)	0.506	1.06 (0.55 to 2.04)	0.841	1.34 (0.70 to 2.56)	0.365
Transient PBO[b]	1.74 (0.94 to 3.23)	0.074	1.67 (0.82 to 3.39)	0.150	**2.72 (1.66 to 4.44)**	**< 0.001**
Transient PBO (adjusted)[a,b]	1.68 (0.96 to 2.93)	0.067	1.75 (0.90 to 3.39)	0.094	**2.49 (1.55 to 4.00)**	**< 0.001**
NDBD	**2.09 (1.39 to 3.14)**	**< 0.001**	**1.85 (1.16 to 2.95)**	**0.008**	**2.95 (2.15 to 4.04)**	**< 0.001**
NDBD (adjusted)[a]	**2.10 (1.43 to 3.08)**	**< 0.001**	**1.76 (1.14 to 2.72)**	**0.010**	**2.83 (2.11 to 3.81)**	**< 0.001**

ACMS, anticonvulsants mood stabilisers; MCM, major congenital malformation; NDBD, neurodevelopment disorders and behavioural disorder; PBO, poor birth outcome.

a The adjusted models include adjustments for age, obesity, alcohol problems, smoking, illicit drug use, antidepressant treatment and anticonvulsant mood stabilisers.

b Comparisons were made between women who received treatment towards the end of pregnancy (cohort B2).

Notes

Bold indicates statistical significance.

The full results of the adjusted models can be found in *Appendix 1*.

behavioural disorders. Hence, of the women prescribed anticonvulsant mood stabilisers in pregnancy (cohort B1), 96 out of 1108 (9%) gave birth to a child who later had records of neurodevelopmental or behavioural disorders, in contrast to 10,217 out of 211,112 (4.8%) among women not prescribed anticonvulsant mood stabilisers (cohort C), resulting in RRR_{adj} of 1.73 (95% CI 1.42 to 2.09) (see *Table 36*).

When comparing women in cohort B1, who were prescribed valproate, with women who were prescribed other anticonvulsant mood stabilisers (lamotrigine and carbamazepine), the relative risk of giving birth to a child who later had records of neurodevelopmental or behavioural disorders doubled RRR_{adj} 2.10 (95% CI 1.43 to 3.08) (see *Table 37*). It was also elevated when comparing women prescribed valproate in pregnancy (cohort B1) with women who discontinued treatment before pregnancy (cohort A), but an almost threefold increase was observed when comparing with women not prescribed anticonvulsant mood stabilisers (cohort C) (RRR_{adj} 2.83, 95% CI 2.11 to 3.81) (see *Table 37*).

The proportion of all women prescribed anticonvulsant mood stabilisers in the later stages of pregnancy (cohort B2) who gave birth to a child with transient poor birth outcomes was 44 out of 1108 (4.0%) compared with 4543 out of 211,112 (2.2%) in women not treated with anticonvulsant mood stabilisers (cohort C). After adjustments, the RRR estimate was 1.76 (95% CI 1.30 to 2.38). However, there were no significant differences between women prescribed anticonvulsant mood stabilisers in pregnancy (cohort B2) and women who discontinued treatment before pregnancy, although the relative risk estimates increased after adjustments (see *Table 37*).

The risks of giving birth to a child with poor birth outcomes were particularly high among women with a record of psychosis or depression who continued treatment in pregnancy (cohort B1) [8/45 (17.8%)]. This was in contrast to 5 out of 103 (4.9%) of the women who discontinued treatment in pregnancy (cohort A) and 9186 out of 211,112 (4.4%) of the women who were not prescribed anticonvulsant mood stabilisers (cohort C) resulting in a two- to threefold increase in relative risks [RRR_{adj} cohort B1 vs. cohort A: 2.97 (95% CI 0.96 to 9.12) and cohort B1 vs. cohort C: 2.38 (95% CI 1.27 to 4.47) (*Table 38*).

TABLE 38 Relative risks of adverse child outcomes associated with anticonvulsant mood stabiliser treatment in pregnancy in women with a record of psychosis or depression. Results from crude and adjusted Poisson regression models. Cohort B1: women prescribed anticonvulsant mood stabilisers in pregnancy; cohort A: women who discontinued anticonvulsant mood stabilisers; and cohort C: women not prescribed anticonvulsant mood stabilisers

	RRR (95% CI)	*p*-value	RRR (95% CI)	*p*-value
Cohort comparisons	B vs. A		B vs. C	
MCM	–	–	–	–
MCM (adjusted)[a]	–	–	–	–
PBO	**3.66 (1.19 to 11.1)**	**0.022**	**4.08 (2.04 to 8.17)**	**< 0.001**
PBO (adjusted)[a]	2.97 (0.96 to 9.12)	0.056	**2.38 (1.27 to 4.47)**	**0.006**
Transient PBO[b]	–	–	–	–
Transient PBO (adjusted)[a,b]	–	–	–	–
NDBD	–	–	–	–
NDBD (adjusted)[a]	–	–	–	–

MCM, major congenital malformations; NDBD, neurodevelopmental and behavioural disorders; PBO, poor birth outcome.
a The adjusted models include adjustments for age, obesity, alcohol problems, smoking, illicit drug use, antidepressant treatment and anticonvulsant mood stabilisers. The full results of the adjusted models can be found in *Appendix 1*.
b Comparisons were made between women who received treatment towards the end of pregnancy (cohort B2).
Notes
En rules represent when no analysis was performed, as there were fewer than five events for one or both of the exposure cohorts.
Bold indicates statistical significance.

There were fewer than five children with a record of the remaining child outcomes among women who had a record of psychosis or depression and were prescribed anticonvulsant mood stabilisers in pregnancy and no further analyses were done.

Discussion

The characteristics of the women varied between as well as within different classes of psychotropic medication. Thus, women prescribed psychotropic medication in pregnancy (cohort B1) were in general older than women not prescribed psychotropic medication (cohort C) and a larger proportion were obese and were recorded as having illicit drug and/or alcohol problems. More than 45% of women prescribed antipsychotics and anticonvulsant mood stabilisers in pregnancy were smokers compared with 37% of women prescribed lithium and 20% in the cohort of women not prescribed psychotropic medication. Concomitant prescription of other psychotropic medications was common. For example, 57% of women who received antipsychotic treatment in pregnancy (cohort B1) also received antidepressant treatment.

Including all women, irrespectively of indication, in anticonvulsant mood stabilisers cohorts slightly changed the characteristics of cohorts. In these cohorts the proportions of individuals with a record of obesity, alcohol problems and smoking were larger in those who discontinued treatment before pregnancy (cohort A) compared with those who continued treatment (cohort B1).

Below we summarise the results of the analyses examining the associations with psychotropic drug treatment in pregnancy for each class of psychotropic medication.

Antipsychotics

Women prescribed antipsychotics in pregnancy (cohort B1) were at higher risks of delivering by caesarean section and giving birth to a child with poor birth outcomes, transient poor birth outcomes, and neurodevelopmental and behavioural disorders than women not prescribed antipsychotics (cohort C). After adjustment for health and lifestyle factors and concomitant medication prescribed, these effects were attenuated and none of the associations were statistically significant. For the remaining pregnancy and birth outcomes, including major congenital malformations, no differences were found between women prescribed antipsychotics in pregnancy and those who were not.

When comparing women who were prescribed antipsychotics in pregnancy (cohort B1) to those who discontinued treatment before pregnancy (cohort A), the former were at lower risk of developing gestational diabetes than women who discontinued treatment after adjustments were made for health, lifestyle factors and concomitant medication prescribed in pregnancy. For the child outcomes the only significant association was between treatment in pregnancy and poor birth outcomes; this association remained after adjustments for concomitant medication, health and lifestyle factors.

Lithium

In terms of caesarean sections, there was no difference between women who were prescribed lithium in pregnancy (cohort B1) and those that discontinued treatment (cohort A) or were not prescribed lithium (cohort C). The numbers prescribed lithium both before and during pregnancy, however, were too few for us to conduct further analyses as there were far too few events that were recorded for both maternal and child outcomes.

Anticonvulsant mood stabilisers

Women prescribed anticonvulsant mood stabilisers in pregnancy (cohort B1) were at a greater risk of having caesarean sections than women not prescribed the drug (cohort C). However, there were no significant differences between cohort B1 and cohort C for the remaining maternal outcomes or between women who continued treatment (cohort B) and those who discontinued treatment (cohort A). In terms of adverse child outcomes, women who continued anticonvulsant mood stabiliser treatment in pregnancy were at higher risks of all child outcomes than women not treated (cohort C) and this persisted after adjustments for health and lifestyle factors, and concomitant medication. There were no significant differences, however, in terms of the child outcomes when comparing women in cohort B with women who discontinued treatment before pregnancy (cohort A).

The comparison between women who were prescribed valproate in pregnancy and women who were prescribed other anticonvulsant mood stabilisers in pregnancy suggests an almost doubling in the risk of giving birth to a child with major congenital malformations in the group prescribed valproate as well as a doubling in the risk of giving birth to a child who later had records of neurodevelopmental or behavioural disorders. The RR was slightly lower when comparing women prescribed valproate in pregnancy (B1) with women who discontinued treatment before pregnancy (cohort A) and an almost threefold increase was observed when comparing with women not prescribed anticonvulsant mood stabilisers (cohort C).

On limiting our analyses for anticonvulsant mood stabilisers to women with a record of psychosis or depression we were unable to conduct most analyses owing to the small number of events. The risk of giving birth to a child with poor birth outcomes was two- to threefold higher in women who continued treatment in pregnancy both than in those who discontinued treatment (cohort A) and those not prescribed anticonvulsant mood stabilisers (cohort C).

Comparisons with existing literature

Antipsychotics

A review of the literature up to 2008 on the use and safety of individual antipsychotics prescribed in pregnancy found no definite associations between antipsychotic use during pregnancy and adverse perinatal or neurodevelopmental outcomes.[1] However, the review highlighted the occurrence of weight gain in women on second-generation antipsychotics; a risk factor for both hypertension and diabetes that exert their own risks on pregnancy outcomes.[74,75] We found that a much larger proportion of women who were prescribed antipsychotics in pregnancy were obese compared with women not prescribed antipsychotics or who discontinued treatment before pregnancy (17.3% in cohort B1 vs. 6.5% in cohort C and 11.5% in cohort A). Other research on antipsychotic treatment in pregnancy includes pharmacovigilance studies from drug companies' safety databases[76,77] as well as cohort studies based on various data sources.[38,50,78–85] A systematic review[19] of many of these studies suggested that women requiring antipsychotic treatment during pregnancy have a higher risk of adverse birth outcomes. However, there was substantial heterogeneity between the studies and Coughlin *et al.*[19] emphasise that most studies had limited adjustment for potential confounding and therefore the observed associations may not be causal. A recent large Canadian study[86] based on health administrative data sought to account for confounding factors and included 1021 women on antipsychotics matched to 1021 non-users on a range of parameters using propensity score matching. The study did not find significant differences in the rates of gestational diabetes, hypertensive disorders and venous thromboembolism, nor did they identify significant differences in child outcomes, such as preterm birth or birthweight, between the matched samples, although the absolute rates of these outcomes were high.[86]

The results of our study are remarkably similar to another large study on antipsychotic treatment in pregnancy and adverse pregnancy and birth outcomes based on the Swedish birth register.[48] Reis and Källén[48] identified 570 women, who when interviewed by midwives, indicated that they were prescribed antipsychotics in early pregnancy. While we cannot directly compare the characteristics of the women in the two studies, there was a large proportion of women on antipsychotics in pregnancy in the Swedish

study who were smoking [219 out of 570 (38%)] and the use of other psychotropic medication was also common. They reported that 172 out of 570 (30%) used antidepressants, 79 out of 570 (14%) used lithium and 23 out of 570 (4%) used anticonvulsant mood stabilisers. In terms of maternal perinatal outcomes, the proportion of women with pre-eclampsia [27/570 (4.7%)], gestational diabetes [14/570 (2.5%)] and caesarean section [135/570 (23.7%)] among women prescribed antipsychotics in pregnancy were almost identical to our findings.[48] In terms of child outcomes, the Swedish study also observed elevated risks of low Apgar scores, low birthweight and preterm birth among women who used antipsychotics in pregnancy. The Swedish study reported an absolute risk of severe congenital malformations of 5.21% among women who continued antipsychotics in pregnancy, which was slightly higher than our estimates of major congenital malformations (3.4%).[48] Odds ratios estimating the risk in women who received antipsychotics in pregnancy relative to women not treated with antipsychotics were 1.78 (95% CI 1.04 to 3.01) for gestational diabetes, 1.43 (95% CI 1.17 to 1.74) for caesarean section and 1.52 (95% CI 1.05 to 2.19), relatively severe congenital malformations, mainly because of cardiovascular defects (atrium or ventricular septum defects). The study authors highlighted the non-specificity of the associations and suggested the excess risks may be because of confounding. When the comparison was made after exclusion of women exposed to concomitant anticonvulsant medication, the difference was no longer statistically significant.[48]

Risks of extrapyramidal and withdrawal syndromes associated with third trimester exposure of first-generation antipsychotics have long been recognised[87] and the US Food and Drug Administration and UK Medicines and Healthcare products Regulatory Agency updated their advice on the risks of extrapyramidal and withdrawal syndromes in 2011 for the entire class of antipsychotic drugs to inform health-care professionals.[88] Our estimates of transient poor pregnancy outcomes, however, were no longer significant after adjustment for concomitant medication, and health and lifestyle factors. Likewise, Vigod *et al.*[86] observed a sevenfold increased risk for neonatal adaptation syndrome, but this was reduced to a small non-significant relative risk in a matched cohort analysis, suggesting that the observed patterns may be attributed to confounding by concomitant medication use as well as alcohol and substance misuse. We, in keeping with others, found a high prevalence of smokers and individuals with illicit drug problems among women who were prescribed antipsychotics in pregnancy, which may have an inverse impact on pregnancy outcomes.[89]

Little is known about adverse developmental effects of antipsychotic exposure in pregnancy.[90] After adjustments for concomitant medication, health and lifestyle factors we found that the association between antipsychotic prescribing in pregnancy and neurodevelopmental disorders attenuated and was not statistically significant.

Lithium

There is very limited information available on pregnancy outcomes in women exposed to lithium, with most evidence coming from case reports.[71] Initial research suggested a substantial increase in Ebstein's anomaly, a rare cardiovascular anomaly, following lithium exposure in pregnancy.[91] However, these findings may be caused by bias in reporting, as four subsequent case–control studies of Ebstein's anomalies did not identify any children born to women who took the drug during pregnancy.[92] One of the largest prospective studies on lithium in pregnancy (including 138 exposed women) did not find any difference in the rates of major congenital malformations among children born to women exposed (2.8%) compared with children exposed to treatment not considered to be teratogenic (2.4%).[93] The Swedish study discussed previously[48] included 79 women using lithium in pregnancy and identified four children with congenital cardiac malformations equivalent to a prevalence rate of 5.1% (95% CI 1.4% to 12.5%). A recent study[51] based on 183 women exposed to lithium during pregnancy who contacted the Israeli Teratology Information Service also suggests lithium treatment in pregnancy is associated with a higher rate of cardiovascular anomalies. We had only 28 mother–child pairs in our study in which the mother had been prescribed lithium in pregnancy and were therefore unable to conduct further analysis on congenital malformations.

Lithium exposure in pregnancy has been associated with high birthweight (large for gestation) even though these women were more likely to be smokers than those not exposed to the drug (32% vs. 16%).[93] However, this did not hold true in another comparative study of lithium-treated women with that of the general population and with another group of women with manic-depressive illness not treated with lithium.[94] A review of the records from the International Register of Lithium Babies published in 1993[94] suggested that more than one out of three of the children exposed to lithium experience preterm (< 37 weeks) births. Some case reports suggest that lithium toxicity can occur, which often presents as a 'floppy infant syndrome', characterised by lethargy, poor sucking, tachypnea, tachycardia and respiratory distress syndrome.[95]

As for antipsychotics, limited information is available on potential physical and developmental anomalies in children whose mothers were exposed to lithium in pregnancy.[96] One study[97] published in 1976 followed 60 children enrolled at the lithium registry at birth and up to 7 years old. This study compared physical and mental anomalies in these children with their 57 siblings not exposed to lithium during pregnancy, but did not find any differences.

Anticonvulsant mood stabilisers

For some time there has been concerns whether or not treatment with anticonvulsant mood stabilisers, in particular valproate, in pregnancy may increase the risks of major congenital malformations.[15,53–58] The NICE guidelines[12,59] for both antenatal mental health care and bipolar disorder issued in 2014 recommend valproate not be prescribed to girls and women of childbearing potential. Limited research has been carried out specifically on women receiving anticonvulsant mood stabilisers for psychiatric illnesses, but a number of observational studies have examined the risks of congenital malformations in women with epilepsy treated with anticonvulsant mood stabilisers. In general, cardiovascular defects, in particular ventricular septal defects, are the most common congenital malformations for children born to both healthy women and women with epilepsy.[33,54,98,99] Neural tube defects, cleft palate and cleft lip, and hypospadias have also been associated with exposure to anticonvulsant mood stabilisers although they are rare events and the estimates vary considerably.[18,98]

Our estimates of absolute risks and risk differences for major congenital malformations match closely with previous reports from UK epilepsy registries.[33] Thus, we identified 6.8% with major congenital malformations among children of women receiving prescriptions of valproate in pregnancy (cohort B1) and 3.1% among children of women who had discontinued anticonvulsant mood stabilisers before pregnancy (cohort A). Morrow *et al.*[33] reported a rate of 6.2% (95% CI 4.6% to 8.2%) for major congenital malformation in women exposed to valproate in pregnancy and 3.5% (95% CI 1.8% to 6.8%) in women with epilepsy who had not taken anticonvulsant mood stabilisers during pregnancy ($n = 239$). Like us, Morrow *et al.*[33] demonstrated that the risks of giving birth to a child with major congenital malformation more than doubled for women exposed to valproate versus carbamazepine. Similar findings have emerged from other registries and population-based samples and have been summarised in a review by Tomson and Battino.[18] One constraint of many registry studies is that they include limited information on general health and lifestyle factors that may confound the associations between drug exposure and congenital malformations.[18] Our comparative studies utilising different cohorts of women with different exposure status demonstrate that confounding may be an issue, as we observed much smaller effects estimates when we made comparisons between women prescribed different anticonvulsants than when we compared with women not prescribed anticonvulsant mood stabilisers. It has been suggested that the risks of major congenital malformations may increase with polytherapy involving valproate as well as with increasing dose.[33] However, we did not examine potential effects of dose or polytherapy.

There has been some debate since the 1970s whether or not exposure to anticonvulsant mood stabilisers during pregnancy can adversely affect neurodevelopment and increase the risk of behavioural disorders in children. Adverse neurodevelopmental outcomes in children which has been linked with anticonvulsant mood stabilisers range from global reduction in intelligence quotient (IQ) to specific developmental concerns such as autism, memory and attention.[15,61,100–105] A first Cochrane review,[102] published in 2004,

concluded that there was little evidence of differences between anticonvulsant mood stabilisers in terms of their effects on cognitive development in utero, but highlighted that there were few studies available on valproate. Subsequently, the Neurodevelopmental Effects of Antiepileptic Drugs study,[103,104] examined cognitive outcomes at 3 and 6 years of age after in-utero exposure to valproate, carbamazepine, lamotrigine or phenytoin. Initial results of the interim analyses on 309 children controlling for maternal IQ and gestational age demonstrated that children exposed to valproate had an average IQ score substantially lower than children exposed to lamotrigine, phenytoin and carbamazepine. IQ scores did not differ significantly between the latter three anticonvulsant mood stabilisers.[104] Another Cochrane review,[105] published in 2014, evaluated 22 prospective cohort studies and six registry-based studies. The review presented the results of a number of comparisons. The main conclusion was that there is a reduction in the IQ in children exposed to valproate in pregnancy compared with other anticonvulsant mood stabilisers.[105] In their summary of the literature, Tomson and Battino[18] also reported poorer performance in children of mothers exposed to valproate in pregnancy, although the studies they reported on were heterogeneous in terms of age at assessment and methods.

Use of anticonvulsant mood stabilisers during pregnancy has also been associated with autism, child behavioural problems and socialising skills.[18,61,106] Thus, a Danish registry study[61] identified 655,615 children born from 1996 through to 2006, of which 5437 were identified with autism spectrum disorder, including 2067 with childhood autism. Exposure to valproate was identified via linkage to their mothers' records during pregnancy from the Danish Prescription Register, which holds information on all prescriptions filled since 1996.[61] The Danish study suggested a substantial increase in diagnoses of autism spectrum disorder (adjusted hazard ratios 2.9, 95% CI 1.7 to 4.9) as well as childhood autism (adjusted hazard ratios 5.2, 95% CI 2.7 to 10.0) in comparison with children of 'healthy mothers'.[61] The association persisted when comparisons were made with women who discontinued treatment before pregnancy. However, the absolute rates of both autism spectrum disorder and childhood autism were doubled in children of mothers with epilepsy, but not treated with valproate, in comparison with the overall population rates.[61]

In our study we used a broad measure for neurodevelopmental and behavioural disorders as we felt it unlikely that we would be able to capture very specific diagnoses/measurements of these disorders in primary care electronic health records. Nonetheless, our relative comparisons are similar to previous findings from the Danish registry study,[61] suggesting a threefold increase in neurodevelopmental and behavioural disorders in children of women who were prescribed valproate in pregnancy (cohort B1) compared with women who were not (cohort C). As for our estimates of major congenital malformations, the risk estimates of neurodevelopmental and behavioural disorders attenuated when comparisons were made with children of women receiving other anticonvulsant mood stabilisers during pregnancy, suggesting that exposures to valproate cannot solely explain the elevated risks.

Finally, a number of prospective cohort studies have examined perinatal outcomes associated with exposure to anticonvulsant mood stabilisers in pregnancy.[15] The use of carbamazepine in pregnancy was significantly related to reduction in head circumference, lower birthweight and reduced length,[107–109] and similarly the use of valproate was associated with neonatal hypoglycaemia and reduced birth dimensions.[110,111] A study based on Swedish Medical Birth registry data from 1995 to 2001 identified a higher proportion of caesarean section (odds ratio 1.64, 95% CI 1.43 to 1.88), pre-eclampsia (odds ratio 1.66, 95% CI 1.32 to 2.08) among women exposed to anticonvulsant mood stabilisers than among women not exposed.[71] Pilo *et al.*[71] demonstrated a higher rate of children born with respiratory distress (odds ratio 2.06, 95% CI 1.62 to 2.63). Another Swedish study[112] also based on national health registries demonstrated that women with bipolar disorder treated with psychotropic medication (anticonvulsant mood stabilisers, lithium or antipsychotics) were more likely to experience caesarean section and preterm delivery.

Chapter 5 Synthesis

Summary of the findings

In this project our aim was to ascertain the risks and benefits of psychotropic medication in women treated for psychosis who become pregnant. The project was divided into two parts. First, we conducted five descriptive studies with a focus on psychotropic drug utilisation, discontinuation and restarting of treatment. This was followed by a series of cohort studies that examined the absolute and relative risks of adverse maternal and child outcomes associated with psychotropic medication. Our studies were based on data from UK primary care using two large databases: THIN and the CPRD. Below we summarise our main findings.

Prevalence, initiation and termination of psychotropic treatment

- The overall patterns of prescribing of psychotropic medication around pregnancy were similar for the three classes of psychotropic medication, following a broad 'u shape'. Thus, prescribing of psychotropic medication was relatively constant before pregnancy, decreased sharply in early pregnancy and then increased after delivery to equal or even surpass pre-pregnancy levels.
- In the 1–3 months before the start of pregnancy, 0.21% of the women were prescribed antipsychotics, 0.015% were prescribed lithium and 0.41% were prescribed anticonvulsant mood stabilisers.
- In the second trimester of pregnancy the figures for psychotropic prescribing were 0.11% for antipsychotics, 0.006% for lithium and 0.11% for anticonvulsant mood stabilisers.
- Quetiapine, olanzapine, risperidone, chlorpromazine, trifluoperazine and flupentixol were the most commonly prescribed atypical and typical antipsychotics. Initially carbamazepine was the most commonly prescribed anticonvulsant mood stabiliser, but was replaced by lamotrigine and valproate.

Patterns of recording that indicate worsening of mental health

- The recording of suicide attempts, overdose or deliberate self-harm was relatively constant in the 18 months prior to pregnancy, but declined during pregnancy. The recording rose after pregnancy, but only to half of what it was prior to pregnancy.

Entries made for mental health hospital admission or invoking of the Mental Health Act[45] more than tripled just after delivery in comparison to the period just before pregnancy and recording of psychosis, mania and hypomania followed similar patterns with a doubling just after delivery.

Time trends in prevalence of psychotropic treatment around and during pregnancy over the calendar period 1995–2012

- Overall, antipsychotic treatment has increased by > 50% before and during pregnancy from 1995/6 to 2011/12 with a shift from typical to atypical antipsychotics in the study period.
- Anticonvulsant mood stabilisers prescribing to women with a record of psychosis or depression has almost doubled since 1997/8. Carbamazepine has recently been superseded by valproate and lamotrigine.
- Lithium was rarely prescribed and prescribing fluctuated over time with annual prescribing after delivery almost halving between 1995/6 and 2011/12.

Discontinuation and factors associated with continuation of psychotropic medication in pregnancy

- The overall patterns of discontinuation of psychotropic medication were remarkably similar between classes of psychotropic medication.
- Both pregnant and non-pregnant women discontinue psychotropic medication, but women who become pregnant discontinue psychotropic medication at a much faster rate just before or in early pregnancy compared with non-pregnant women, suggesting that pregnancy is a strong determinant for discontinuation of psychotropic medication.
- By the sixth week of pregnancy (when the women are likely to become aware of the pregnancy) only 54% received further atypical antipsychotic prescriptions, 37% anticonvulsant mood stabilisers, 35% typical antipsychotics and 33% lithium. By the start of the third trimester the figures were 38% for atypical antipsychotics, 27% for lithium, 19% for typical antipsychotics and 14% for anticonvulsant mood stabilisers.
- Women with a record of epilepsy who were prescribed anticonvulsants were much more likely to continue medication in pregnancy than women with a record of psychosis, depression or other indications.
- Factors associated with continuation of treatment in pregnancy included duration of prior treatment, dose, age and comedication.
- In general, few women switched between typical and atypical antipsychotic treatment just before or in pregnancy. Likewise, few women switched from lithium to antipsychotics.

Restarting and factors associated with restarting psychotropic medication in pregnancy

- Depending on the psychotropic drug prescribed, between 40% and 76% of women who discontinued psychotropic medication before or in early pregnancy had restarted treatment at 15 months after delivery.
- Overall, there were no clear predictors of restarting of treatment within 6 months of delivery, except for typical antipsychotics in which women who were on a high dose before pregnancy were most likely to restart treatment.

Absolute and relative risks of adverse effects of psychotropic medication in pregnancy on maternal and child outcomes

Characteristics of women

- Women prescribed psychotropic medication in pregnancy were in general older than women not prescribed psychotropic medication. A large proportion of the women prescribed psychotropic medication in pregnancy were obese and many had records of illicit drug use and alcohol problems.
- More than 45% of women prescribed antipsychotics and anticonvulsant mood stabilisers in pregnancy were smokers compared with 37% of women prescribed lithium and 20% in the cohorts of women not prescribed psychotropic medication.
- Concomitant prescriptions of other psychotropic medications were common. For example, 57% of women who received antipsychotic treatment in pregnancy also received antidepressant treatment.

Associations between prescribed psychotropic medication in pregnancy and adverse maternal and child outcomes

- Women prescribed antipsychotic medication in pregnancy were *not* at higher risk of giving birth to a child with major congenital malformation than women not prescribed antipsychotics.
- Women who were prescribed antipsychotics in pregnancy were at a higher risk of delivering by caesarean section and giving birth to a child with poor birth outcomes, transient poor birth outcomes, and neurodevelopmental and behavioural disorders than women not prescribed antipsychotics. However, these associations were confounded by health, lifestyle and concomitant medication and after adjustment the effects attenuated and none of the associations was statistically significant.
- There was no significant difference in the risk of developing gestational diabetes between women who continued antipsychotics in pregnancy and those who discontinued. However, gestational diabetes appears to be strongly associated with obesity and after adjustment for health, lifestyle factors and concomitant medication, women who continued antipsychotics in pregnancy were at lower risk of developing gestational diabetes.
- Few women were prescribed lithium before and during pregnancy and we were unable to conduct further analyses owing to the small number of events.
- Women prescribed anticonvulsant mood stabilisers in pregnancy were at higher risk of giving birth by caesarean section than women not prescribed anticonvulsant mood stabilisers.
- There were no significant differences for the remaining maternal outcomes or between women who continued treatment and those who discontinued treatment.
- Women who continued anticonvulsant mood stabiliser treatment in pregnancy experienced higher risks of *all* child outcomes in comparison to women not treated, but no difference was observed when comparing with women who discontinued treatment before pregnancy.
- Comparing women who were prescribed valproate in pregnancy with women who were prescribed other anticonvulsant mood stabilisers in pregnancy suggested a doubling in the risk of giving birth to a child with major congenital malformations or giving birth to a child who later had records of neurodevelopmental or behavioural disorders.
- The risk of giving birth to a child with major congenital malformations and the risk of giving birth to a child who later had records of neurodevelopmental or behavioural disorders were increased threefold in comparison with women not prescribed anticonvulsant mood stabilisers.
- By limiting the analyses to women with a record of psychosis or depression we were unable to conduct most analyses owing to the small number of events. However, the risk of giving birth to a child with poor birth outcomes was two- to threefold higher in women who continued treatment in pregnancy both in comparison with those who discontinued treatment and those not prescribed anticonvulsant mood stabilisers. The increased risk persisted after adjustment for health and lifestyle factors.

Risks and benefits of psychotropic medication in pregnancy

Many women treated with psychotropic medication face a dilemma on getting pregnant as they must decide whether or not to continue their medication in pregnancy.[12,18,20] In this project we demonstrated that the majority of these women discontinue psychotropic medication either before or in early pregnancy.[46,47] For each individual woman this is likely to result from an informal 'risk–benefit' evaluation, which may include a range of factors such as previous medical history, current state of illness, likelihood of relapse in pregnancy and postpartum, family circumstances, known teratogenic risks and fear of doing harm to the unborn child.[4,14,20] For some women the answer to this evaluation is 'clear-cut' with the benefits of continuing treatment in pregnancy noticeably outweighing the potential risks.[4,12,18,20] For example, this may be the case if they were to experience an acute psychiatric episode or have previously experienced postnatal psychosis. For other women potential teratogenic risks will clearly outweigh the potential benefits to the mother's health of continued psychotropic treatment. One might expect such women to discontinue treatment at the beginning of pregnancy and then restart treatment when the perceived teratogenic risk is lower, such as after the first trimester, after delivery or after they finish

breastfeeding. Yet, although our study on restarting of treatment suggested that a large proportion of the women restarted treatment, no clear patterns in the timing of restarting were observed. This suggests that for many women it may be far less straightforward to balance the risks and benefits of using psychotropic medication in pregnancy. The occurrence of an acute event/relapse of mental illness after discontinuation may further complicate decisions around restarting of psychotropic medication. However, our analyses shows that little of the information recorded in the women's electronic health records prior to pregnancy were predictive of continuation as well as restarting of psychotropic medication.

We performed comprehensive studies on the risks associated with prescribing of psychotropic medication in pregnancy. The results of our cohort studies on antipsychotics and anticonvulsant mood stabilisers demonstrate on the one hand that women prescribed anticonvulsant mood stabilisers, in particular valproate, were at *increased* risk of giving birth to a child with major congenital malformation in comparison with women who were not prescribed these medications and women who discontinued treatment before pregnancy. Our analyses also suggest that children born to women prescribed anticonvulsant mood stabilisers, and again in particular valproate, were at elevated risk of giving birth to a child who later had records of neurodevelopmental or behavioural disorders. On the other hand, we observed no risk of major congenital malformations for women prescribed antipsychotics in pregnancy. This confirms previous research and recent guidelines.[12,18,19,56,58,59] There are, however, some studies that suggest associations between antipsychotic treatment in pregnancy and adverse maternal and child outcomes, but most previous research has not been able to account for potential confounding[19] and our research reveals that these associations are likely to be confounded by the health, lifestyle characteristics and concomitant medication. In addition, it is important to recognise that although antipsychotics may not increase the risk of adverse maternal and child outcomes per se, many of the women prescribed antipsychotics in pregnancy may be more likely to experience some of the adverse outcomes because of other factors such as obesity, alcohol problems, smoking and illicit drug use.

In this project we have not been able to fully address the question about benefits of psychotropic medication in pregnancy. One obvious benefit of continuation of psychotropic medication in pregnancy would be prevention of relapse of mental illnesses in pregnancy and postpartum psychosis. However, electronic health records, such as THIN and the CPRD, are not well suited to address questions about the benefits of treatment with psychotropic medication in pregnancy for various reasons. First, the decision to prescribe psychotropic medication in pregnancy is likely to be driven by the prognosis of future illness (as well as the current status of the women's mental health). This clinical judgement is not recorded well in electronic health records and, therefore, it is difficult, if not impossible, to identify comparison groups to evaluate effectiveness of psychotropic drugs in preventing relapse and/or postpartum psychosis using data that are based on clinical management.[113] Second, it may be challenging to clearly define what constitutes a relapse or deterioration of mental illnesses based on the records in primary care databases, as GPs may not enter this directly in the patient electronic records. Finally, as we highlight in *Chapter 7*, *Lived experience advisory panel meetings*, the evaluation of risks and benefits of psychotropic medication may reach much further for the individual woman and include a number of social aspects as well as medical conditions/outcomes. However, the social aspects are unlikely to be well defined/recorded in electronic health records.

Strengths and limitations

The overall strength of this project is that it relies on 'real-life' data on psychotropic medication prescribed to women of childbearing potential in UK primary care. To our knowledge it is the largest study to date and most comprehensive study of its kind. The study utilised the detailed prescribing information available in primary care databases to thoroughly investigate the prescribing of psychotropic medication in and around pregnancy. Below we outline some of the challenges and limitations specific to this project, including the identification of pregnancies, misclassification of exposures, outcomes and covariates, confounding and comparison cohorts, and statistical testing. Notably, most of these limitations are linked to the fact that primary care electronic health records are designed for clinical management rather than research, and therefore data on important factors are often incomplete.

Identification of pregnancies

The primary care databases used in this project are broadly representative of the UK population.[27,28] However, any subcohorts selected from within these databases may have been selective in terms of inclusion/exclusion of certain individuals. Although we made a great effort to ensure that our algorithm would have captured the vast majority of eligible pregnancies recorded in primary care electronic health records, we cannot exclude that a few women would have received parts of their antenatal and postnatal care in specialist and hospital settings. This may not be fully captured in their primary care records. Likewise, we were only able to capture mother–child dyads if the child was registered with the same general practice as the mother.

Many pregnancy studies using electronic healthcare records, including our study, exclude pregnancies ending in spontaneous or induced terminations as it is difficult to accurately identify the duration of many of these pregnancies. This can lead to selection bias whereby major congenital malformations that are more likely to result in terminations are not accounted for.[114] In short, a selection bias can arise if two conditions are met: (1) the proportion of, for example, major congenital malformations are different in those who terminated compared with those who did not terminate and (2) the proportion of those who terminated are different among exposed and unexposed. If just one of these conditions is met the effects will cancel out in relative estimates. There are some studies that suggest women on antipsychotic treatment are more likely to terminate pregnancies than women not treated with antipsychotics in different parts of the world.[77,115] However, our sensitivity analyses to evaluate the potential impact on excluding pregnancies that ended in terminations suggest that these were unlikely to have a major impact on our study findings (see *Appendix 1*).

Misclassification of exposure, outcome and covariates

As we utilised data recorded for the purpose of clinical management of patients, it is likely that some misclassification of exposure, outcome and covariate status may have occurred. In particular, there may be some discrepancies between prescribing data and actual drug consumption. Studies from different countries including the UK, the USA and the Netherlands have thus reported varying rates of prescription redemption.[116–120] We are aware that pregnancy may be a period during which women are particularly susceptible to non-adherence/non-compliance and if there is a genuine effect of a drug exposure this effect may be diluted by such exposure misclassification. In our studies women in cohort B would have received prescriptions of psychotropic medication both before and during the first trimester. This may increase the likelihood that the women were actually using the treatment. In terms of our outcomes we were unable to validate the prevalence of each outcome, but we noted that several of our prevalence estimates were close to previous published prevalence figures associated with specific drug exposures.[33,48] On the other hand, our prevalence rates for perinatal death were lower than figures from the ONS suggesting that not all events have been captured in primary care records.

For some of our covariates we observed a large proportion of missing data, for example, for ethnicity and deprivation scores (Townsend). We reported the level of missing data on each of these variables, but the high proportion of missing data limited the use of these variables in the further analysis. Therefore, we cannot exclude confounding by ethnicity and social deprivation.

Confounding and comparison cohorts

As mentioned previously (see *Chapter 4, Psychotropic medication exposures*), one way we sought to investigate the potential issues of confounding was by selecting multiple comparison groups (cohorts A and C) and, specifically for anticonvulsant mood stabilisers, by comparing the risks of adverse maternal and child outcomes between women prescribed valproate compared with other anticonvulsant mood stabilisers. For other classes of psychotropic medication we felt the sample sizes would have been too small for between-drug comparisons. As we noted previously (see *Chapter 4*, *Characteristics of the women in the pregnancy cohort* and *Characteristics of the children in the mother–child study cohorts*), the measured characteristics of women who continued treatment in pregnancy (cohort B1) and women who were not on treatment (cohort C) differed substantially. In general, the women in cohort A and B1 were more similar to each other than to women in cohort C; therefore, it seems likely that cohort A and B1 (B2) were closer to each other in terms of unmeasured characteristics and the resulting analysis less likely to be subject to confounding. Thus, in the analysis of valproate (see *Table 37*) we observed a twofold increase in major congenital malformations when comparing cohort B with cohort C. However, the effect attenuated when we compared cohort B with A and when we compared women prescribed valproate with other anticonvulsants. We are aware, however, that there is still likely to be some substantial differences between women who discontinue treatment before pregnancy and those who continue psychotropic medication in pregnancy, which will result in residual confounding.

Statistical testing and type 1 errors

Owing to the large number of statistical analyses included in this project we cannot exclude that some of the results might be statistically significant by chance (with an alpha level of 5% this may be the case for approximately 1 out of 20 tests). However, we have sought to minimise the number of tests by combining various child outcomes into poor birth outcomes, transient poor birth outcomes, and neurodevelopmental and behavioural outcomes. We discuss the limitations of this approach in *Chapter 4, Child outcomes*. In general we have sought to provide more emphasis on the actual estimates and their 95% CIs rather than *p*-values when we interpreted the results of the analyses.

Chapter 6 Conclusions and recommendations

Conclusions

The use of psychotropic drugs around pregnancy has increased with an increasing number of women using atypical antipsychotics, lamotrigine and, the potentially teratogenic drug, valproate. However, our findings indicate that many women discontinue treatment before or during early pregnancy and then restart again in late pregnancy or after delivery. Lithium continues to be prescribed around pregnancy but its use is decreasing.

Our results support previous findings of associations between valproate prescribed in pregnancy and major congenital malformations as well as neurodevelopmental or behavioural disorders. In contrast, our study offers no support for the discontinuation of antipsychotic medication in pregnancy in order to reduce the risk of gestational diabetes. The increased risk of adverse maternal and child outcomes in women who continue antipsychotic treatment in pregnancy may be associated with health and lifestyle factors (obesity, smoking, alcohol abuse and illicit drug use, and concomitant medication) rather than specific drug effects. It was not possible to investigate the risk associated with lithium use or anticonvulsant use specifically for psychoses owing to the small numbers of women in these groups.

Recommendations

Below we outline our recommendations for further research and implications of our research for clinical practice.

Valproate

Our findings suggest that women who are prescribed valproate in pregnancy are at an increased risk of giving birth to a child with major congenital malformations as well as neurodevelopmental and behavioural disorders. At the same time, we observed that valproate was still commonly prescribed both before and during pregnancy in women with a record of psychosis or recent depression. Therefore, we recommend further research is conducted to: (1) describe the utilisation of valproate in women of childbearing potential in terms of sociodemographics and underlying illnesses and (2) investigate how use of valproate can be curtailed in women of childbearing potential.

Benefits of continuing psychotropic medication

Further studies are needed to quantify the potential benefits of continuation of psychotropic treatment in pregnancy, but as we outlined in *Chapter 5, Risks and benefits of psychotropic medication in pregnancy*, it is difficult to address this in data collected for clinical management owing to confounding, that is, women who are at high risk of relapse and/or postpartum psychoses may be more likely to continue psychotropic medication in pregnancy. We recommend that a study be set up to evaluate the feasibility of a RCT to examine if the use of antipsychotics in pregnancy can reduce the risk of relapse and/or postpartum psychoses. Such a study should evaluate sample size for the RCT, whether or not it would be feasible to recruit women and potential barriers for recruitment. This should be done by interviewing health-care professionals (psychiatrists, GPs, obstetricians and midwives) as well as women prescribed psychotropic medication.

Associations between health and lifestyle factors, and adverse pregnancy outcomes

Our findings highlight that the characteristics of many women who continue psychotropic medication in pregnancy differed substantially from women who discontinued or were not prescribed psychotropic medication. Further research is needed to investigate the risks associated with alcohol abuse, illicit drug use and obesity in women with psychosis who then become pregnant.

Implication for clinical practice

The results of our research reinforce the guidance provided in the 2014 NICE guidelines.[12,59] Furthermore, our studies highlight the relationship between general health and lifestyle factors and the risks of adverse maternal and child outcomes in women who are prescribed psychotropic medication in pregnancy. Health-care providers should be alerted to the fact that many of the women prescribed psychotropic medication may be at a heightened risk of giving birth to a child with major congenital malformations caused by obesity, alcohol abuse, illicit drug use and concomitant use of anticonvulsants.

Chapter 7 Patient and public involvement

Introduction

Patient and public involvement (PPI) in research is a part of the National Institute for Health Research HTA programme and is actively supported by major UK funding bodies. The level and type of involvement and engagement varies between projects. It is now common to see service user representatives on research study steering groups and other approaches to PPI are increasingly being applied to UK-funded research. In this project we developed a plan for extensive engagement with service users through the charity Rethink Mental Illness. This involved recruiting a lived experience advisory panel (LEAP) of mental health service users to follow the study and examine its results in order to assist the research team with developing practical guidance and communication based on the findings. At the start of the project we initiated discussions with members of staff from Rethink Mental Illness to set up and develop the LEAP. However, in 2013, Rethink Mental Illness underwent a restructure and was no longer able to support these activities. Rather, they recommended that we continued our PPI with The McPin Foundation, which is a mental health research charity. In this chapter we report on the work with The McPin Foundation and the LEAP at key stages of the research.

Lived experience advisory panel

Recruitment of lived experience advisory panel

The LEAP was recruited by The McPin Foundation through open advert. We sought to work with women who would be able to draw on their own experiences. The following criteria were therefore developed:

- women who currently or recently have been prescribed psychotropic medication (antipsychotics, lithium or anticonvulsant mood stabilisers)
- women who have been pregnant or considered becoming pregnant
- women who have experienced, or have a demonstrable interest in research.

The selection of the panel was carried out by staff at The McPin Foundation and in this process they carefully considered the experiences the women were able to share with the project team and how comfortable they felt using lived experience in a research study as advisors. It was also a requirement that they were willing to commit to the study for 12 months and be available to work flexibly, as meetings would happen in stages. The members of the LEAP were paid for their travel and their time participating in meetings.

Lived experience advisory panel meetings

An information meeting was held at The McPin Foundation in summer 2013 for four women who were interested in this study, and all women decided to join the LEAP. The women had a range of experiences relevant to the study. One member had experienced pregnancy and had children, whereas others had considered, or were considering, starting a family. The initial function of the LEAP was to provide advice and guidance on the risks and benefits of psychotropic medication use and pregnancy from the mental health service user's perspective. The full advisory panel met face to face with members of the research team on four occasions – July 2013, August 2013, May 2014 and September 2014. Two members of the advisory panel also met with IP in May 2015 to discuss key findings from the project and one further meeting is planned to focus on dissemination of study findings.

Initially, the members of the advisory panel were invited to comment on women's discontinuation of psychotropic medication and the advisory panel were shown graphs from our work on discontinuation of psychotropic medication in pregnancy (see *Chapter 3, Discontinuation and factors associated with continuation of psychotropic medication in pregnancy)*. The advisory panel then drew on their own experiences and reflected on factors that may influence discontinuation of psychotropic medication. A summary of the factors that the panel felt may be associated with the decision to continue or discontinue psychotropic medication is listed below:

- Planned versus unplanned pregnancies.
- Who is prescribing the psychotropic medicine, for example consultant or GP?
- Where do women seek their advice?
- Current dose of psychotropic medication.
- Length of diagnosis history.
- Relapse history (number of relapses).
- Moving to other psychotropic medication as an option. Experience of this in the past.
- Have they been offered alternative therapy if coming off medicine, for example cognitive–behavioural therapy?
- Relationship status: partner/married/no stable relationship.
- Culture, ethnicity factors linked to beliefs about medication.
- Age.
- Previous pregnancy history.
- Previous miscarriages.
- Number of different psychotropic medications, for example a woman might come off antipsychotics but stay on antidepressants.
- Weight loss/gain/obesity (strategy for weight management).
- History of postpartum psychosis.
- Some women may restart medication in second or third trimester?
- Are women who are told they cannot come off psychotropic medication more likely to terminate?
- Social issues: friends, family and their opinion of whether or not you should continue your medication when you are pregnant.
    - Social class: stigma of mental health medication – the way women who take medication perceive themselves.
- Past experiences of medication discontinuation.

We found this discussion very helpful and were able to incorporate some of these factors, where possible, in our further analysis and discussion (see *Chapter 3*, *Discontinuation and factors associated with continuation of psychotropic medication* and *Chapter 3*, *Discussion*).

We also sought the advisory panel's opinion about adverse outcomes of pregnancy and how to classify these. During these discussions it became clear that the advisory panel felt that it was necessary to take a broader perspective on the mother's general functioning, well-being and the wider family. Hence, it was not enough just to focus on adverse pregnancy outcomes such as birth defects. It was discussed whether or not it would be possible to 'rank' the adverse outcomes, but the LEAP did not feel that was neither possible nor appropriate. Some of the points raised in the discussion are listed below:

- Obstetricians are likely to have a very different focus from the pregnant woman – likely to focus on health only
- Women are more interested in social aspects, for example:
    - they want to be well functioning mothers
    - they want to meet other new mothers
    - they want to provide consistent care to their baby
    - they want to breastfeed.

- Concern about the involvement of social services.
- Fear of a major deterioration in the long term after pregnancy – this is not just a fear of relapse, but a fear that it might take longer to find stability after pregnancy than before.
- Women want to enjoy pregnancy – they do not want to come off drugs that keep them happy.
- Some mothers would not mind a disabled child – it would be loved just as much. Others would feel guilt for having taken drugs.
- 'Whatever you do will be wrong.'
- Quality of life is a key factor for women – what is the point of having a baby if you are too ill to enjoy it?
- The quality of mental health input is important, just as much as what is provided.
- The experience of a first pregnancy may affect the choice to have further children.
- Some women may decide not to have children – there is no right decision to make.
- Concern about having a premature baby.
- Concern about bonding with the baby if the mother is poorly or in hospital.
- Concern about not being able to breastfeed if on medication – the child will miss out on the benefits of breastfeeding.
- Concern about the mother harming the baby when she is ill.
- Concern about neglect of the child but also the mother neglecting herself.
- Support for new mothers tails off over time, but the baby's needs actually get more complex over time – language and social development.
- The biggest fear is an incapacitating relapse – psychosis or depression. If you do not get the early bonding days you can never get them back.
- Concern about social services taking the child away at birth.
- Adverse outcomes for the child include:

    - permanent disability
    - lack of stability
    - losing mother to suicide
    - not having care needs met
    - being harmed by mother during a psychotic episode.

- Fear about having a disabled child – if this happened, the mother would feel guilty that medication might have caused it, and this guilt might impair the mother's relationship with the child. The mother may also feel anxiety that some disability might show up later – this anxiety might have a further impact on the relationship with the child.
- Concern about passing on the mental illness to the child.
- Concern about drug withdrawal for the child after birth.
- This is a great big spider's web – drugs are just one tiny part.
- Does the baby get brothers and sisters? The woman must decide whether or not to have further children. Is a woman more likely to keep taking medication if she did this in a previous pregnancy?
- The woman's partner does not want to see her go through the struggle again – this may lead to a decision to have no further children.
- A lot of the adverse outcomes are actually risk factors for future illness rather than actual negative outcomes themselves.
- Pre-eclampsia can be managed.

Finally, we sought the opinion from the advisory panel on the interpretation of some of the key findings from the project and decisions around the cohort definitions. For example, we discussed reasons why some women may not have a record of psychosis despite being prescribed psychotropic medication and the panel provided a range of explanations. The panel felt it is likely that many GPs would not want to label women with a diagnosis early on and may decide to try antipsychotic treatment, for example to deal with the symptoms before making a more definite diagnosis. We also sought the panel's opinion on the characteristics of cohorts of women who continued psychotropic medication in pregnancy (cohort B) in our studies of absolute and relative risks of psychotropic medication in pregnancy (see *Chapter 4*). The advisory panel highlighted that the findings from our study did match up with the 'picture' of mental health service users on antipsychotics in terms of health and lifestyle factors as well as concomitant medication. Again, the advisory panel emphasised that drug exposure in pregnancy should be considered in a much broader context and we discussed the potential of 'self-medication' with alcohol and the impact of illicit drug use/methadone on potential adverse pregnancy and birth outcomes. As one member of the advisory panel suggested 'for some women the antipsychotics is the least of their problems'.

Inspired by this project and the preliminary findings, The McPin Foundation decided to work with the four members of the advisory panel on an independent study. In this study the women interviewed other women with severe mental illnesses, who had given birth in the previous 5 years, about their decision to continue or discontinue psychotropic medication in pregnancy. The women from the advisory panel developed a protocol and, following ethical approval, interviewed 12 women with support from The McPin Foundation and University College London staff during 2013 and 2014. Although these interviews were not a part of this project, the advisory panel drew on the experiences and insights that they gained from these interviews in our subsequent discussions about risks and benefits of psychotropic medication in pregnancy. For example, it came out of these interviews that many women find it very difficult to access information on risks and benefits of psychotropic medication in pregnancy. Many websites were based on US data and drug names and, therefore, proved difficult to apply into UK settings.

Lived experience advisory panel impact on project and vice versa

The discussions with the advisory panel have helped inform the interpretations and discussion sections of this report and published papers.[46,47] Our work with the advisory panel has, in particular, drawn our attention to the women's dilemma in balancing their own health needs with that of the unborn child.

At the first advisory panel meeting, IP gave a presentation to introduce electronic health records research and the project on risks and benefits of psychotropic medication. Although some of the advisory panel members had previous experience of research methodology from Doctor of Philosophy and/or Master's courses, electronic health records research and the challenges of working with clinical records were new to the majority of the panel members. We also hosted a specific session where RLM gave an introduction to statistical analysis to help advisory panel members understand the methodologies being applied in the project and for appraisal of scientific papers. One member of the advisory panel was fully versed with statistical procedures, but welcomed the opportunity to discuss these in further detail. Another member commented: 'I found this a valuable development opportunity which helped me as a LEAP member feel more confident'.

The advisory panel members sometimes found it emotionally demanding, as talking about their personal experiences of managing severe mental illness, decisions around motherhood and medication use involved considerable challenges. This was something that the staff at The McPin Foundation was aware of and provided support for the individual women as necessary.

We plan to continue our work with the advisory panel to develop material for dissemination and will also seek feedback from the advisory panel on the contents of scientific papers arising from this project.

Strengths, limitations and recommendations for future public and patient engagement

We found the experience of working with the advisory panel valuable in many ways. In particular, we have benefited from listening to debates among the members of the advisory panel. We also found it helpful to be able to pose specific questions relating to use of psychotropic medication. It would have been difficult to have had the same level of discussions and insight from the service users had we just had a single individual attending steering group meetings.

A lived experienced advisory panel requires substantial resources and time from both organisers and participants. Over the course of the project we saw changes in the staff at The McPin Foundation who managed the advisory panel and there were periods where members of the advisory panel were less active because of relapse of illness or other demands on their time (work and/or studies). However, despite this, all women took an active part in the advisory panel over the course of the study.

Although the work of the advisory panel informed the development of the project and the discussion and synthesis of the study results, we did not expect direct involvement from the advisory panel in the research process or write up of the project. For future projects involving a LEAP the level of direct engagement in the research process may vary and we recommend that the role and activities of the advisory panel be clearly mapped out at the planning stage and evaluated over the course of the project.

Acknowledgements

Contributions of authors

Irene Petersen (Reader in Epidemiology and Statistics). IP was principal investigator on the project and managed the project on a day-to-day basis. She led the development of the original project protocol, developed data management and analysis plans for the individual studies in collaboration with RLM, CJS and IN. IP drafted the first version of the report with input from the remaining authors. She also led the write-up of the first paper arising from this project and was senior author on the second paper.[46,47] IP first developed the pregnancy and mother–child cohorts that were the basis for this project. She later worked with RLM and CS on further development of the cohorts and to identify and remove duplicates in THIN and the CPRD. IP worked with the LEAP together with RLM and FS.

Rachel L McCrea (Research Associate in Statistics). RLM developed the data management and analysis plans in collaboration with IP, CJS and IN. RLM conducted the data extraction and analysis on the studies described in *Chapter 3* and contributed to the writing of this document. Furthermore, RLM led the write-up of the results from the study on Lithium prescribing during pregnancy for publication in *PLOS ONE*.[46] RLM participated in meetings with the LEAP and provided training for the panel on statistical analysis methodology.

Cormac J Sammon (Research Associate in Epidemiology and Statistics). CJS joined the team in September 2014 and conducted the data extraction and analysis on the studies described in *Chapter 4* and contributed to the writing of this document. He combined the records from THIN and the CPRD, and removed the duplicates. He worked with IP, RLM and IN in developing data management and analysis plans for the individual studies.

David PJ Osborn (Professor of Psychiatry). DO was a coapplicant on the project and a member of the steering committee. He contributed to the discussion and interpretation of the study results from a clinical perspective.

Stephen J Evans (Professor of Statistics). SE was a coapplicant on the project and a member of the steering committee. He contributed to the development of the study design, discussion and interpretation of the study results from a pharmacoepidemiological perspective.

Phillip J Cowen (Professor of Psychiatry) PJC was a coapplicant on the project and a member of the steering committee. He contributed to the discussion and interpretation of the study results from a clinical perspective.

Nick Freemantle (Professor of Clinical Statistics). NF was a coapplicant on the project and a member of the steering committee. He helped in developing the study design and contributed to the discussion of the study results.

Irwin Nazareth (Professor of Primary Care). IN was a coapplicant on the project and a member of the steering committee and project management group. He contributed to the development of the cohort definitions, reviewed Read code lists and contributed to the development of the data management and analysis plans in collaboration with IP, CJS and RLM. He contributed to the discussion and interpretation of the study results from a clinical perspective.

Other contributions and publications

We thank Charlotte Walker, Ceri Dare, Ruth Lambley and Harminder Kaur for providing feedback and input to the project as a member of a LEAP. We would also like to thank Vanessa Pinfold, director of The McPin Foundation, Sarah Hamilton and other members of staff at The McPin Foundation for setting up and managing the LEAP. Finally, we would like to thank Fiona Stevenson (senior lecturer), University College London for supporting meetings with the LEAP.

Publications

The work from this project has so far resulted in two publications:

Petersen I, McCrea RL, Osborn DJP, Evans S, Pinfold V, Cowen PJ, *et al.* Discontinuation of antipsychotic medication in pregnancy: a cohort study. *Schizophr Res* 2014;**59**:218–25.

McCrea RL, Nazareth I, Evans SJW, Osborn DPJ, Pinfold V, Cowen PJ, *et al.* Lithium prescribing during pregnancy: a UK primary care database study. *PLOS ONE* 2015;**10**:e0121024.

Data sharing statement

Data for this study were obtained from THIN primary care database and the CPRD. A licence to the data can be obtained from Cegedim Strategic Data Medical research, for further details please see (www.csdmruk.imshealth.com) or CPRD www.cprd.com/intro.asp. Access to the data is subject to a licence fee.

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Appendix 1 Additional information

Details of combining records from The Health Improvement Network and Clinical Practice Research Datalink

Transformation of Clinical Practice Research Datalink into The Health Improvement Network data format

Although THIN and the CPRD contain data from general practices using similar software for patient management (Vision), the providers of each database restructure their data somewhat differently before releasing it for research use. As a result, before deduplication and analysis could be carried out it was necessary to transform the CPRD and THIN data into a similar format. This was a time-consuming process that required a good knowledge of the structure of both databases (a fact that should be taken into account by any researchers intending to carry out an analysis on a combined CPRD–THIN dataset in the future). Notably, while a single Read code list can be used to identify clinical events in both databases, no common identifiers for therapy (drugs) records and additional health data (AHD) records are available. As a result, separate lists of drug and AHD codes were derived for each database using the same search criteria.

Removal of duplicate practices

The datasets from THIN and the CPRD used in this study contain neither a common patient identifier nor a practice identifier. As a result, straightforward matching of patients on a single variable could not be carried out and alternative means of deduplication had to be pursued. The overlap between the two databases occurs at a practice level, that is, entire practices contribute to either one or both datasets. Our approach was therefore to identify those practices contributing to both datasets and ensure patients from these practices were included only once in the analysis. We combined patient- and practice-level comparisons; making patient-to-patient comparisons of longitudinal clinical records and then assessing whether or not these comparisons indicated the population of patients in the two practices matched to a sufficient extent. First, we identified practices where there was an overlap between individuals based on a subset of 20 Read coded events and their dates per individual. After running this pre-screening step the longitudinal medical record of each of the women in THIN was compared with the longitudinal records of the women in the dataset from the CPRD where we had initially identified an overlap. However, we excluded Read codes from chapter 8 as these are administrative codes which are likely to be common across many patients. We noticed there were a few individuals who matched across two or more practices, but few individuals matched within these practices. After manual review of these records we were able to exclude unlikely matches resulting in the identification of 358 practices which were likely to provide data to both THIN and the CPRD, equivalent to 63% of the THIN practices and 54% of the CPRD practices. We excluded records from THIN where these were duplicated in the CPRD in our further analyses.

Characteristics of women in exposure cohort B2

TABLE 39 Characteristics of women prescribed antipsychotics in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

Characteristics	Exposure cohort		
	A	B2	C
	n (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	670 (100)	322 (100)	318,434 (100)
Age (years)			
Mean (SD)	30 (5.9)	33 (5.9)	30 (5.9)
12–19	21 (3.1)	0 (0)	14,004 (4.4)
20–29	291 (43.4)	107 (33.2)	123,704 (38.8)
30–39	326 (48.7)	175 (54.3)	165,353 (51.9)
40–49	32 (4.8)	40 (12.4)	15,373 (4.8)
Year			
1995–9	42 (6.3)	11 (3.4)	46,548 (14.6)
2000–4	184 (27.5)	44 (13.7)	80,542 (25.3)
2005–9	232 (34.6)	77 (23.9)	99,765 (31.3)
2010–12	212 (31.6)	190 (59)	91,579 (28.8)
Lifestyle variables			
Obesity	73 (10.9)	56 (17.4)	16,979 (5.3)
Illicit drug use	56 (8.4)	35 (10.9)	2002 (0.6)
Alcohol problems	37 (5.5)	18 (5.6)	1624 (0.5)
Smoker	254 (37.9)	152 (47.2)	62,746 (19.7)
BMI (kg/m^2)			
Mean (SD)	27 (6.8)	29 (6.7)	26 (6.3)
Underweight	5 (0.7)	4 (1.2)	3632 (1.1)
Normal weight	89 (13.3)	40 (12.4)	42,138 (13.2)
Overweight	56 (8.4)	39 (12.1)	20,071 (6.3)
Obese	77 (11.5)	63 (19.6)	20,554 (6.5)
Missing	443 (66.1)	176 (54.7)	232,039 (72.9)
Townsend score			
1	24 (13.1)	4 (6.7)	71,024 (23.4)
2	23 (12.6)	10 (16.7)	60,407 (19.9)
3	37 (20.2)	12 (20)	64,868 (21.4)
4	48 (26.2)	14 (23.3)	61,191 (20.2)
5	51 (27.9)	20 (33.3)	45,942 (15.1)
Missing	487 (72.7)	262 (81.4)	15,002 (4.7)

TABLE 39 Characteristics of women prescribed antipsychotics in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Ethnicity			
White	320 (47.8)	176 (54.7)	133,856 (42)
Mixed	2 (0.3)	1 (0.3)	1786 (0.6)
Asian	8 (1.2)	9 (2.8)	9937 (3.1)
Black	7 (1)	12 (3.7)	4615 (1.4)
Other	2 (0.3)	2 (0.6)	1803 (0.6)
Missing	331 (49.4)	122 (37.9)	166,437 (52.3)
Use of psychiatric drugs during exposure period B2			
Hypnotics	32 (4.8)	42 (13)	598 (0.2)
Anticonvulsant mood stabilisers	11 (1.6)	27 (8.4)	1346 (0.4)
Lithium	3 (0.4)	8 (2.5)	13 (0)
Antipsychotics	0 (0)	322 (100)	0 (0)
Antidepressants	145 (21.6)	165 (51.2)	4525 (1.4)
Anxiolytics	22 (3.3)	35 (10.9)	612 (0.2)
Pre-existing medical conditions			
Depression	217 (32.4)	69 (21.4)	20,374 (6.4)
Epilepsy	30 (4.5)	27 (8.4)	4846 (1.5)
SMI	204 (30.4)	220 (68.3)	1480 (0.5)
Pre-existing hypertension	66 (9.9)	46 (14.3)	26,232 (8.2)
Pre-existing diabetes	9 (1.3)	11 (3.4)	2762 (0.9)

SMI, severe mental illness.
Notes
Period B2 refers to the period within 92 days prior to the delivery date.

TABLE 40 Characteristics of women in the mother–child cohort prescribed antipsychotics in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	492 (100)	233 (100)	210,966 (100)
Age (years)			
Mean (SD)	30 (5.7)	33 (5.9)	30 (5.9)
12–19	12 (2.4)	0 (0)	8955 (4.2)
20–29	222 (45.1)	77 (33)	80,491 (38.2)
30–39	236 (48)	124 (53.2)	110,839 (52.5)
40–49	22 (4.5)	32 (13.7)	10,681 (5.1)
Year			
1995–9	25 (5.1)	8 (3.4)	13,339 (6.3)
2000–4	134 (27.2)	25 (10.7)	46,707 (22.1)
2005–9	173 (35.2)	55 (23.6)	77,626 (36.8)
2010–12	160 (32.5)	145 (62.2)	73,294 (34.7)
Lifestyle variables			
Obesity	61 (12.4)	42 (18)	12,766 (6.1)
Illicit drug use	40 (8.1)	26 (11.2)	1354 (0.6)
Alcohol problems	28 (5.7)	14 (6)	1124 (0.5)
Smoker	183 (37.2)	115 (49.4)	42,502 (20.1)
BMI (kg/m^2)			
Mean (SD)	27 (6.8)	29 (6.7)	26 (6.4)
Underweight	5 (1)	3 (1.3)	2494 (1.2)
Normal weight	67 (13.6)	27 (11.6)	29,603 (14)
Overweight	43 (8.7)	29 (12.4)	14,609 (6.9)
Obese	62 (12.6)	48 (20.6)	15,363 (7.3)
Missing	315 (64)	126 (54.1)	148,897 (70.6)
Townsend score			
1	16 (14.5)	3 (7.5)	47,381 (23.5)
2	21 (19.1)	8 (20)	40,309 (20)
3	19 (17.3)	7 (17.5)	43,152 (21.4)
4	25 (22.7)	8 (20)	40,915 (20.3)
5	29 (26.4)	14 (35)	30,120 (14.9)
Missing	382 (77.6)	193 (82.8)	9089 (4.3)

TABLE 40 Characteristics of women in the mother–child cohort prescribed antipsychotics in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Ethnicity			
White	256 (52)	146 (62.7)	104,928 (49.7)
Mixed	2 (0.4)	1 (0.4)	1504 (0.7)
Asian	7 (1.4)	9 (3.9)	7461 (3.5)
Black	3 (0.6)	9 (3.9)	3446 (1.6)
Other	2 (0.4)	1 (0.4)	1350 (0.6)
Missing	222 (45.1)	67 (28.8)	92,277 (43.7)
Use of psychiatric drugs during exposure period B2			
Hypnotics	28 (5.7)	30 (12.9)	423 (0.2)
Anticonvulsant mood stabilisers	9 (1.8)	18 (7.7)	910 (0.4)
Lithium	2 (0.4)	7 (3)	7 (0)
Antipsychotics	0 (0)	233 (100)	0 (0)
Antidepressants	115 (23.4)	118 (50.6)	3277 (1.6)
Anxiolytics	17 (3.5)	21 (9)	373 (0.2)
Pre-existing medical conditions			
Depression	152 (30.9)	54 (23.2)	14,626 (6.9)
Epilepsy	22 (4.5)	15 (6.4)	3254 (1.5)
SMI	144 (29.3)	158 (67.8)	882 (0.4)
Pre-existing hypertension	47 (9.6)	37 (15.9)	19,570 (9.3)
Pre-existing diabetes	6 (1.2)	8 (3.4)	2005 (1)

SMI, severe mental illness.
Notes
Period B2 refers to the period within 92 days prior to the delivery date.

TABLE 41 Characteristics of women prescribed lithium in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	57 (100)	18 (100)	212,531 (100)
Age (years)			
Mean (SD)	34 (5.1)	35 (6.6)	30 (5.9)
12–19	0 (0)	0 (0)	8975 (4.2)
20–29	14 (24.6)	4 (22.2)	81,287 (38.2)
30–39	37 (64.9)	10 (55.6)	111,496 (52.5)
40–49	6 (10.5)	4 (22.2)	10,773 (5.1)
Year			
1995–9	7 (12.3)	2 (11.1)	13,427 (6.3)
2000–4	17 (29.8)	4 (22.2)	47,128 (22.2)
2005–9	20 (35.1)	5 (27.8)	78,169 (36.8)
2010–12	13 (22.8)	7 (38.9)	73,807 (34.7)
Lifestyle variables			
Obesity	8 (14)	4 (22.2)	12,982 (6.1)
Illicit drug use	2 (3.5)	0 (0)	1453 (0.7)
Alcohol problems	3 (5.3)	2 (11.1)	1188 (0.6)
Smoker	15 (26.3)	7 (38.9)	43,146 (20.3)
BMI (kg/m^2)			
Mean (SD)	27 (6.1)	29 (4.5)	26 (6.4)
Underweight	0 (0)	0 (0)	2565 (1.2)
Normal weight	8 (14)	3 (16.7)	29,842 (14)
Overweight	5 (8.8)	3 (16.7)	14,713 (6.9)
Obese	8 (14)	4 (22.2)	15,619 (7.3)
Missing	36 (63.2)	8 (44.4)	149,792 (70.5)
Townsend score			
1	1 (8.3)	0 (0)	47,623 (23.4)
2	3 (25)	0 (0)	40,530 (19.9)
3	3 (25)	3 (75)	43,385 (21.3)
4	3 (25)	1 (25)	41,380 (20.3)
5	2 (16.7)	0 (0)	30,492 (15)
Missing	45 (78.9)	14 (77.8)	9121 (4.3)

TABLE 41 Characteristics of women prescribed lithium in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Ethnicity			
White	26 (45.6)	13 (72.2)	105,638 (49.7)
Mixed	0 (0)	0 (0)	1505 (0.7)
Asian	1 (1.8)	1 (5.6)	7476 (3.5)
Black	1 (1.8)	0 (0)	3455 (1.6)
Other	0 (0)	0 (0)	1360 (0.6)
Missing	29 (50.9)	4 (22.2)	93,097 (43.8)
Use of psychiatric drugs during exposure period B2			
Hypnotics	3 (5.3)	2 (11.1)	472 (0.2)
Anticonvulsant mood stabilisers	3 (5.3)	0 (0)	932 (0.4)
Lithium	0 (0)	18 (100)	0 (0)
Antipsychotics	11 (19.3)	8 (44.4)	218 (0.1)
Antidepressants	16 (28.1)	9 (50)	3574 (1.7)
Anxiolytics	2 (3.5)	3 (16.7)	415 (0.2)
Pre-existing medical conditions			
Depression	17 (29.8)	0 (0)	15,100 (7.1)
Epilepsy	2 (3.5)	2 (11.1)	3296 (1.6)
SMI	40 (70.2)	17 (94.4)	1168 (0.5)
Pre-existing hypertension	6 (10.5)	2 (11.1)	19,634 (9.2)
Pre-existing diabetes	3 (5.3)	2 (11.1)	2022 (1)

SMI, severe mental illness.
Notes
Period B2 refers to the period within 92 days prior to the delivery date.

TABLE 42 Characteristics of women in the mother–child cohort prescribed lithium in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	84 (100)	20 (100)	320,853 (100)
Age (years)			
Mean (SD)	33 (5.3)	35 (6.3)	30 (5.9)
12–19	1 (1.2)	0 (0)	14,034 (4.4)
20–29	22 (26.2)	4 (20)	124,982 (39)
30–39	53 (63.1)	12 (60)	166,294 (51.8)
40–49	8 (9.5)	4 (20)	15,543 (4.8)
Year			
1995–9	13 (15.5)	2 (10)	46,855 (14.6)
2000–4	26 (31)	4 (20)	81,190 (25.3)
2005–9	29 (34.5)	5 (25)	100,574 (31.3)
2010–12	16 (19)	9 (45)	92,234 (28.7)
Lifestyle variables			
Obesity	9 (10.7)	4 (20)	17,241 (5.4)
Illicit drug use	6 (7.1)	0 (0)	2167 (0.7)
Alcohol problems	4 (4.8)	2 (10)	1718 (0.5)
Smoker	24 (28.6)	7 (35)	63,778 (19.9)
BMI (kg/m^2)			
Mean (SD)	27 (5.5)	28 (4.5)	26 (6.3)
Underweight	0 (0)	0 (0)	3741 (1.2)
Normal weight	10 (11.9)	4 (20)	42,462 (13.2)
Overweight	9 (10.7)	3 (15)	20,246 (6.3)
Obese	9 (10.7)	4 (20)	20,870 (6.5)
Missing	56 (66.7)	9 (45)	233,534 (72.8)
Townsend score			
1	3 (17.6)	0 (0)	71,307 (23.3)
2	3 (17.6)	0 (0)	60,753 (19.9)
3	4 (23.5)	3 (60)	65,291 (21.4)
4	5 (29.4)	1 (20)	61,850 (20.2)
5	2 (11.8)	1 (20)	46,548 (15.2)
Missing	67 (79.8)	15 (75)	15,104 (4.7)

TABLE 42 Characteristics of women in the mother–child cohort prescribed lithium in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Ethnicity			
White	35 (41.7)	15 (75)	134,809 (42)
Mixed	0 (0)	0 (0)	1788 (0.6)
Asian	1 (1.2)	1 (5)	9978 (3.1)
Black	1 (1.2)	0 (0)	4641 (1.4)
Other	0 (0)	0 (0)	1822 (0.6)
Missing	47 (56)	4 (20)	167,815 (52.3)
Use of psychiatric drugs during exposure period B2			
Hypnotics	5 (6)	2 (10)	690 (0.2)
Anticonvulsant mood stabilisers	5 (6)	0 (0)	1389 (0.4)
Lithium	0 (0)	20 (100)	0 (0)
Antipsychotics	15 (17.9)	8 (40)	336 (0.1)
Antidepressants	25 (29.8)	9 (45)	4983 (1.6)
Anxiolytics	3 (3.6)	3 (15)	683 (0.2)
Pre-existing medical conditions			
Depression	23 (27.4)	0 (0)	21,084 (6.6)
Epilepsy	3 (3.6)	2 (10)	4925 (1.5)
SMI	57 (67.9)	19 (95)	1945 (0.6)
Pre-existing hypertension	8 (9.5)	2 (10)	26,362 (8.2)
Pre-existing diabetes	3 (3.6)	2 (10)	2803 (0.9)

SMI, severe mental illness.
Notes
Period B2 refers to the period within 92 days prior to the delivery date.

TABLE 43 Characteristics of women with a record of psychoses or depression prescribed anticonvulsant mood stabilisers in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	131 (100)	22 (100)	318,612 (100)
Age (years)			
Mean (SD)	32 (5.5)	32 (4.9)	30 (5.9)
12–19	2 (1.5)	0 (0)	14,008 (4.4)
20–29	43 (32.8)	5 (22.7)	123,740 (38.8)
30–39	77 (58.8)	17 (77.3)	165,396 (51.9)
40–49	9 (6.9)	0 (0)	15,468 (4.9)
Year			
1995–9	3 (2.3)	1 (4.5)	46,638 (14.6)
2000–4	17 (13)	4 (18.2)	80,466 (25.3)
2005–9	54 (41.2)	10 (45.5)	100,009 (31.4)
2010–12	57 (43.5)	7 (31.8)	91,499 (28.7)
Lifestyle variables			
Obesity	14 (10.7)	6 (27.3)	17,058 (5.4)
Illicit drug use	8 (6.1)	1 (4.5)	2110 (0.7)
Alcohol problems	7 (5.3)	1 (4.5)	1653 (0.5)
Smoker	49 (37.4)	11 (50)	63,085 (19.8)
BMI (kg/m²)			
Mean (SD)	27 (5.5)	33 (4.1)	26 (6.3)
Underweight	2 (1.5)	0 (0)	3685 (1.2)
Normal weight	18 (13.7)	0 (0)	42,093 (13.2)
Overweight	20 (15.3)	0 (0)	20,083 (6.3)
Obese	14 (10.7)	6 (27.3)	18,018 (5.7)
Missing	77 (58.8)	16 (72.7)	234,733 (73.7)
Townsend score			
1	5 (20)	0 (0)	70,879 (23.3)
2	2 (8)	1 (20)	60,417 (19.9)
3	5 (20)	2 (40)	64,877 (21.4)
4	9 (36)	2 (40)	61,357 (20.2)
5	4 (16)	0 (0)	46,074 (15.2)
Missing	106 (80.9)	17 (77.3)	15,008 (4.7)

TABLE 43 Characteristics of women with a record of psychoses or depression prescribed anticonvulsant mood stabilisers in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Ethnicity			
White	50 (38.2)	8 (36.4)	133,929 (42)
Mixed	2 (1.5)	0 (0)	1772 (0.6)
Asian	4 (3.1)	0 (0)	9943 (3.1)
Black	14 (10.7)	1 (4.5)	4619 (1.4)
Other	1 (0.8)	0 (0)	1827 (0.6)
Missing	60 (45.8)	13 (59.1)	166,522 (52.3)
Use of psychiatric drugs during exposure period B2			
Hypnotics	6 (4.6)	4 (18.2)	670 (0.2)
Anticonvulsant mood stabilisers	0 (0)	22 (100)	145 (0)
Lithium	2 (1.5)	0 (0)	24 (0)
Antipsychotics	29 (22.1)	12 (54.5)	301 (0.1)
Antidepressants	36 (27.5)	13 (59.1)	4872 (1.5)
Anxiolytics	4 (3.1)	2 (9.1)	645 (0.2)
Pre-existing medical conditions			
Depression	61 (46.6)	5 (22.7)	20,722 (6.5)
Epilepsy	0 (0)	0 (0)	3268 (1)
SMI	88 (67.2)	20 (90.9)	1840 (0.6)
Pre-existing hypertension	16 (12.2)	2 (9.1)	26,228 (8.2)
Pre-existing diabetes	2 (1.5)	1 (4.5)	2767 (0.9)

SMI, severe mental illness.
Notes
Period B2 refers to the period within 92 days prior to the delivery date.

TABLE 44 Characteristics of women in the mother–child cohort with a record of psychoses or depression prescribed anticonvulsant mood stabilisers in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	103 (100)	16 (100)	211,112 (100)
Age (years)			
Mean (SD)	31 (5.3)	32 (4.9)	30 (5.9)
12–19	2 (1.9)	0 (0)	8951 (4.2)
20–29	35 (34)	4 (25)	80,581 (38.2)
30–39	61 (59.2)	12 (75)	110,873 (52.5)
40–49	5 (4.9)	0 (0)	10,707 (5.1)
Year			
1995–9	2 (1.9)	1 (6.3)	13,389 (6.3)
2000–4	13 (12.6)	4 (25)	46,601 (22.1)
2005–9	39 (37.9)	6 (37.5)	77,886 (36.9)
2010–12	49 (47.6)	5 (31.3)	73,236 (34.7)
Lifestyle variables			
Obesity	12 (11.7)	5 (31.3)	12,831 (6.1)
Illicit drug use	6 (5.8)	0 (0)	1419 (0.7)
Alcohol problems	4 (3.9)	0 (0)	1125 (0.5)
Smoker	39 (37.9)	8 (50)	42,707 (20.2)
BMI (kg/m²)			
Mean (SD)	28 (5.7)	33 (4.5)	26 (6.4)
Underweight	1 (1)	0 (0)	2522 (1.2)
Normal weight	14 (13.6)	0 (0)	29,546 (14)
Overweight	18 (17.5)	0 (0)	14,628 (6.9)
Obese	12 (11.7)	5 (31.3)	13,596 (6.4)
Missing	58 (56.3)	11 (68.8)	150,820 (71.4)
Townsend score			
1	5 (22.7)	0 (0)	47,305 (23.4)
2	2 (9.1)	1 (25)	40,308 (20)
3	4 (18.2)	1 (25)	43,152 (21.4)
4	8 (36.4)	2 (50)	41,067 (20.3)
5	3 (13.6)	0 (0)	30,207 (15)
Missing	81 (78.6)	12 (75)	9073 (4.3)

TABLE 44 Characteristics of women in the mother–child cohort with a record of psychoses or depression prescribed anticonvulsant mood stabilisers in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Ethnicity			
White	48 (46.6)	6 (37.5)	104,998 (49.7)
Mixed	2 (1.9)	0 (0)	1489 (0.7)
Asian	3 (2.9)	0 (0)	7468 (3.5)
Black	10 (9.7)	1 (6.3)	3434 (1.6)
Other	1 (1)	0 (0)	1375 (0.7)
Missing	39 (37.9)	9 (56.3)	92,348 (43.7)
Use of psychiatric drugs during exposure period B2			
Hypnotics	5 (4.9)	3 (18.8)	454 (0.2)
Anticonvulsant mood stabilisers	0 (0)	16 (100)	97 (0)
Lithium	1 (1)	0 (0)	13 (0)
Antipsychotics	21 (20.4)	9 (56.3)	197 (0.1)
Antidepressants	27 (26.2)	8 (50)	3509 (1.7)
Anxiolytics	3 (2.9)	1 (6.3)	393 (0.2)
Pre-existing medical conditions			
Depression	46 (44.7)	5 (31.3)	14,879 (7)
Epilepsy	0 (0)	0 (0)	2186 (1)
SMI	71 (68.9)	14 (87.5)	1093 (0.5)
Pre-existing hypertension	12 (11.7)	1 (6.3)	19,570 (9.3)
Pre-existing diabetes	1 (1)	0 (0)	1998 (0.9)

SMI, severe mental illness.
Notes
Period B2 refers to the period within 92 days prior to the delivery date.

TABLE 45 Characteristics of women prescribed anticonvulsant mood stabilisers, including all women irrespective of indication, in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	558 (100)	1375 (100)	318,612 (100)
Age (years)			
Mean (SD)	30 (5.8)	30 (5.6)	30 (5.9)
12–19	24 (4.3)	50 (3.6)	14,008 (4.4)
20–29	237 (42.5)	563 (40.9)	123,740 (38.8)
30–39	276 (49.5)	705 (51.3)	165,396 (51.9)
40–49	21 (3.8)	57 (4.1)	15,468 (4.9)
Year			
1995–9	41 (7.3)	175 (12.7)	46,638 (14.6)
2000–4	114 (20.4)	320 (23.3)	80,466 (25.3)
2005–9	218 (39.1)	486 (35.3)	100,009 (31.4)
2010–12	185 (33.2)	394 (28.7)	91,499 (28.7)
Lifestyle variables			
Obesity	45 (8.1)	110 (8)	17,058 (5.4)
Illicit drug use	17 (3)	18 (1.3)	2110 (0.7)
Alcohol problems	12 (2.2)	14 (1)	1653 (0.5)
Smoker	185 (33.2)	315 (22.9)	63,085 (19.8)
BMI (kg/m²)			
Mean (SD)	27 (6.8)	27 (6.2)	26 (6.3)
Underweight	6 (1.1)	12 (0.9)	3685 (1.2)
Normal weight	73 (13.1)	158 (11.5)	42,093 (13.2)
Overweight	47 (8.4)	117 (8.5)	20,083 (6.3)
Obese	47 (8.4)	112 (8.1)	18,018 (5.7)
Missing	385 (69)	976 (71)	234,733 (73.7)
Townsend score			
1	19 (18.8)	43 (19.2)	70,879 (23.3)
2	19 (18.8)	32 (14.3)	60,417 (19.9)
3	16 (15.8)	51 (22.8)	64,877 (21.4)
4	23 (22.8)	50 (22.3)	61,357 (20.2)
5	24 (23.8)	48 (21.4)	46,074 (15.2)
Missing	457 (81.9)	1151 (83.7)	15,008 (4.7)

TABLE 45 Characteristics of women prescribed anticonvulsant mood stabilisers, including all women irrespective of indication, in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Ethnicity			
White	222 (39.8)	541 (39.3)	133,929 (42)
Mixed	2 (0.4)	6 (0.4)	1772 (0.6)
Asian	9 (1.6)	21 (1.5)	9943 (3.1)
Black	51 (9.1)	114 (8.3)	4619 (1.4)
Other	2 (0.4)	14 (1)	1827 (0.6)
Missing	272 (48.7)	679 (49.4)	166,522 (52.3)
Use of psychiatric drugs during exposure period B2			
Hypnotics	19 (3.4)	28 (2)	670 (0.2)
Anticonvulsant mood stabilisers	41 (7.3)	1375 (100)	145 (0)
Lithium	3 (0.5)	0 (0)	24 (0)
Antipsychotics	35 (6.3)	22 (1.6)	301 (0.1)
Antidepressants	72 (12.9)	68 (4.9)	4872 (1.5)
Anxiolytics	7 (1.3)	23 (1.7)	645 (0.2)
Pre-existing medical conditions			
Depression	87 (15.6)	106 (7.7)	20,722 (6.5)
Epilepsy	249 (44.6)	1326 (96.4)	3268 (1)
SMI	97 (17.4)	38 (2.8)	1840 (0.6)
Pre-existing hypertension	69 (12.4)	135 (9.8)	26,228 (8.2)
Pre-existing diabetes	4 (0.7)	20 (1.5)	2767 (0.9)

SMI, severe mental illness.
Notes
Period B2 refers to the period within 92 days prior to the delivery date.

TABLE 46 Characteristics of women in the mother–child cohort prescribed anticonvulsant mood stabilisers, including all women irrespective of indication, in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Total	429 (100)	999 (100)	211,112 (100)
Age (years)			
Mean (SD)	30 (5.7)	30 (5.5)	30 (5.9)
12–19	19 (4.4)	37 (3.7)	8951 (4.2)
20–29	181 (42.2)	394 (39.4)	80,581 (38.2)
30–39	217 (50.6)	529 (53)	110,873 (52.5)
40–49	12 (2.8)	39 (3.9)	10,707 (5.1)
Year			
1995–9	24 (5.6)	112 (11.2)	13,389 (6.3)
2000–4	83 (19.3)	218 (21.8)	46,601 (22.1)
2005–9	168 (39.2)	363 (36.3)	77,886 (36.9)
2010–12	154 (35.9)	306 (30.6)	73,236 (34.7)
Lifestyle variables			
Obesity	38 (8.9)	88 (8.8)	12,831 (6.1)
Illicit drug use	10 (2.3)	13 (1.3)	1419 (0.7)
Alcohol problems	9 (2.1)	6 (0.6)	1125 (0.5)
Smoker	139 (32.4)	224 (22.4)	42,707 (20.2)
BMI (kg/m^2)			
Mean (SD)	27 (6.7)	27 (6.5)	26 (6.4)
Underweight	4 (0.9)	11 (1.1)	2522 (1.2)
Normal weight	54 (12.6)	120 (12)	29,546 (14)
Overweight	36 (8.4)	85 (8.5)	14,628 (6.9)
Obese	39 (9.1)	90 (9)	13,596 (6.4)
Missing	296 (69)	693 (69.4)	150,820 (71.4)
Townsend score			
1	11 (16.7)	23 (15.2)	47,305 (23.4)
2	16 (24.2)	20 (13.2)	40,308 (20)
3	10 (15.2)	34 (22.5)	43,152 (21.4)
4	17 (25.8)	38 (25.2)	41,067 (20.3)
5	12 (18.2)	36 (23.8)	30,207 (15)
Missing	363 (84.6)	848 (84.9)	9073 (4.3)

TABLE 46 Characteristics of women in the mother–child cohort prescribed anticonvulsant mood stabilisers, including all women irrespective of indication, in pregnancy (cohort B2) vs. women who discontinued (cohort A) and women not prescribed antipsychotics (cohort C) (*continued*)

	Exposure cohort		
	A	B2	C
Characteristics	*n* (% or SD)	*n* (% or SD)	*n* (% or SD)
Ethnicity			
White	196 (45.7)	419 (41.9)	104,998 (49.7)
Mixed	2 (0.5)	6 (0.6)	1489 (0.7)
Asian	7 (1.6)	16 (1.6)	7468 (3.5)
Black	36 (8.4)	94 (9.4)	3434 (1.6)
Other	2 (0.5)	8 (0.8)	1375 (0.7)
Missing	186 (43.4)	456 (45.6)	92,348 (43.7)
Use of psychiatric drugs during exposure period B2			
Hypnotics	13 (3)	23 (2.3)	454 (0.2)
Anticonvulsant mood stabilisers	32 (7.5)	999 (100)	97 (0)
Lithium	1 (0.2)	0 (0)	13 (0)
Antipsychotics	27 (6.3)	16 (1.6)	197 (0.1)
Antidepressants	51 (11.9)	50 (5)	3509 (1.7)
Anxiolytics	4 (0.9)	16 (1.6)	393 (0.2)
Pre-existing medical conditions			
Depression	68 (15.9)	78 (7.8)	14,879 (7)
Epilepsy	192 (44.8)	964 (96.5)	2186 (1)
SMI	78 (18.2)	28 (2.8)	1093 (0.5)
Pre-existing hypertension	54 (12.6)	110 (11)	19,570 (9.3)
Pre-existing diabetes	2 (0.5)	16 (1.6)	1998 (0.9)

SMI, severe mental illness.

Notes

Period B2 refers to the period within 92 days prior to the delivery date.

Results on relative risks for health, lifestyle and concomitant medication in the fully adjusted models in *Chapter 4, Results*

TABLE 47 Adjusted relative risks of maternal outcomes in the antipsychotic exposed cohorts

	Cohort B1 vs. cohort A		Cohort B1 vs. cohort C	
Maternal outcomes	RR_{adj}	95% CI	RR_{adj}	95% CI
Gestational hypertension and/or pre-eclampsia				
Cohort comparison	0.69	0.37 to 1.29	1.24	0.79 to 1.96
Age (tertiles)				
1	1		1	
2	1.11	0.54 to 2.30	0.99	0.94 to 1.04
3	1.17	0.55 to 2.47	**1.19**	**1.13 to 1.24**
Lifestyle variables				
Obesity	2.37	**1.27 to 4.41**	**1.92**	**1.80 to 2.06**
Alcohol problems	1.27	0.43 to 3.74	0.77	0.56 to 1.07
Smoker	0.92	0.52 to 1.63	0.83	0.78 to 0.88
Illicit drug use	1.49	0.68 to 3.28	0.94	0.72 to 1.22
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs	2.26	**1.19 to 4.29**	**1.20**	**1.05 to 1.37**
Antiepileptic drugs	1.02	0.35 to 2.98	1.13	0.85 to 1.51
Gestational diabetes				
Cohort comparison	**0.43**	**0.20 to 0.933**	0.95	0.53 to 1.69
Age (tertiles)				
1	1		1	
2	2.17	0.71 to 6.61	**1.59**	**1.48 to 1.71**
3	**3.17**	**1.01 to 9.90**	**2.46**	**2.30 to 2.64**
Lifestyle variables				
Obesity	**5.49**	**2.67 to 11.2**	**3.32**	**3.08 to 3.57**
Alcohol problems	0.50	0.07 to 3.56	0.92	0.61 to 1.37
Smoker	1.39	0.64 to 3.02	0.86	0.80, 0.93
Illicit drug use			1.21	0.87 to 1.67
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs	**3.73**	**1.75 to 7.96**	**1.51**	**1.29 to 1.75**
Antiepileptic drugs	1.54	0.53 to 4.45	0.96	0.65 to 1.42

TABLE 47 Adjusted relative risks of maternal outcomes in the antipsychotic exposed cohorts (*continued*)

Maternal outcomes	Cohort B1 vs. cohort A		Cohort B1 vs. cohort C	
	RR_{adj}	95% CI	RR_{adj}	95% CI
Caesarean section				
Cohort comparison	1.05	0.82 to 1.34	1.09	0.92 to 1.30
Age (tertiles)				
1	1		1	
2	1.23	0.89 to 1.68	**1.32**	**1.29 to 1.34**
3	**1.79**	**1.34 to 2.40**	**1.67**	**1.64 to 1.70**
Lifestyle variables				
Obesity	**1.45**	**1.10 to 1.90**	**1.55**	**1.51 to 1.59**
Alcohol problems	0.97	0.61 to 1.54	0.98	0.88 to 1.09
Smoker	0.99	0.78 to 1.25	0.98	0.96 to 1.00
Illicit drug use	1.21	0.85 to 1.72	0.98	0.89 to 1.08
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs	0.95	0.74 to 1.22	**1.16**	**1.10 to 1.21**
Antiepileptic drugs	1.02	0.64 to 1.62	**1.17**	**1.06 to 1.29**
Perinatal death				
Cohort comparison			0.94	0.22 to 3.88
Age (tertiles)				
1			1	
2			0.93	0.79 to 1.09
3			**1.26**	**1.08 to 1.46**
Lifestyle variables				
Obesity			**1.50**	**1.18 to 1.89**
Alcohol problems			**2.35**	**1.37 to 4.01**
Smoker			**1.49**	**1.28 to 1.73**
Illicit drug use			1.07	0.54 to 2.10
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs			1.41	0.97 to 2.05
Antiepileptic drugs			1.39	0.61 to 3.13

RR_{adj}, adjusted relative risk.
Notes
Bold indicates statistical significance.
Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

TABLE 48 Adjusted relative risks of child outcomes in the antipsychotic exposed cohorts

	Cohort B1 vs. cohort A		Cohort B1 vs. cohort C	
Child outcomes	RR_{adj}	95% CI	RR_{adj}	95% CI
Major congenital malformations				
Cohort comparison	1.79	0.72 to 4.47	1.59	0.84 to 3.00
Age (tertiles)				
1	1		1	
2	1.33	0.42 to 4.16	0.92	0.86 to 1.00
3	1.28	0.41 to 3.96	1.01	0.94 to 1.09
Lifestyle variables				
Obesity	0.57	0.13 to 2.53	0.99	0.87 to 1.12
Alcohol problems			1.10	0.75 to 1.62
Smoker	0.14	0.03 to 0.623	1.03	0.95 to 1.11
Illicit drug use			1.03	0.72 to 1.48
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs	0.89	0.37 to 2.17	1.01	0.82 to 1.24
Antiepileptic drugs			**1.68**	**1.18 to 2.40**
Poor birth outcomes				
Cohort comparison	**1.83**	**1.05 to 3.20**	1.39	0.98 to 1.97
Age (tertiles)				
1	1		1	
2	1.08	0.55 to 2.12	0.93	0.88 to 0.982
3	1.28	0.67 to 2.45	1.04	0.99 to 1.09
Lifestyle variables				
Obesity	0.80	0.38 to 1.65	**1.11**	**1.03 to 1.20**
Alcohol problems	0.34	0.08 to 1.35	**1.31**	**1.07 to 1.61**
Smoker	1.06	0.62 to 1.80	**1.37**	**1.31 to 1.44**
Illicit drug use	**2.14**	**1.15 to 3.98**	**1.86**	**1.58 to 2.18**
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs	1.38	0.79 to 2.41	**1.54**	**1.39 to 1.72**
Antiepileptic drugs	1.27	0.53 to 3.00	**1.35**	**1.06 to 1.72**

TABLE 48 Adjusted relative risks of child outcomes in the antipsychotic exposed cohorts (*continued*)

	Cohort B1 vs. cohort A		Cohort B1 vs. cohort C	
Child outcomes	RR_{adj}	95% CI	RR_{adj}	95% CI
Transient poor birth outcomes				
Cohort comparison	1.20	0.57 to 2.53	1.59	0.92 to 2.74
Age (tertiles)				
1	1		1	
2	1.66	0.73 to 3.75	0.85	0.79 to 0.913
3	1.06	0.42 to 2.62	0.92	0.85 to 0.987
Lifestyle variables				
Obesity	1.61	0.74 to 3.52	**1.45**	**1.30 to 1.60**
Alcohol problems	1.76	0.53 to 5.87	**1.36**	**1.01 to 1.85**
Smoker	1.48	0.74 to 2.96	**1.26**	**1.17 to 1.35**
Illicit drug use	0.77	0.25 to 2.39	**1.78**	**1.39 to 2.28**
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs	0.78	0.38 to 1.61	**1.48**	**1.24 to 1.78**
Antiepileptic drugs	3.62	1.29 to 10.1	**1.70**	**1.23 to 2.34**
Neurodevelopmental/behavioural disorders				
Cohort comparison	0.83	0.49 to 1.39	1.22	0.80 to 1.84
Age (tertiles)				
1	1		1	
2	0.60	0.33 to 1.07	0.94	0.89 to 0.988
3	0.85	0.51 to 1.41	1.00	0.96 to 1.05
Lifestyle variables				
Obesity	0.93	0.48 to 1.81	**1.15**	**1.07 to 1.24**
Alcohol problems	1.69	0.84 to 3.40	1.14	0.90 to 1.43
Smoker	1.11	0.70 to 1.76	**1.16**	**1.11 to 1.21**
Illicit drug use	1.45	0.77 to 2.75	1.01	0.80 to 1.26
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs	0.65	0.37 to 1.11	**1.26**	**1.12 to 1.42**
Antiepileptic drugs	0.95	0.31 to 2.95	**1.52**	**1.21 to 1.92**

RR_{adj}, adjusted relative risk.

Notes

Bold indicates statistical significance.

Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

TABLE 49 Adjusted relative risks of maternal outcomes in the anticonvulsant mood stabilisers exposed cohorts

	Cohort B1 vs. cohort A		Cohort B1 vs. cohort C	
Maternal outcomes	RR_{adj}	95% CI	RR_{adj}	CI95
Gestational hypertension and/or pre-eclampsia				
Cohort comparison	1.34	0.76 to 2.36	1.22	0.95 to 1.58
Age (tertiles)				
1	1		1	0
2	0.93	0.53 to 1.63	0.97	0.92 to 1.02
3	1.23	0.69 to 2.20	**1.17**	**1.11 to 1.22**
Lifestyle variables				
Obesity	**2.66**	**1.53 to 4.61**	**1.91**	**1.78 to 2.04**
Alcohol problems	1.02	0.11 to 8.77	0.67	0.47 to 0.952
Smoker	0.61	0.33 to 1.13	0.81	0.77 to 0.865
Illicit drug use	1.52	0.38 to 6.10	1.04	0.81 to 1.34
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs, lithium or antipsychotics	1.14	0.59 to 2.20	**1.21**	**1.07 to 1.38**
Gestational diabetes				
Cohort comparison	2.17	0.93 to 5.10	1.26	0.90 to 1.76
Age (tertiles)				
1	1		1	0
2	1.16	0.49 to 2.77	**1.59**	**1.48 to 1.72**
3	**2.40**	**1.05 to 5.46**	**2.48**	**2.31 to 2.66**
Lifestyle variables				
Obesity	2.05	0.95 to 4.41	**3.26**	**3.03 to 3.51**
Alcohol problems			0.86	0.57 to 1.30
Smoker	0.42	0.16 to 1.12	0.87	0.81 to 0.942
Illicit drug use			1.24	0.90 to 1.69
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs, lithium or antipsychotics	**3.20**	**1.61 to 6.35**	**1.49**	**1.29 to 1.72**

TABLE 49 Adjusted relative risks of maternal outcomes in the anticonvulsant mood stabilisers exposed cohorts (*continued*)

	Cohort B1 vs. cohort A		Cohort B1 vs. cohort C	
Maternal outcomes	**RR_{adj}**	**95% CI**	**RR_{adj}**	**CI95**
Caesarean section				
Cohort comparison	1.07	0.88 to 1.30	**1.14**	**1.04 to 1.26**
Age (tertiles)				
1	1		1	0
2	**1.27**	**1.02 to 1.59**	**1.32**	**1.29 to 1.34**
3	**1.86**	**1.50 to 2.32**	**1.67**	**1.64 to 1.70**
Lifestyle variables				
Obesity	**1.49**	**1.16 to 1.89**	**1.55**	**1.51 to 1.59**
Alcohol problems	0.56	0.23 to 1.38	0.98	0.89 to 1.09
Smoker	0.89	0.73 to 1.09	0.98	0.96 to 0.998
Illicit drug use	1.02	0.54 to 1.92	1.02	0.93 to 1.12
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs, lithium or antipsychotics	1.16	0.91 to 1.49	**1.18**	**1.13 to 1.23**
Perinatal death				
Cohort comparison			1.42	0.67 to 2.99
Age (tertiles)				
1			1	0
2			0.95	0.81 to 1.11
3			**1.28**	**1.10 to 1.49**
Lifestyle variables				
Obesity			**1.54**	**1.22 to 1.94**
Alcohol problems			**1.91**	**1.07 to 3.40**
Smoker			**1.45**	**1.25 to 1.68**
Illicit drug use			1.31	0.71 to 2.39
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs, lithium or antipsychotics			1.41	0.98 to 2.02

RR_{adj}, adjusted relative risk.

Notes

Bold indicates statistical significance.

Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

TABLE 50 Adjusted relative risks of child outcomes in the anticonvulsant mood stabilisers exposed cohorts

Child outcomes	Cohort B1 vs. cohort A		Cohort B1 vs. cohort C	
	RR_{adj}	95% CI	RR_{adj}	95% CI
Major congenital malformations				
Cohort comparison	1.89	0.93 to 3.85	**2.05**	**1.53 to 2.74**
Age (tertiles)				
1	1		1	0
2	0.79	0.41 to 1.53	0.91	0.84 to 0.982
3	1.36	0.74 to 2.51	1.03	0.95 to 1.10
Lifestyle variables				
Obesity	0.39	0.09 to 1.63	1.06	0.93 to 1.19
Alcohol problems			1.18	0.81 to 1.70
Smoker	0.87	0.46 to 1.67	1.03	0.96 to 1.12
Illicit drug use			1.09	0.78 to 1.54
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs, lithium or antipsychotics	0.71	0.26 to 1.97	1.14	0.95 to 1.38
Poor birth outcomes				
Cohort comparison	1.25	0.78 to 2.01	**1.33**	**1.06 to 1.67**
Age (tertiles)				
1	1		1	0
2	0.85	0.50 to 1.43	0.94	0.90,.994
3	1.72	1.07 to 2.76	1.04	0.99 to 1.10
Lifestyle variables				
Obesity	1.28	0.69 to 2.37	**1.13**	**1.04 to 1.22**
Alcohol problems	1.01	0.26 to 3.80	**1.31**	**1.06 to 1.60**
Smoker	**1.85**	**1.20 to 2.85**	**1.37**	**1.30 to 1.43**
Illicit drug use	1.63	0.62 to 4.26	**1.89**	**1.61 to 2.21**
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs, lithium or antipsychotics	1.28	0.76 to 2.15	**1.54**	**1.39 to 1.70**

TABLE 50 Adjusted relative risks of child outcomes in the anticonvulsant mood stabilisers exposed cohorts (*continued*)

Child outcomes	Cohort B1 vs. cohort A		Cohort B1 vs. cohort C	
	RR_{adj}	95% CI	RR_{adj}	95% CI
Transient poor birth outcomes				
Cohort comparison	1.28	0.73 to 2.26	**1.71**	**1.28 to 2.29**
Age (tertiles)				
1	1		1	0
2	0.55	0.28 to 1.07	0.87	0.81 to 0.934
3	1.25	0.70 to 2.20	0.90	0.84 to 0.972
Lifestyle variables				
Obesity	1.47	0.67 to 3.24	1.43	1.29 to 1.58
Alcohol problems			1.26	0.93 to 1.72
Smoker	**2.71**	**1.61 to 4.53**	**1.24**	**1.16 to 1.33**
Illicit drug use	1.81	0.59 to 5.54	**1.85**	**1.46 to 2.34**
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs, lithium or antipsychotics	1.52	0.79 to 2.93	**1.48**	**1.27 to 1.72**
Neurodevelopmental/behavioural disorders				
Cohort comparison	1.10	0.75 to 1.61	**1.73**	**1.42 to 2.09**
Age (tertiles)				
1	1		1	0
2	1.07	0.72 to 1.59	0.94	0.89, 0.985
3	0.97	0.63 to 1.49	1.00	0.95 to 1.04
Lifestyle variables				
Obesity	0.96	0.53 to 1.74	**1.14**	**1.06 to 1.23**
Alcohol problems	1.21	0.33 to 4.46	1.15	0.91 to 1.44
Smoker	1.01	0.68 to 1.50	**1.16**	**1.11 to 1.22**
Illicit drug use	0.96	0.25 to 3.57	1.07	0.87 to 1.32
Use of psychiatric drugs during exposure period B1				
Antidepressant drugs, lithium or antipsychotics	0.60	0.30 to 1.23	**1.31**	**1.17 to 1.46**

RR_{adj}, adjusted relative risk.

Notes

Bold indicates statistical significance.

Period B1 refers to the period between 31 and 105 days (inclusive) after the start of pregnancy.

Sensitivity analysis exploring the potential impact of excluding non-live births

In an ideal study of adverse pregnancy outcomes we would identify all pregnancies from conception and follow these up to their various outcomes (termination, miscarriage, live birth, stillbirth). For pragmatic reasons this approach is rarely possible, with studies instead typically identifying pregnancies ending in live births and occasionally stillbirths, terminations and/or miscarriages. However, the exclusion of non-live births can potentially produce a selection bias.[121,122] Here we provide an example of how a selection bias might work for terminations of pregnancy in our study setting. Antenatal scanning now allows potential parents to identify whether or not a fetus has certain congenital malformations. This may lead to an increase in the termination of malformed pregnancies and hence a lower rate of malformations in pregnancies resulting in live birth. Figures supporting this theory are not directly available, however, based on extrapolations from Department of Health[123] and ONS data[124] for England and Wales, and the European surveillance of congenital abnormalities (EUROCAT),[125] we estimate that in 2013 approximately 29% of terminated pregnancies were malformed whereas only 20% of live and stillbirths were malformed (*Table 51*).

This discrepancy in malformation rates among terminations does not bias relative risk estimates by itself, as a selection bias will only arise if two conditions are met: (1) the proportion of, for example, major congenital malformations are different in those who terminated compared with those who did not terminate and (2) the proportion of those who terminated are different among exposed and unexposed. If just one of these conditions is met, the effects will cancel out in relative estimates.

By making assumptions such as those described in *Table 51*, we can model the impact of a potential selection bias and estimate the potential direction and magnitude.

Below we provide two examples of sensitivity analyses based on the results presented in *Chapter 4, Child outcomes*, comparing the risk of major congenital malformations in women who continued antipsychotics in pregnancy (cohort B1) to the risk in women who discontinued antipsychotics before pregnancy (cohort A) and women who were unexposed to antipsychotics both before and during pregnancy (cohort C).

TABLE 51 Sensitivity analysis exploring the potential impact of excluding non-live births

Estimates	Data source
698,512 births in England and Wales in 2013	ONS
2% malformations (≈ 14,000)	EUROCAT
168,000 terminations before gestational week 13	DoH
0.2% (389) of which are grounds E[a]	DoH
Many may have terminated before malformation were observed. We therefore make the assumption that the true rate was the same as in general population ≈ 2% (≈ 3360)	
15,716 terminations after gestational week 13	DoH
15% (2,343) of which are grounds E[a]	DoH

DoH, Depertment of Health.
a Grounds E indicates termination on the basis that there is a risk that the child would be born handicapped; only ≈50% of these likely to be attributed to malformations, therefore, 29% is an estimate.

Notes
Based on this information we estimated that in 2013 there were a total of 19,703 (14,000 + 3360 + 2343) malformations and 862,525 [(698,512 + 168,000 + 15,716) – 19703] non-malformations among all live births, stillbirths and terminations in England and Wales in 2013.
Terminations account for 5703 (3360 + 2343) out of 19,703 (29%) malformed pregnancies. In other words the probability a malformed pregnancy is a termination is 0.29.
Terminations account for 178,013 [(168,000 + 15,716) – 5703] out of 862,525 (21%) without malformations. In other words, the probability of a non-malformed pregnancy ending in termination is 0.21.

Based on the information in *Table 51* we make the assumption that the probability is 0.21 for a non-malformed, unexposed pregnancy to be terminated. We then vary the probability for a malformed unexposed pregnancy to be terminated between 0.20 and 0.50 as well as the difference in termination probabilities between exposed and unexposed. *Figures 14* and *15* demonstrate that if there is *no* difference between termination probabilities between women who continue antipsychotics (cohort B) and women who discontinue antipsychotics (cohort A) or are not treated with antipsychotics (cohort C), the risk estimate will remain unaltered at 1.54 and 1.74, respectively. Likewise, convergence of the five lines in the figures illustrate that if the probability of a malformed and non-malformed pregnancy being aborted was the same (i.e. 0.20) then unbiased estimates are obtained regardless of the exclusion of non-live births. On the other hand, using the probability of 0.29 as a reference point, it is clear that even if the probability of termination in cohort B1 is 20% greater or smaller than in the other two cohorts, changes in the relative risk estimates are minimal. Using more extreme assumptions, as shown towards the right of these figures, may result in changes in relative risk estimates. However, these assumptions may not be plausible, for example a probability of 0.5 for termination of malformed pregnancies among unexposed *and* a 20% increase among exposed pregnancies.

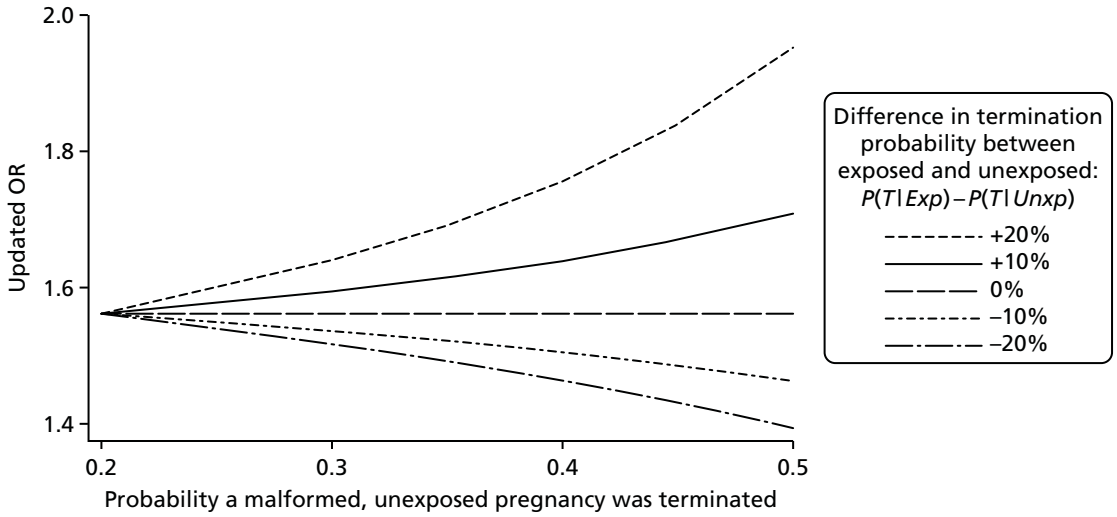

FIGURE 14 Sensitivity analysis assessing potential selection bias introduced by excluding terminations from the analyses comparing the risk of major congenital malformations in women continuing antipsychotic use in pregnancy (cohort B1) and women who discontinued antipsychotic use before pregnancy (cohort A). OR, odds ratio.

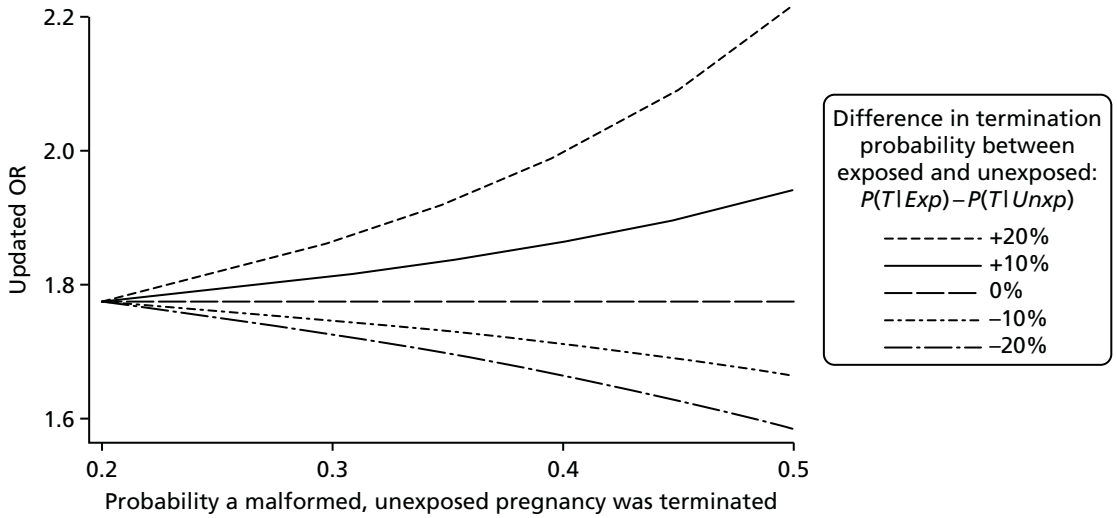

FIGURE 15 Sensitivity analysis assessing potential selection bias introduced by excluding terminations from the analyses comparing the risk of major congenital malformations in women continuing antipsychotic use in pregnancy (cohort B1) and women who did not use antipsychotic before/during pregnancy (cohort C). OR, odds ratio.

Variable definitions for *Chapter 3*

Below we provide information on how each of the outcomes were defined for the studies describing patterns of recording that indicate worsening of mental health; 18 months before, during the course of pregnancy and up to 15 months after delivery.

We examined the medical records in THIN for the presence of Read codes for symptoms or illness-related events within each 3-month period from 18 months before pregnancy to 15 months after delivery. We did not make any distinction between new codes and repeated codes. For each 3-month period we looked for the following categories of codes:

- Attempted suicide, overdose or deliberate self-harm, including 'events of undetermined intent' (*Table 52*). For this outcome we also searched the medical records for any entries associated with the single word free-text comment 'OVERDOSE'.
- Psychiatric hospital admission or Mental Health Act examination (*Table 53*).
- Psychosis, psychotic disorders and psychotic symptoms, including psychotic depression, mania and hypomania (*Table 54*).

For each Read code list we provide a maximum of the 50 most frequently used codes.

TABLE 52 Read codes used to identify attempted suicide, overdose or deliberate self-harm

Read code	Description
SL. . .15	Overdose of drug
TK05.00	Suicide + selfinflicted poisoning by drug or medicine
U20..11	[X]Deliberate drug overdose/other poisoning
TK. . .11	Cause of overdose – deliberate
U2. . .00	[X]Intentional self-harm
ZX1..13	Deliberate self-harm
TK. . .15	Attempted suicide
U20..00	[X]Intentional self poisoning/exposure to noxious sub
U29..00	[X]Intentional self harm by sharp object
U200.11	[X]Overdose – paracetamol
ZX. . .00	Self-harm
U2. . .11	[X]Self inflicted injury
TK. . .00	Suicide and selfinflicted injury
TK60100	Self inflicted lacerations to wrist
SL. . .14	Overdose of biological substance
TK. . .13	Poisoning – self-inflicted
TK00.00	Suicide + selfinflicted poisoning by analgesic/antipy
ZX14200	Pulling out sutures
TK. . .12	Injury – self-inflicted
U2E..00	[X]Self mutilation
TKz..00	Suicide and selfinflicted injury NOS
TN82.00	Injury?accidental, by scald

TABLE 52 Read codes used to identify attempted suicide, overdose or deliberate self-harm (*continued*)

Read code	Description
TK. . .17	Para-suicide
ZX13100	Cutting own wrists
TN81.00	Injury?accidental, by burns or fire
ZX13.00	Cutting self
U2. . .15	[X]Para-suicide
U200.00	[X]Intent self poison/exposure to nonopioid analgesic
TK. . .14	Suicide and self harm
TK0..00	Suicide + selfinflicted poisoning by solid/liquid sub
U30..11	[X]Deliberate drug poisoning
TK60111	Slashed wrists self inflicted
TN61.00	Injury?accidental, by stabbing instrument
TK6..00	Suicide and selfinflicted injury by cutting and stabb
TK60.00	Suicide and selfinflicted injury by cutting
U2. . .14	[X]Attempted suicide
TK04.00	Suicide + selfinflicted poisoning by other drugs/medi
U2. . .12	[X]Injury – self-inflicted
U209.00	[X]Intent self poison/exposure to alcohol
ZX1P.00	Swallowing substances
14K1.00	Intentional overdose of prescription only medication
U200.13	[X]Overdose – aspirin
ZX1..00	Self-injurious behaviour
ZX11500	Biting own tongue
TK03.00	Suicide + selfinflicted poisoning tranquilliser/psych
U21..00	[X]Intent self harm by hanging strangulation/suffoc
ZX1D.00	Picking own skin
U208z00	[X]Intent self poison oth/unsp drug/medic unspecif pl
ZX17100	Banging own head against object
ZX1G.00	Scratches self

NOS, not otherwise specified.
[X], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

TABLE 53 Read codes used to identify psychiatric hospital admissions or mental health act examinations

Read code	Description
13Hj.00	Sub com trt ordr S17 A MHA 1983
69F..00	Mental Health Act examination
69F..11	Section' exam,Ment Health Act
69F1.00	Section' exam – patient's GP
69F2.00	Section' exam-approved doctor
69F3.00	Section' exam – social worker
69FZ.00	Mental Health Act exam NOS
8H23.00	Admit psychiatric emergency
8H23000	Emerg psychiatric admiss MHA
8H2 T.00	Emergency voluntary psychiatric admission Mental Heal
8H38.00	Non-urgent psychiatric admisn.
8HM9.00	Listed for Psychiatric admissn
8Ha..00	Voluntary admission
8Hb..00	Involuntary admission
9H. . .11	Patient 'sectioned'
9H1..00	Form 4-admit to hosp-assess
9H11.00	Form 4 completed
9H12.00	Form 4 passed to social worker
9H1Z.00	Form 4 NOS
9H2..00	Form 5/7-emerg admit-assess
9H21.00	Form 7-medical recommendation
9H22.00	Form 5-nearest relative recom
9H23.00	Form 7-fee to soc services
9H2Z.00	Form 5/7 – NOS
9H4..00	Section 2 form – compulsory admission for assessment
9H41.00	Form 2 completed
9H42.00	Form 2 passed to social worker
9H43.00	Form 2 passed to nearest relative
9H4Z.00	Form 2 NOS
9H5..00	Section 3 form – compulsory admission for treatment
9H51.00	Form 3 completed
9H52.00	Form 3 passed to social worker
9H53.00	Form 3 passed to nearest relative
9H5Z.00	Form 3 NOS
9Ng5.00	Aftercare under Section 117 MHA 1983
9Ng5.11	Section 117 aftercare
Z171100	Aftercare under Section 117 MHA 1983
Z171111	S117 MHA – Aftercare under Section 117 MHA 1983
Z922.00	Care planning under section 117 of Mental Health Act
Z922.11	S117 MHA – Care plan s117 MHA

MHA, Mental Health Act; NOS, not otherwise specified.

TABLE 54 Read codes used to identify psychosis, mania or hypomania

Read code	Description
1B1E.00	Hallucinations
Eu30000	[X]Hypomania
E10..00	Schizophrenic disorders
E13z.11	Psychotic episode NOS
Eu2z.11	[X]Psychosis NOS
R001000	[D]Hallucinations, auditory
Eu22015	[X]Paranoia
1BH3.00	Paranoid ideation
Eu25.00	[X]Schizoaffective disorders
E13z.00	Nonorganic psychosis NOS
E103.00	Paranoid schizophrenia
E11..12	Depressive psychoses
E12..00	Paranoid states
Eu32300	[X]Severe depressive episode with psychotic symptoms
Eu53111	[X]Puerperal psychosis NOS
1BH..00	Delusions
Eu22011	[X]Paranoid psychosis
Eu30.00	[X]Manic episode
E10z.00	Schizophrenia NOS
1BY..00	Elevated mood
E120.00	Simple paranoid state
E130.11	Psychotic reactive depression
E107.00	Schizo-affective schizophrenia
R001.00	[D]Hallucinations
R001400	[D]Visual hallucinations
Eu23.00	[X]Acute and transient psychotic disorders
E110100	Single manic episode, mild
Eu30z11	[X]Mania NOS
E12z.00	Paranoid psychosis NOS
F481K00	Visual hallucinations
Eu20.00	[X]Schizophrenia
E1. . .00	Non-organic psychoses
E110.11	Hypomanic psychoses
Eu30100	[X]Mania without psychotic symptoms
E116.00	Mixed bipolar affective disorder
Eu31000	[X]Bipolar affective disorder, current episode hypoma
1S42.00	Manic mood

continued

TABLE 54 Read codes used to identify psychosis, mania or hypomania (*continued*)

Read code	Description
E110000	Single manic episode, unspecified
1BH..11	Delusion
Eu33311	[X]Endogenous depression with psychotic symptoms
Eu30.11	[X]Bipolar disorder, single manic episode
Eu22012	[X]Paranoid state
E113400	Recurrent major depressive episodes, severe, with psy
Eu30200	[X]Mania with psychotic symptoms
Eu22000	[X]Delusional disorder
E130.00	Reactive depressive psychosis
R001z00	[D]Hallucinations NOS
Eu33300	[X]Recurrent depress disorder cur epi severe with psy
Eu20000	[X]Paranoid schizophrenia
E100000	Unspecified schizophrenia

[D], working diagnosis; NOS, not otherwise specified.
[X], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

Variable definitions for *Chapter 4*

Below we provide information on how each of the outcomes was defined for the studies in *Chapter 4*. For each Read code list we provide a maximum of 50 codes. These were the most frequent codes used.

Maternal outcomes

Pre-eclampsia and/or gestational hypertension

Read codes for eclampsia, pre-eclampsia or proteinuric hypertension of pregnancy (*Table 55*) recorded in the mother's medical or AHD record between the 20th week of pregnancy and 3 months after delivery were identified as having pre-eclampsia.

Women with evidence of gestational hypertension were identified separately by searching for any of the following records between the 20th week of pregnancy and 3 months after delivery:

- Read codes specific to hypertension in pregnancy (*Table 56*) both in the medical records and in the AHD records
- Read codes for hypertension and hypertension monitoring that are not specific to pregnancy (*Table 57*), again both in the medical records and in the AHD records
- two blood pressure measurements with systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg
- any of the women identified as having gestational hypertension above were reclassified as having pre-existing hypertension if they had:
    - a diagnosis of hypertension or a code for hypertension monitoring prior to pregnancy
    - two blood pressure measurements with systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg prior to pregnancy
    - a prescription from the BNF chapter 2.5 in the 6 months prior to pregnancy.

TABLE 55 Read codes used to identify pre-eclampsia

Read code	Description
L124600	Pre-eclampsia, unspecified
L125.00	Severe pre-eclampsia
L124.11	Mild pre-eclampsia
L129.00	Moderate pre-eclampsia
L124.12	Toxaemia NOS
L126.00	Eclampsia
L124.00	Mild or unspecified pre-eclampsia
L124z00	Mild or unspecified pre-eclampsia NOS
L12B.00	Proteinuric hypertension of pregnancy
L124100	Mild or unspecified pre-eclampsia – delivered
L124000	Mild or unspecified pre-eclampsia unspecified
L126500	Eclampsia in pregnancy
L126300	Eclampsia – not delivered
L125100	Severe pre-eclampsia – delivered
L125z00	Severe pre-eclampsia NOS
L127100	Pre-eclampsia or eclampsia with hypertension – delive
L124300	Mild or unspecified pre-eclampsia – not delivered
L126600	Eclampsia in labour
L127000	Pre-eclampsia or eclampsia with hypertension unspecif
L126000	Eclampsia unspecified
L126100	Eclampsia – delivered
L125000	Severe pre-eclampsia unspecified
L127.00	Pre-eclampsia or eclampsia with pre-existing hyperten
L125300	Severe pre-eclampsia – not delivered
L126400	Eclampsia with postnatal complication
L126z00	Eclampsia NOS
L125400	Severe pre-eclampsia with postnatal complication

NOS, not otherwise specified.

TABLE 56 Read codes used to identify hypertension in pregnancy

Read code	Description
L12..00	Hypertension complicating pregnancy/childbirth/puerpe
L12z300	Unspecified hypertension in preg/childb/puerp – not d
L123500	Gestational hypertension
L123.00	Transient hypertension of pregnancy
L120.00	Benign essential hypertension in pregnancy/childbirth
L12z.00	Unspecified hypertension in pregnancy/childbirth/puer
L120000	Benign essential hypertension in preg/childb/puerp un
L12zz00	Unspecified hypertension in preg/childb/puerp NOS
L123z00	Transient hypertension of pregnancy NOS
L12z100	Unspecified hypertension in preg/childb/puerp – deliv
L123100	Transient hypertension of pregnancy – delivered
L120z00	Benign essential hypertension in preg/childb/puerp NO
L12z000	Unspecified hypertension in preg/childb/puerp unspeci
L123400	Transient hypertension of pregnancy + postnatal compl
L120300	Benign essential hypertension in preg/childb/puerp-no
L120400	Benign essential hypertension in preg/childb/puerp +*p*
L121.00	Renal hypertension in pregnancy/childbirth/puerperium
L123300	Transient hypertension of pregnancy – not delivered

NO/NOS, not otherwise specified.

TABLE 57 Read codes used to identify hypertension

Read code	Description
662P.00	Hypertension monitoring
G20..00	Essential hypertension
G2. . .00	Hypertensive disease
G20..11	High blood pressure
9OI4.00	Hypertens.monitor.1st letter
9OIA.00	Hypertension monitor.chck done
G20z.00	Essential hypertension NOS
G20z.11	Hypertension NOS
662d.00	Hypertension annual review
9N1y200	Seen in hypertension clinic
G2z..00	Hypertensive disease NOS
246M.00	White coat hypertension
9OI5.00	Hypertens.monitor 2nd letter
9OI..00	Hypertension monitoring admin.
662G.00	Hypertensive treatm.changed

TABLE 57 Read codes used to identify hypertension (*continued*)

Read code	Description
9N4L.00	DNA – Did not attend hypertension clinic
9h32.00	Excepted from hypertension qual indicators: Informed
662O.00	On treatment for hypertension
662c.00	Hypertension six month review
G24..00	Secondary hypertension
9OI6.00	Hypertens.monitor 3rd letter
9h31.00	Excepted from hypertension qual indicators: Patient u
6627	Good hypertension control
G201.00	Benign essential hypertension
6146200	Hypertension induced by oral contraceptive pill
6628	Poor hypertension control
G2. . .11	BP – hypertensive disease
8B26.00	Antihypertensive therapy
662H.00	Hypertension treatm.stopped
9OI1.00	Attends hypertension monitor.
8BL0.00	Patient on maximal tolerated antihypertensive therapy
662F.00	Hypertension treatm. started
9OI8.00	Hypertens.monitor phone invite
G24z100	Hypertension secondary to drug
G2y..00	Other specified hypertensive disease
8HT5.00	Referral to hypertension clinic
G22z.00	Hypertensive renal disease NOS
G22..00	Hypertensive renal disease
G24zz00	Secondary hypertension NOS
662b.00	Moderate hypertension control
G200.00	Malignant essential hypertension
9OIA.11	Hypertension monitored
9h3..00	Exception reporting: hypertension quality indicators
L128200	Pre-exist 2ndry hypertens comp preg childbth and puer
9OI7.00	Hypertens.monitor verbal inv.
TJC7.00	Adverse reaction to other antihypertensives
G241z00	Secondary benign hypertension NOS
Gyu2000	[X]Other secondary hypertension
G202.00	Systolic hypertension
G21z011	Other codes

BP, blood pressure; NOS, not otherwise specified.
[X], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

Gestational diabetes

Women with gestational diabetes were identified as those with any of the following records:

- Read codes for gestational diabetes or diabetes mellitus in pregnancy (*Table 58*), either in the medical records or in the AHD records between the 24th week of pregnancy and 3 months after delivery
- Read code for diabetes or diabetes monitoring more generally (*Table 59*), either in the medical records or in the AHD records between the 24th week of pregnancy and 3 months after delivery
- prescription for insulin from the BNF chapter 6.1.1 between the 24th week of pregnancy and delivery.

Any of the women identified as having gestational diabetes above were reclassified as having pre-existing diabetes if they had:

- a Read code for diabetes or diabetes monitoring prior to pregnancy (but no codes specific to pregnancy), either in the medical records or in the AHD records
- insulin prescriptions in the 6 months before pregnancy from the BNF chapter 6.1.1.

TABLE 58 Read codes used to identify gestational diabetes

Read code	Description
L180811	Gestational diabetes mellitus
L180.00	Diabetes mellitus during pregnancy/childbirth/puerper
L180800	Diabetes mellitus arising in pregnancy
L180z00	Diabetes mellitus in pregnancy/childbirth/puerperium
L180300	Diabetes mellitus during pregnancy – baby not yet del
L180100	Diabetes mellitus during pregnancy – baby delivered

TABLE 59 Read codes used to identify diabetes

Read code	Description
9N1Q.00	Seen in diabetic clinic
9OL..00	Diabetes monitoring admin.
66A..00	Diabetic monitoring
C10..00	Diabetes mellitus
66AS.00	Diabetic annual review
C10E.00	Type 1 diabetes mellitus
68A7.00	Diabetic retinopathy screening
C109.12	Type 2 diabetes mellitus
C108.00	Insulin dependent diabetes mellitus
66A2.00	Follow-up diabetic assessment
9OL4.00	Diabetes monitoring 1st letter
66A5.00	Diabetic on insulin
9NND.00	Under care of diabetic foot screener
66AQ.00	Diabetes: shared care programme
9OL5.00	Diabetes monitoring 2nd letter

TABLE 59 Read codes used to identify diabetes (*continued*)

Read code	Description
C101.00	Diabetes mellitus with ketoacidosis
66AJ.00	Diabetic – poor control
2G5E.00	O/E – Right diabetic foot at low risk
F420.00	Diabetic retinopathy
2G5I.00	O/E – Left diabetic foot at low risk
9h42.00	Excepted from diabetes quality indicators: Informed d
8B3l.00	Diabetes medication review
9OL6.00	Diabetes monitoring 3rd letter
9OL1.00	Attends diabetes monitoring
9N2d.00	Seen by diabetologist
66AZ.00	Diabetic monitoring NOS
9h41.00	Excepted from diabetes qual indicators: Patient unsui
66AU.00	Diabetes care by hospital only
66Ac.00	Diabetic peripheral neuropathy screening
66AD.00	Fundoscopy – diabetic check
2BBJ.00	O/E – no right diabetic retinopathy
2BBK.00	O/E – no left diabetic retinopathy
C109.00	Non-insulin dependent diabetes mellitus
66AP.00	Diabetes: practice programme
66AR.00	Diabetes management plan given
8H4F.00	Referral to diabetologist
13B1.00	Diabetic diet
1434.00	H/O: diabetes mellitus
9N4I.00	DNA – Did not attend diabetic clinic
8I3X.00	Diabetic retinopathy screening refused
2BBP.00	O/E – right eye background diabetic retinopathy
66A4.00	Diabetic on oral treatment
C108.11	IDDM-Insulin dependent diabetes mellitus
2BBQ.00	O/E – left eye background diabetic retinopathy
F420000	Background diabetic retinopathy
9N1v.00	Seen in diabetic eye clinic
C10EM00	Type 1 diabetes mellitus with ketoacidosis
66AI.00	Diabetic – good control
66Aq.00	Diabetic foot screen

O/E, on examination; H/O, history of.

The Read codes that were used to identify pre-existing diabetes included diabetes monitoring and administration codes to be as sensitive as possible.

Caesarean section

Pregnancies ending in a caesarean section were identified in one of three ways:

- by searching for relevant Read codes (*Table 60*) in the mother's or child's medical records between 4 weeks prior to the EDD and 6 months after the delivery date
- by searching for relevant Read codes (see *Table 60*) in the mother's or child's AHD records between 4 weeks prior to the EDD and 6 months after the delivery date
- by searching the mother's or child's AHD records for AHD codes for 'CHS [Child Health Surveillence] – delivery details' recorded between 4 weeks prior to the EDD and 6 months after the delivery date, and identifying whether or not the values recorded against the AHD code indicated the mode of delivery was caesarean.

TABLE 60 Read codes used to identify caesarean delivery

Read code	Description
14Y0.00	Born by caesarean section
14Y2.00	Born by elective caesarean section
14Y6.00	Born by emergency caesarean section
7F12.00	Elective caesarean delivery
7F12000	Elective upper uterine segment caesarean delivery
7F12100	Elective lower uterine segment caesarean delivery
7F12111	Elective lower uterine segment caesarean section (LSC
7F12y00	Other specified elective caesarean delivery
7F12z00	Elective caesarean delivery NOS
7F13.00	Other caesarean delivery
7F13000	Upper uterine segment caesarean delivery NEC
7F13100	Lower uterine segment caesarean delivery NEC
7F13111	Lower uterine segment caesarean section (LSCS) NEC
7F13200	Extraperitoneal caesarean section
7F13300	Emergency caesarean section
7F13y00	Other specified other caesarean delivery
7F13z00	Other caesarean delivery NOS
7F1A000	Caesarean hysterectomy
L213200	Multiple delivery, all by caesarean section
L398.00	Caesarean delivery
L398000	Caesarean delivery unspecified
L398100	Caesarean delivery – delivered
L398200	Caesarean section – pregnancy at term
L398300	Delivery by elective caesarean section
L398400	Delivery by emergency caesarean section
L398500	Delivery by caesarean hysterectomy

TABLE 60 Read codes used to identify caesarean delivery (*continued*)

Read code	Description
L398600	Caesarean delivery following previous Caesarean deliv
L398z00	Caesarean delivery NOS
L441.00	Caesarean wound disruption
L441000	Caesarean wound disruption unspecified
L441100	Caesarean wound disruption – delivered with *p/n* compl
L441200	Caesarean wound disruption with postnatal complicatio
L441z00	Caesarean wound disruption NOS
Lyu5200	[X]Other single delivery by caesarean section
Lyu6A00	[X]Infection of caesarean section wound following del
Q021300	Fetus/neonate affected by placental damage-caesarean
Q034.00	Fetus or neonate affected by caesarean section
Z254500	Delivered by caesarean section – pregnancy at term
Z254600	Deliv caes following prev caes

LSC, lower segment caesarean; NEC, not elsewhere classified; NOC, not otherwise specified; p/n, postnatal.
[X], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

Perinatal death

Fetal losses and neonatal deaths were identified in one of three ways:

- by searching for relevant Read codes (*Table 61*) in the mother's medical records between 20 weeks' gestation and 1 week after birth
- by searching for relevant Read codes (see *Table 61*) in the mother's AHD records between 20 weeks' gestation and 1 week after birth
- by searching the mother's AHD records for AHD codes for 'maternity outcome' and 'maternity infant details' recorded between 20 weeks' gestation and 1 week after birth, and identifying whether or not the values recorded against the AHD code indicated a stillbirth had occurred.

For the pregnancies in THIN only, all free text recorded in pregnancy in either the medical or AHD records of the unlinked pregnancies was obtained and a string search used to identify any more perinatal deaths. No free text was available from the CPRD.

Child outcomes

Major congenital anomalies

Read codes starting with 'P' (indicating some form of congenital anomaly) recorded in our study population during the first year of a linked child's life were identified. Read codes for malformations recorded in the mother's notes at any time during pregnancy were also identified. These Read code lists were then compared with the EUROCAT guidelines and reviewed by a GP (IN) to identify whether the codes indicated a major or minor malformation occurred. Following this review a number of Read codes remained that were too vague to allow for a decision whether the malformation was major or minor. In the THIN cohort, the free-text record of children with these vague codes was obtained and reviewed, whereas in the CPRD cohort the Read coded medical record of children with these codes was reviewed without additional free-text information. Children in whom the free-text or coded record indicated that the malformation was major were included as a case; children in whom the record did not provide evidence the malformation was major were not included as a case. The list of Read codes used in the final extraction is provided in *Table 62*.

TABLE 61 Read codes used to identify perinatal death

Read code	Description
633..12	stillbirth [prevention record]
6332.00	single stillbirth
6335.00	twins – both still born
6339.00	triplets – 3 still born
L264.00	intrauterine death
L264.11	fetal death in utero
L264000	intrauterine death unspecified
L264100	intrauterine death – delivered
L264200	intrauterine death with antenatal problem
L264z00	intrauterine death nos
Q48D.00	[x] stillbirth
Q48D000	[x]fresh stillbirth
Q48D100	[x]macerated stillbirth
Q48y600	early neonatal death
Q48y700	late neonatal death
Q4z..11	infant death
Q4z..12	neonatal death
Q4z..13	newborn death
Q4z..14	perinatal death
Q4z..15	stillbirth nec
ZV27.12	[v]stillbirth
ZV27100	[v]single stillbirth
ZV27400	[v]twins, both stillborn
ZV27700	[v]other multiple birth, all stillborn
ZVu2C00	[x]other multiple births, all stillborn
L39X.00	obstetric death of unspecified cause
Lyu7500	[x]obstetric death of unspecified cause
Q210.00	fetal death due to prelabour anoxia
Q211.00	fetal death due to labour anoxia

nos, not otherwise specified.

Notes

[v] corresponds to the ICD-9 chapter that allows the recording of supplementary factors influencing health status or contact with health services other than for illness.

[x], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

TABLE 62 Read codes used to identify major congenital malformation

Read code	Description
P54..00	Ventricular septal defect
PC60.00	Hypospadias
PA5..00	Congenital hypertrophic pyloric stenosis
P550.00	Atrial septal defect NOS
P90..00	Cleft palate
PD23.11	Congenital dilated renal pelvis
PE1..12	Sternomastoid tumour
P71..00	Coarctation of aorta
PD34.11	Duplex kidneys
P52..00	Tetralogy of Fallot
PF0..00	Polydactyly – supernumerary digits
PG0y000	Brachycephaly
P92..00	Cleft palate with cleft lip
PD23.00	Congenital hydronephrosis
P55..00	Ostium secundum atrial septal defect
PG0z.11	Dysmorphic features
PB26.00	Imperforate anus
PF1..00	Syndactyly – webbing of digits
PG71.00	Gastroschisis
P6y2.00	Pulmonary infundibular stenosis
PB30.00	Hirschsprung's disease
PC33.00	Bicornuate uterus
PF13.11	Webbed toes
P9. . .00	Cleft palate and lip
PF01.00	Accessory fingers
P21..00	Microcephalus
P91..00	Cleft lip (harelip)
PD11.00	Polycystic kidney disease
P360.00	Congenital ptosis
PG03.00	Craniosynostosis
P1. . .00	Spina bifida
PD02.00	Congenital absence of kidney
PG0C.00	Pierre – Robin syndrome
PD13.11	Multicystic kidney
P6z..00	Congenital heart anomaly NOS
PH3y200	Epidermolysis bullosa
P51..00	Transposition of great vessels

continued

TABLE 62 Read codes used to identify major congenital malformation (*continued*)

Read code	Description
PKy9300	Prader – Willi syndrome
P641.00	Bicuspid aortic valve
P67..00	Hypoplastic left heart syndrome
P602.00	Congenital pulmonary stenosis
PK5..00	Tuberous sclerosis
P31..00	Microphthalmos
P63..00	Congenital aortic valve stenosis
PH1..00	Ichthyosis congenital
P344200	Coloboma of iris
P3y0.00	Ocular albinism
P80..00	Choanal atresia
PA30.00	Atresia of oesophagus
PC60312	Hypospadias, glandular

NOS, not otherwise specified.

Preterm birth (< 37 weeks)

Preterm births were identified in one of the following ways:

- by searching for relevant Read codes (*Table 63*) in the mother's and child's medical records between 4 weeks prior to delivery and 6 months after delivery
- by searching for relevant Read codes (see *Table 63*) in the mother's and child's AHD records between 4 weeks prior to delivery and 6 months after delivery
- by searching the mother's and child's AHD records for AHD codes for 'CHS [Child Health Surveillence] – gestation' and 'Maternity outcome gestational age of baby' recorded between 4 weeks prior to delivery and 6 months after delivery, and identifying whether or not the values recorded against the AHD code indicated the pregnancy ended prematurely
- by using the LMP dates, or the dates on which antenatal and postnatal codes were recorded to estimate whether or not the delivery date occurred before 37 weeks' gestation.

Low birthweight (< 2500 g)

Children born with a low birthweight were identified in one of the following ways:

- by searching for relevant Read codes (*Table 64*) in the mother's and child's medical records between 4 weeks prior to delivery and 6 months after delivery
- by searching for relevant Read codes (see *Table 64*) in the mother's and child's AHD records between 4 weeks prior to delivery and 6 months after delivery
- by searching the mother's and child's AHD records for AHD codes for 'Maternity infant details' recorded between 4 weeks prior to delivery and 6 months after delivery, and identifying whether or not the values recorded against the AHD code indicated the child weighed < 2500 g.

TABLE 63 Read codes used to identify preterm birth

Read code	Description
635..13	Premature baby
6352.00	Baby v. premature 32–36 weeks
6353.00	Baby extremely prem.28–32 week
6356.00	Baby premature 26–28 weeks
6357.00	Baby premature 24–26 weeks
635B.00	Baby premature 36 weeks
F422011	Retinopathy of prematurity
L142.00	Early onset of delivery
L142.11	Premature delivery
L142000	Early onset of delivery unspecified
L142100	Early onset of delivery – delivered
L142z00	Early onset of delivery NOS
L143.00	Premature labour and delivery
L143100	Premature labour with premature delivery
L143300	Premature delivery without labour
Q11..00	Short gestation and unspecified low birthweight probl
Q11..11	Baby born premature
Q110.00	Very premature – less than 1000 g or less than 28 week
Q110.11	Immature baby
Q111.00	Premature – weight 1000 g-2499 g or gestation of 28–37w
Q112.00	Extreme immaturity
Q112.11	Extreme prematurity – less than 28 weeks
Q116.00	Premature infant 28–37 weeks
Q11z.00	Born premature NOS
Q317100	Prematurity with interstitial pulmonary fibrosis
Q432.00	Preterm delivery associated jaundice
Q456.00	Anaemia of prematurity
Qyu1100	[X]Other preterm infants

NOS, not otherwise specified.
[X], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

TABLE 64 Read codes used to identify low birthweight

Read code	Description
6361.00	Baby BW = < 3% (under 2500 g)
636 A.00	Baby BW = below 751gm
636B.00	Baby BW = 751g-1kg
636C.00	Baby BW = 1.0–1.5kg
636D.00	Baby BW = 1.5–2.0kg
636E.00	Baby BW = 2.0 – 2.5kg
Q114.00	Low birthweight
Q114000	Birth weight 1000–2499 g
Q115.00	Extremely low birth weight infant
Q115000	Birth weight 999 g or less
Qyu1000	[X]Other low birth weight

BW, birthweight.
[X], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

Low weight for gestation/poor fetal growth

Children born small for their gestational age were identified in one of the following ways:

- by searching for relevant Read codes (*Table 65*) in the mother's and child's medical record between 2 weeks prior to delivery and 8 weeks after delivery.
- by searching for relevant Read codes (see *Table 65*) in the mother's and child's AHD record between 2 weeks prior to delivery and 8 weeks after delivery.

TABLE 65 Read codes used to identify SGA

Read code	Description
L265.00	Small-for-dates fetus in pregnancy
L265000	Small-for-dates unspecified
L265100	Small-for-dates – delivered
L265200	Small-for-dates with antenatal problem
L265300	Maternal care for poor fetal growth
L265311	Maternal care for intrauterine growth retardation
L265z00	Small-for-dates NOS
L514.00	Maternal care for poor fetal growth
Q10..00	Slow fetal growth and fetal malnutrition
Q100.00	Fetus small-for-dates, without mention of malnutritio
Q100.11	Fetus small-for-dates (SFD), without mention of malnu
Q101.00	Fetus small-for-dates with signs of malnutrition
Q101.11	Fetus small-for-dates (SFD) with signs of malnutritio
Q10z.00	Fetal growth retardation NOS
Q10z.11	Intrauterine growth retardation
Q113.00	Light for gestational age
Q13..00	Light for gestational age

NOS, not otherwise specified.

Low Apgar scores (< 7) at 5 minutes

Children born with a low Apgar score were identified in one of the following ways:

- by searching for relevant Read codes (*Table 66*) in the mother's and child's medical records between 4 weeks prior to delivery and 6 months after delivery.
- by searching for relevant Read codes (see *Table 66*) in the mother's and child's AHD records between 4 weeks prior to delivery and 6 months after delivery.
- by searching the mother's and child's AHD records for AHD codes for 'CHS – APGAR Score At 5 Minutes' and 'Maternity infant details' recorded between 4 weeks prior to delivery and 6 months after delivery, and identifying whether or not the values recorded against the AHD code indicated the Apgar score was ≥ 0 and ≤ 6.

Extrapyramidal syndromes/signs/symptoms/effects or withdrawal symptoms in neonate to be included in 'transient' poor birth outcomes.

Preliminary investigations suggested it would not be possible to reliably identify cases of neonatal abstinence syndrome in primary care databases. Instead, an outcome of extrapyramidal-type symptoms was defined to include children with any record for a symptom related to the syndrome.

Operationally this outcome was defined as any child with a Read code for one of the following symptoms recorded in the medical or AHD records in the three months after birth:

- abnormally increased or decreased muscle tone
- agitation, restlessness and irritability
- tremor/shaking and abnormal movements
- difficulty breathing/respiratory distress – we will look at respiratory distress syndrome separately.

The full list of Read codes related to these symptoms is provided in *Table 67*.

TABLE 66 Read codes used to identify low Apgar score

Read code	Description
63A1.00	Apgar at 5 minutes = 0
63A2.00	Apgar at 5 minutes = 1
63A3.00	Apgar at 5 minutes = 2
63A4.00	Apgar at 5 minutes = 3
63A5.00	Apgar at 5 minutes = 4
63A6.00	Apgar at 5 minutes = 5
63A7.00	Apgar at 5 minutes = 6

TABLE 67 Read codes used to identify transient poor birth outcomes

Read code	Description
Q30..00	Respiratory distress syndrome
1738.00	Difficulty breathing
1B15.11	Irritable – symptom
232C.00	Noisy breathing
Q316.00	Newborn transitory tachypnoea
R060600	[D]Respiratory distress
R060400	[D]Apnoea
Q31yz11	Grunting baby
Q48B.00	Jittery baby
1739.00	Shortness of breath
Q31y200	Perinatal respiratory distress NOS
2324.00	O/E – respiratory distress
Q31y600	Apnoea of newborn
R060300	[D]Tachypnoea
Q31y611	Neonatal apnoeic attack
R025.00	[D]Cyanosis
2326.00	O/E – expiratory wheeze
R060800	[D]Shortness of breath
Q31y111	Cyanotic attacks of the newborn
F132300	Myoclonic jerks
225A.00	O/E – irritable
1B22.12	Shaking
Q31y000	Perinatal apnoeic spells NOS
Q310.00	Congenital pneumonia
1B1O.00	Restless
Q48y211	Floppy infant
173..13	Shortness of breath symptom
N135.00	Torticollis unspecified
F132.00	Myoclonus
F13z500	Benign neonatal sleep myoclonus
Q31y100	Perinatal cyanotic attacks NOS
Q48y200	Congenital hypotonia
R060900	[D]Wheezing
R010.00	[D]Abnormal involuntary movements
16A3.11	Torticollis – symptom
1673.11	Blue – symptom
PE1..00	Congenital sternomastoid torticollis
F138200	Spasmodic torticollis

TABLE 67 Read codes used to identify transient poor birth outcomes (*continued*)

Read code	Description
232F.00	O/E – subcostal recession
173..12	Dyspnoea – symptom
Q3z..00	Fetal or newborn respiratory problems NOS
2276000.00	Blue lips
2276.00	O/E – central cyanosis
R010300	[D]Tremor NOS
1B15.00	Irritable
1B22.11	Tremor symptom
N23y400	Spasm of muscle
R060z00	[D]Respiratory abnormalities NOS
Q3. . .00	Fetus and newborn respiratory conditions

[D], working diagnosis; NOS, not otherwise specified; O/E, on examination.

Neurodevelopmental and behavioural disorders

Children with neurodevelopmental and/or behavioural disorders were identified in one of three ways:

- by searching for relevant Read codes (*Table 68*) in the child's medical records up to 5 years after the delivery date
- by searching for relevant Read codes (see *Table 68*) in the child's AHD records up to 5 years after the delivery date
- by searching the mother's or child's AHD records for AHD codes for 'CHS – Gait', 'CHS – Language 3 Years', 'CHS – Speech & Language', 'CHS – Speech 3 Years' or 'CHS – Behaviour' recorded up to 5 years after the delivery date, and identifying whether the values recorded against the AHD code indicate there a problem was identified.

Note that Read codes for neurodevelopmental and behavioural disorders were identified as those relating to conditions listed as neurodevelopmental or behavioural disorders in Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition.

TABLE 68 Read codes used to identify neurodevelopmental and behavioural disorder

Read code	Description
9N29.00	Seen by speech therapist
R012.00	[D]Gait abnormality
1B9..00	Speech problem
ZV40.11	[V]Behavioural problems
ZS67300	Speech delay
E2C..11	Behaviour disorder
E2Cy000	Breath holder
1B1X.00	Behavioural problem
E2F..00	Specific delays in development
E2Fy.00	Other development delays
ZD. . .00	Speech and language therapy

continued

TABLE 68 Read codes used to identify neurodevelopmental and behavioural disorder (*continued*)

Read code	Description
R012z00	[D]Gait abnormality NOS
1469.00	H/O: behaviour problem
E2C1200	Tantrums
E140.12	Autism
64R3.11	Child referral- speech therapy
Eu84011	[X]Autistic disorder
1B9..11	Speech problem – symptom
1P00.00	Hyperactive behaviour
E2F5.11	Global delay
1B92.11	Stammer – symptom
Eu95300	[X]Involuntary excessive blinking
R034700	[D]Gross motor development delay
ZS7B400	Developmental language delay
1B92.12	Stutter – symptom
Eu85.00	[X]Global developmental delay
64R3.00	Child: speech therapy
ZV57300	[V]Speech therapy
E2F3.12	Speech development disorder
ZS7B100	Expressive language delay
ZL4C.00	Under care of speech and language therapist
E2Fz.00	Developmental disorder NOS
918e.00	On learning disability register
13Z4E00	Learning difficulties
2B4 A.00	O/E – speech delay
E2E..00	Childhood hyperkinetic syndrome
Eu90011	[X]Attention deficit hyperactivity disorder
E2F3.11	Language development disorder
ZV40300	[V]Other behavioural problems
13ZA.00	Language difficulty
Eu80.00	[X]Specific developmental disorders of speech and lan
13Z4C00	Behavioural problems at school
E2F3.00	Speech or language developmental disorder
E140.00	Infantile autism
Eu81z11	[X]Learning disability NOS
R034A00	[D]Communication skills development delay
ZS. . .00	Speech and language disorder
E2E0.00	Child attention deficit disorder
ZT45.00	Difficulty communicating

[D], working diagnosis; H/O, history of; NOS, not otherwise specified; O/E, on examination.

Notes

[V] corresponds to the ICD-9 chapter that allows the recording of supplementary factors influencing health status or contact with health services other than for illness.

[X], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

Covariates

Down syndrome (for exclusion from cohort)

Children with Down syndrome or trisomy 21 were identified by searching for relevant Read codes (*Table 69*) anywhere in the child's medical record. As this is a congenital condition, and was being used as an exclusion criterion, individuals with a code recorded against a missing date were considered to have the condition.

Children whose mothers had codes recorded in their medical record during pregnancy were not considered to have Down syndrome or trisomy 21 as exploratory work revealed that some practices are using the Read codes for Down syndrome to record (negative) screening tests for Down syndrome.

Townsend score

Townsend scores and Townsend quintiles are provided by the THIN data provider for any consenting practice. These data were therefore directly extracted from the relevant table for each pregnancy. The CPRD also provides Townsend score data for consenting English practices. However, these data were not available at the time of analysis.

Pre-pregnancy body mass index

The pre-pregnancy BMI of women was identified in one of two ways:

- By searching the mother's AHD records for AHD codes for 'Weight' and identifying whether or not a valid BMI was recorded against it in the year prior to the estimated LMP.
- By searching the mother's AHD records for AHD codes for 'Weight' and identifying whether or not a weight in kilograms was recorded against it in the year prior to the estimated LMP. If a weight was recorded in the year prior to the estimated LMP, the mother's records were searched for a height record. If height records were identified, the closest one to the estimated LMP was used to calculate the BMI.

As part of the data cleaning process BMI records ≥ 70 kg/m^2, weight records > 180 kg or < 40 kg, and height records > 1.95 cm and < 1.4 cm were excluded.

TABLE 69 Read codes used to identify Down syndrome

Read code	Description
PJ0..00	Down's syndrome – trisomy 21
PJ0..11	Mongolism
PJ0..12	Trisomy 21
PJ00.00	Trisomy 21, meiotic nondisjunction
PJ01.00	Trisomy 21, mosaicism
PJ01.11	Trisomy 21, mitotic nondisjunction
PJ02.00	Trisomy 21, translocation
PJ02.11	Partial trisomy 21 in Down's syndrome
PJ0z.00	Down's syndrome NOS
PJ0z.11	Trisomy 21 NOS

NOS, not otherwise specified.

Pre-pregnancy obesity

Women with pre-pregnancy obesity were identified in one of four ways:

- By searching for relevant Read codes (*Table 70*) in the mother's medical records up to 1 year before the estimated LMP.
- By searching for relevant Read codes (see *Table 70*) in the mother's AHD records up to 1 year before the estimated LMP.
- By searching the mother's AHD records for AHD codes for 'Weight' and identifying whether a BMI ≥ 30 kg/m^2 was recorded against it in the year prior to the estimated LMP.
- By searching the mother's AHD record for AHD codes for 'Weight' and identifying whether or not a weight in kilograms was recorded against it in the year prior to the estimated LMP. If a weight was recorded in the year prior to the estimated LMP the mother's record was searched for a height record. If height records were identified the closest one to the estimated LMP was used to calculate the BMI. If the BMI was ≥ 30 kg/m^2 the woman was classified as obese.

As part of the data cleaning process BMI records > 70 kg/m^2, weight records > 180 kg or < 40 kg, and height records > 1.95 m and < 1.4 m were excluded.

Pre-pregnancy smoking status

Pre-pregnancy smoking status was identified by searching the mother's AHD records for AHD codes for 'Smoking' in the 3 years prior to the estimated LMP.

Pre-pregnancy alcohol abuse

Women with pre-pregnancy alcohol abuse were identified in one of three ways:

- by searching for relevant Read codes (*Table 71*) in the mother's medical records up to 3 years before the estimated LMP
- by searching for relevant Read codes (see *Table 71*) in the mother's AHD records up to 3 years before the estimated LMP
- by searching the mother's AHD records for AHD codes for 'Alcohol' and identifying whether or not the value recorded against it was indicative of alcohol abuse.

TABLE 70 Read codes used to identify obesity

Read code	Description
222 A.00	O/E – obese
22A5.11	O/E – obese
22K5.00	Body mass index 30 + – obesity
22K7.00	Body mass index 40 + – severely obese
66C..00	Obesity monitoring
66C1.00	Initial obesity assessment
66C2.00	Follow-up obesity assessment
66C4.00	Has seen dietitian – obesity
66C5.00	Treatment of obesity changed
66C6.00	Treatment of obesity started
66C7.00	Treatment of obesity stopped

TABLE 70 Read codes used to identify obesity (*continued*)

Read code	Description
66CE.00	Reason for obesity therapy – occupational
66CZ.00	Obesity monitoring NOS
9OK..00	Obesity monitoring admin.
9OK..11	Obesity clinic administration
9OK1.00	Attends obesity monitoring
9OK2.00	Refuses obesity monitoring
9OK3.00	Obesity monitoring default
9OK4.00	Obesity monitoring 1st letter
9OK5.00	Obesity monitoring 2nd letter
9OK6.00	Obesity monitoring 3rd letter
9OK7.00	Obesity monitoring verbal inv.
9OK8.00	Obesity monitor phone invite
9OK9.00	Obesity monitoring deleted
9OKA.00	Obesity monitoring check done
9OKZ.00	Obesity monitoring admin.NOS
9hN..00	Exception reporting: obesity quality indicators
9hN0.00	Excepted from obesity quality indicators: patient uns
9hN1.00	Excepted from obesity quality indicators: informed di
C380.00	Obesity
C380000	Obesity due to excess calories
C380100	Drug-induced obesity
C380200	Extreme obesity with alveolar hypoventilation
C380300	Morbid obesity
C380400	Central obesity
C380500	Generalised obesity
C380600	Adult-onset obesity
C380700	Lifelong obesity
C38y011	Obesity hypoventilation syndrome
C38z000	Simple obesity NOS
Cyu7000	[X]Other obesity
ZC2CM00	Dietary advice for obesity
ZV65319	[V]Dietary counselling in obesity

O/E, on examination; NOS, not otherwise specified.

Notes

[V] corresponds to the ICD-9 chapter that allows the recording of supplementary factors influencing health status or contact with health services other than for illness.

[X], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

TABLE 71 Read codes used to identify alcohol problems

Read code	Description
1365.00	Heavy drinker – 7–9u/day
1366.00	Very heavy drinker – > 9u/day
1369.00	Suspect alcohol abuse – denied
136P.00	Heavy drinker
136Q.00	Very heavy drinker
136S.00	Hazardous alcohol use
136T.00	Harmful alcohol use
136W.00	Alcohol misuse
136Y.00	Drinks in morning to get rid of hangover
13Y8.00	Alcoholics anonymous
66e..00	Alcohol disorder monitoring
7P22100	Delivery of rehabilitation for alcohol addiction
8BA8.00	Alcohol detoxification
8H7p.00	Referral to community alcohol team
8HHe.00	Referral to community drug and alcohol team
9NN2.00	Under care of community alcohol team
9k1..00	Alcohol misuse – enhanced services administration
E01y000	Alcohol withdrawal syndrome
E23..00	Alcohol dependence syndrome
E23..11	Alcoholism
E23..12	Alcohol problem drinking
E230.00	Acute alcoholic intoxication in alcoholism
E231.00	Chronic alcoholism
E231000	Unspecified chronic alcoholism
E231100	Continuous chronic alcoholism
E231200	Episodic chronic alcoholism
E231300	Chronic alcoholism in remission
E231z00	Chronic alcoholism NOS
E23z.00	Alcohol dependence syndrome NOS
E250.00	Nondependent alcohol abuse
E250.14	Intoxication – alcohol
E250000	Nondependent alcohol abuse, unspecified
E250200	Nondependent alcohol abuse, episodic
Eu10011	[X]Acute alcoholic drunkenness
Eu10211	[X]Alcohol addiction
J153.00	Alcoholic gastritis
R103.00	[D]Alcohol blood level excessive

[D], working diagnosis; NOS, no otherwise specified; u/day, units per day.
[X], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

Pre-pregnancy illicit drug use

Women with pre-pregnancy illicit drug use were identified in one of three ways:

- by searching for relevant Read codes (*Table 72*) in the mother's medical records up to 3 years before the estimated LMP
- by searching for relevant Read codes (see *Table 72*) in the mother's AHD records up to 3 years before the estimated LMP
- by searching the mother's prescription records for drugs used in the treatment of illicit drug use.

TABLE 72 Read codes used to identify illicit drug use

Read code	Description
8B23.00	Drug addiction therapy
46QB.00	Urine methadone
46QA.00	Urine cocaine
E24..00	Drug dependence
46Q5.00	Urine amphetamine
E24z.00	Drug dependence NOS
8B23.12	FP10(MDA) issued
8B23.11	Drug addictn therap-methadone
E240.00	Opioid type drug dependence
ZV6D700	[V]Drug abuse counselling and surveillance
46QH.00	Urine cocaine metabolite screen
46Qf.00	Urine methadone metabolite level
46Q5.11	Amphetamine in urine
E240.11	Heroin dependence
E24..11	Drug addiction
13c..00	Drug user
E25z.00	Misuse of drugs NOS
Eu11212	[X]Heroin addiction
1463.00	H/O: drug dependency
E020.00	Drug withdrawal syndrome
8HHe.00	Referral to community drug and alcohol team
9NN1.00	Under care of community drug team
146F.00	H/O: drug abuse
8BA9.00	Detoxification dependence drug
E240z00	Opioid drug dependence NOS
1J1..00	Suspected drug abuse
8H7x.00	Referral to drug abuse counsellor
9N0Z.00	Seen in drug rehabilitation centre
E25..00	Nondependent abuse of drugs
Eu11211	[X]Drug addiction – opioids

continued

TABLE 72 Read codes used to identify illicit drug use (*continued*)

Read code	Description
46Qr.00	Urine buprenorphine level
E252.00	Nondependent cannabis abuse
44uK.00	Plasma methadone level
E243.00	Cannabis type drug dependence
ZV4K100	[V]Drug use
8B2P.00	Drug addiction maintenance therapy – methadone
E240.12	Methadone dependence
E244.00	Amphetamine or other psychostimulant dependence
13cM.00	Substance misuse
E242.00	Cocaine type drug dependence
Eu12211	[X]Drug addiction – cannabis
1T8..00	H/O cannabis misuse
9OhB.00	Non-steroidal anti-inflammatory drug risk assessmnt completd
L183.00	Drug dependence in pregnancy, childbirth and the puerperium
ZG23200	Advice on drugs of addiction
Eu19211	[X]Drug addiction NOS
146E.00	H/O: recreational drug use
ZV57B00	[V]Drug rehabilitation

FP10(MDA), prescription for daily dispensing of methadone; H/O, history of; NOS, not otherwise specified.
Notes
[V] corresponds to the ICD-9 chapter that allows the recording of supplementary factors influencing health status or contact with health services other than for illness.
[X], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

Ethnicity

The ethnicity of a pregnancy was determined in one of two ways:

- by searching for relevant Read codes (*Table 73*) in the mother's or child's medical records and using the one closest to the estimated LMP
- by searching for relevant Read codes (see *Table 73*) in the mother's or child's medical records and using the one closest to the estimated LMP.

Pregnancies were then classified into one of five ethnicity categories from the ONS based on the information in the Read code description.

TABLE 73 Read codes used to identify ethnicity

Read code	Description
9S10.00	White British
9i0..00	British or mixed British – ethnic category 2001 census
9S13.00	White Scottish
9S1..00	White
9i20.00	English – ethnic category 2001 census
9i2..00	Other White background – ethnic category 2001 census

TABLE 73 Read codes used to identify ethnicity (*continued*)

Read code	Description
9S12.00	Other white ethnic group
9i7..00	Indian or British Indian – ethnic category 2001 census
9i8..00	Pakistani or British Pakistani – ethnic category 2001 census
9S7..00	Pakistani
9S6..00	Indian
9iC..00	African – ethnic category 2001 census
9i9..00	Bangladeshi or British Bangladeshi – ethn categ 2001 census
9i24.00	Northern Irish – ethnic category 2001 census
9S3..00	Black African
9i2F.00	Polish – ethnic category 2001 census
9SJ..00	Other ethnic group
9i2R.00	Oth White European/European unsp/Mixed European 2001 census
9i1..00	Irish – ethnic category 2001 census
9i2 T.00	Other White or White unspecified ethnic category 2001 census
9i22.00	Welsh – ethnic category 2001 census
9SH..00	Other Asian ethnic group
9S8..00	Bangladeshi
9i21.00	Scottish – ethnic category 2001 census
9iA..00	Other Asian background – ethnic category 2001 census
134 N.00	RACE: White
9iB..00	Caribbean – ethnic category 2001 census
9S11.00	White Irish
9iAA.00	Other Asian or Asian unspecified ethnic category 2001 census
9i6..00	Other Mixed background – ethnic category 2001 census
9i3..00	White and Black Caribbean – ethnic category 2001 census
9iA8.00	British Asian – ethnic category 2001 census
9S2..00	Black Caribbean
9S14.00	Other white British ethnic group
9i2B.00	Italian – ethnic category 2001 census
9i4..00	White and Black African – ethnic category 2001 census
9iF..00	Other – ethnic category 2001 census
9i5..00	White and Asian – ethnic category 2001 census
9iD2.00	Black British – ethnic category 2001 census
9S9..00	Chinese
9iE..00	Chinese – ethnic category 2001 census
9SB2.00	Other ethnic, Asian/White orig
9iD0.00	Somali – ethnic category 2001 census
9iFK.00	Any other group – ethnic category 2001 census
9iF2.00	Filipino – ethnic category 2001 census
9iF7.00	Muslim – ethnic category 2001 census
9iD..00	Other Black background – ethnic category 2001 census
134B.00	RACE: Caucasian
9SAC.00	Other European (NMO)

NMO, non-mixed origin.

Covariate drug use

Covariate drug use was identified within the same time periods as the exposure of interest, therefore, for comparisons involving the B1 exposure cohorts covariate use of anticonvulsant mood stabilisers, lithium, antipsychotics, antidepressants, hypnotics and anxiolytics was identified by searching for prescriptions for these drugs between 31 days (≈ 1 month) and 105 days (15 weeks) (inclusive) after pregnancy start. Likewise, for the B2 exposure cohorts, covariate drug use was identified by searching for women with prescriptions for these drugs within the 92 days prior to the delivery date.

Pre-existing hypertension

The definition of pre-existing hypertension is described under the outcome *Pre-eclampsia and/or gestational hypertension*.

Pre-existing diabetes

The definition of pre-existing hypertension is described under the outcome *Gestational diabetes.*

Recent depression

Women with a recent history of depression were identified by searching the mother's medical records for relevant Read codes (*Table 74*) in the 3 years prior to the estimated LMP.

TABLE 74 Read codes used to identify depression

Read code	Description
E2B..00	depressive disorder nec
Eu32z11	[x]depression nos
E200300	anxiety with depression
E204.11	postnatal depression
1B17.00	Depressed
9H92.00	depression interim review
1465.00	h/o: depression
1BT..00	depressed mood
Eu32.00	[x]depressive episode
E204.00	neurotic depression reactive type
2257.00	o/e – depressed
E113.11	endogenous depression – recurrent
8BK0.00	depression management programme
E112.11	agitated depression
Eu32z00	[x]depressive episode, unspecified
Eu32100	[x]moderate depressive episode
E112.13	endogenous depression first episode
Eu32z14	[x] reactive depression nos
E113700	recurrent depression
E112.14	endogenous depression
Eu33.00	[x]recurrent depressive disorder
E2B1.00	chronic depression
Eu41200	[x]mixed anxiety and depressive disorder

TABLE 74 Read codes used to identify depression (*continued*)

Read code	Description
9H91.00	depression medication review
E112.00	single major depressive episode
Eu32000	[x]mild depressive episode
62T1.00	puerperal depression
Eu32200	[x]severe depressive episode without psychotic symptoms
E113.00	recurrent major depressive episode
9k4..00	depression – enhanced services administration
Eu32z12	[x]depressive disorder nos
8CAa.00	patient given advice about management of depression
9Ov0.00	depression monitoring first letter
9Ov..00	depression monitoring administration
9hC0.00	excepted from depression quality indicators: patient unsuita
Eu53011	[x]postnatal depression nos
9H90.00	depression annual review
9hC1.00	excepted from depression quality indicators: informed dissen
9HA0.00	on depression register
E113200	recurrent major depressive episodes, moderate
9Ov1.00	depression monitoring second letter
Eu32400	[x]mild depression
Eu34114	[x]persistant anxiety depression
Eu32.11	[x]single episode of depressive reaction
E112200	single major depressive episode, moderate
9Ov2.00	depression monitoring third letter
9k40.00	depression – enhanced service completed
Eu33.11	[x]recurrent episodes of depressive reaction
Eu33100	[x]recurrent depressive disorder, current episode moderate

h/o, history of; nec, not elsewhere classified, nos, not otherwise classified.
[x], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

Severe mental illness

Women with a history of a severe mental illness were identified by searching the mother's medical records for relevant Read codes (*Table 75*) recorded at any point before the estimated LMP.

Epilepsy

Women with a history of epilepsy were identified by searching the mother's medical records for relevant Read codes (*Table 76*) recorded at any point before the estimated LMP.

TABLE 75 Read codes used to identify severe mental illnesses

Read code	Description
Eu31.00	[x]bipolar affective disorder
9H8..00	on severe mental illness register
E10..00	schizophrenic disorders
9H6..00	on national service framework mental health
Eu2z.11	[x]psychosis nos
Eu30000	[x]hypomania
E13z.11	psychotic episode nos
E11..11	bipolar psychoses
Eu25.00	[x]schizoaffective disorders
Eu22015	[x]paranoia
E103.00	paranoid schizophrenia
E13z.00	nonorganic psychosis nos
Eu31.11	[x]manic-depressive illness
E10z.00	schizophrenia nos
Eu32300	[x]severe depressive episode with psychotic symptoms
E117.00	unspecified bipolar affective disorder
Eu22011	[x]paranoid psychosis
E12..00	paranoid states
1464.00	h/o: schizophrenia
E110100	single manic episode, mild
E107.00	schizo-affective schizophrenia
146H.00	h/o: psychosis
E11..12	depressive psychoses
Eu30.00	[x]manic episode
E11..00	affective psychoses
E130.11	psychotic reactive depression
E12z.00	paranoid psychosis nos
Eu20.00	[x]schizophrenia
Eu23.00	[x]acute and transient psychotic disorders
Eu31700	[x]bipolar affective disorder, currently in remission
E13..00	other nonorganic psychoses

TABLE 75 Read codes used to identify severe mental illnesses (*continued*)

Read code	Description
Eu30z11	[x]mania nos
E110.11	hypomanic psychoses
E120.00	simple paranoid state
146D.00	h/o: manic depressive disorder
E116.00	mixed bipolar affective disorder
Eu30100	[x]mania without psychotic symptoms
Eu2..00	[x]schizophrenia, schizotypal and delusional disorders
E110000	single manic episode, unspecified
E115.11	manic-depressive – now depressed
Eu33300	[x]recurrent depress disorder cur epi severe with psyc symp
E114.11	manic-depressive – now manic
Eu30.11	[x]bipolar disorder, single manic episode
Eu32313	[x]single episode of psychotic depression
E100000	unspecified schizophrenia
E1. . .00	non-organic psychoses
E100200	chronic schizophrenic
Eu20000	[x]paranoid schizophrenia
Eu31000	[x]bipolar affective disorder, current episode hypomanic

h/o, history of; nec, not elsewhere classified, nos, not otherwise classified.
[x], signifies Read codes that have been added to ensure mapping to all ICD codes, necessary for hospital recording.

TABLE 76 Read codes used to identify epilepsy

Read code	Description
F25..00	Epilepsy
8BIF.00	epilepsy medication review
667F.00	seizure free > 12 months
6675.00	fit frequency
667..00	epilepsy monitoring
6676.00	last fit
6110.00	contraceptive advice for patients with epilepsy
67IJ000	pre-conception advice for patients with epilepsy
67AF.00	pregnancy advice for patients with epilepsy
9Of0.00	epilepsy screen invite 1
R003z11	[d]seizure nos
9Of1.00	epilepsy screen invite 2
8IB4.00	pregnancy advice for patients with epilepsy not indicated
8IB3.00	pre-conception advic fr patients with epilepsy not indicated

continued

TABLE 76 Read codes used to identify epilepsy (*continued*)

Read code	Description
9h62.00	excepted from epilepsy quality indicators: informed dissent
8IB2.00	Contraceptive advice for patients with epilepsy not indicated
667Q.00	1–12 seizures a year
1473.00	h/o: epilepsy
F25z.11	Fit (in known epileptic) nos
9N0r.00	Seen in epilepsy clinic
F251600	Grand mal seizure
F251000	Grand mal (major) epilepsy
9Of2.00	Epilepsy screen invite 3
9h61.00	Excepted from epilepsy quality indicators: patient unsuitabl
F254000	Temporal lobe epilepsy
667P.00	No seizures on treatment
6672.00	Follow-up epilepsy assessment
F250000	petit mal (minor) epilepsy
667R.00	Two to four seizures a month
667C.00	Epilepsy control good
667S.00	One to seven seizures a week
282..13	o/e – a seizure
667Z.00	Epilepsy monitoring nos
F25z.00	Epilepsy nos
9Of5.00	Epilepsy monitoring call first letter
2828.00	Absence seizure
8IAh.00	Pre-conception advice for patients with epilepsy declined
8IAg.00	Contraceptive advice for patients with epilepsy declined
F254500	Complex partial epileptic seizure
8IAi.00	Pregnancy advice for patients with epilepsy declined
9Of..00	Epilepsy screen administration
F251400	Epileptic seizures – tonic
F250011	Epileptic absences
9Of6.00	Epilepsy monitoring call second letter
9N4V.00	DNA – did not attend epilepsy clinic
F251011	Tonic–clonic epilepsy
667T.00	Daily seizures
F255011	Focal epilepsy
F251200	Epileptic seizures – clonic

[d], working diagnosis; h/o, history of; o/e, on examination; nos, not otherwise specified.

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