Maternal perinatal mental illnesses and adverse pregnancy outcomes: Population-based studies using data from United Kingdom primary care

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Abstract

Background: Perinatal mental illness, especially depression, is a leading cause of maternal morbidity and mortality in high-income countries. In the United Kingdom (UK), mental illness commonly presents to and is treated at primary care level; however there are no up-to-date estimates of the burden of different mental illnesses in women in and around pregnancy. The potential impact of mental illness with or without psychotropic medication on the risk of non-live pregnancy outcomes is unclear. In this context, the safety of psychotropic drugs, especially antidepressants, remains controversial.

Aim and objectives: To estimate the clinical burden of depression, anxiety and serious mental illness (defined as bipolar disorder, schizophrenia and other related psychotic disorders) presenting to and/or being treated in UK primary care, and to investigate the effects on pregnancy outcomes while trying to differentiate the effects of psychotropic medication from mental illness itself.

Methods: Women aged 15-45 years from 1990 to 2009 were identified from The Health Improvement Network, a UK primary care database. Coding of mental illness diagnoses and psychotropic drug prescriptions were examined by separately assessing the proportions of women with recordings of diagnoses, symptoms, and drug prescriptions over the study period. Three separate studies were then carried out. A cross-sectional study was firstly conducted to estimate the prevalence and diagnostic overlap of mental illnesses before, during and after pregnancy and the variation by maternal age, socioeconomic status and other maternal factors. The second study examined the risks of non-live pregnancy outcomes (defined as perinatal death, miscarriage, and termination) in women with no history of depression and anxiety, a diagnosis of such illness prior to pregnancy, illness during pregnancy or illness during pregnancy with use of medication (stratified by medication type).

Multinomial logistic regression models were used to compare risks of non-live outcomes across these groups, adjusting for important socio-demographic and lifestyle characteristics. The third study examined the risks of major and system-specific congenital anomalies in children born to women with depression or anxiety that was untreated or treated with psychotropic medication. Logistic regression with a generalised estimating equation was used to compare risks of major congenital anomalies in children exposed and unexposed to psychotropic medication during the first trimester of pregnancy, adjusting for important socio-demographic, lifestyle and chronic comorbidity in the mother.

Results: There were 344,042 women who had one or more singleton pregnancies identified between age 15 and 45 from 1990 to 2009. Recording of mental illness and prescriptions of psychotropic drugs increased considerably over the study period. There was high prevalence and overlap of different maternal mental illnesses, especially depression and anxiety, during and after pregnancy, and the prevalence was generally highest in younger, socioeconomically deprived women who had smoked before childbirth, were outside the normal range of BMI and had other chronic medical conditions, such as diabetes. Socioeconomic deprivation was associated with increased risk of all mental illnesses, although the impact of deprivation was more marked in older women. Those aged 35-45 in the most deprived group had 2.63 times the odds of antenatal depression (95% confidence interval [CI] 2.22-3.13) compared with the least deprived; in women aged 15-25 the increased odds associated with deprivation was more modest (odds ratio [OR]=1.35, 95%CI 1.07-1.70). Similar patterns were found for anxiety and serious mental illness.

Women with antenatal exposure to antidepressant or anti-anxiety drugs showed the greatest increased risks for non-live pregnancy outcomes, relative to those with no history of depression or anxiety, although women with prior (but currently un-medicated) illness also showed modest increased risks. Compared with un-

medicated antenatal morbidity, there was weak evidence of an excess risk in women taking tricyclic antidepressants (TCAs), and stronger evidence for other medications.

The absolute risks of major and system-specific congenital anomalies were small in the general population (269 per 10,000 children for major congenital anomalies). Compared with un-medicated antenatal depression or anxiety (278 per 10,000 children for major congenital anomalies), the use of antidepressants during early pregnancy was associated with excess risks, especially for selective serotonin reuptake inhibitors (SSRIs) (290 per 10,000 children for major congenital anomalies). Compared with children born to women with no depression or anxiety, there was an increased risk of heart anomalies in children with antenatal exposure to SSRIs (adjusted OR=1.25, 95% 95%CI 1.02-1.53), particularly in those exposed to paroxetine (adjusted OR=1.89, 95%CI 1.24-2.88). Children exposed to sertraline and escitalopram also had similar increased risks, although fewer women were exposed to these drugs. No increased risks of major congenital anomalies were found in children exposed to TCAs or benzodiazepines; however, the risks of right ventricular outflow tract anomalies were notably higher for all drug classes.

Conclusion: Strong socioeconomic inequalities in perinatal mental illnesses occur and persist with increasing maternal age. Women with depression or anxiety have higher risks of miscarriage, perinatal death and therapeutic terminations than women without these diagnoses and the risks are even higher if prescribed psychotropic medication during early pregnancy than if not. There is also an increased risk of congenital heart anomalies in children exposed to paroxetine and other SSRIs during the first trimester compared with those who are unexposed, although the absolute risk is small. There could be other associated factors also related to depression, anxiety or use of medications, which yet unlikely fully explain the observed excess risks. Whilst medicated depression or anxiety could be a marker of more severe illness than un-medicated ones, my findings indicate there may be some specific drug effects.

Targeting detection and effective interventions to women at risk of mental illness during pregnancy may reduce inequity and avoid substantial psychiatric morbidity, and subsequently reduce the need for further psychotropic treatment. GPs and other health care professionals should take a cautious approach when managing mental illness in pregnant women. The findings in this thesis provide vital information for this purpose, namely helping communicate the magnitude of risk of major congenital anomalies to women with the use of different psychotropic drugs in the context of the baseline risk in the general population.

List of Publications from the Work

Peer Reviewed Journal Publications

- Ban L, Gibson JE, West J, Fiaschi L, Oates M and Tata LJ. 2012. Impact of socioeconomic deprivation on maternal perinatal mental illnesses presenting to UK general practice. British Journal of General Practice; 62: 524-525.

- Ban L, Tata LJ, West J, Fiaschi L and Gibson JE. 2012. Live and non-live pregnancy outcomes among women with depression and anxiety: a population-based study. PLoS ONE; 7(8): e43462.

Conference Presentations

- Ban L, Gibson JE, West J and Tata LJ. 2011. Variations in perinatal depression, anxiety and severe mental illnesses by maternal age and socioeconomic group: a population-based study in UK primary care data. Journal of Epidemiology & Community Health; 65 (Supplement 1: IEA World Congress of Epidemiology 2011 Abstracts): A324.

- Ban L, Tata LJ, West J and Gibson JE. 2010. Changes in antidepressant prescribing and switching in women: a United Kingdom population-based study. International Journal of Longitudinal and Life Course Studies (Supplement: CELSE2010 Abstracts); 1(3):180.

- Ban L, Gibson JE, West J and Tata LJ. 2010. Prevalence and overlap of mental illnesses in and around pregnancy: a United Kingdom population-based study. International Journal of Longitudinal and Life Course Studies (Supplement: CELSE2010 Abstracts); 1(3):295.

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Data were obtained from Cegedim Strategic Data for Medical Research (CSD-MR), and were initially processed by Mr Chris Smith. Dr Linda Fiaschi extracted and provided me basic data for analyses in this thesis, including a linked mother-and-child dataset. Rachel Sokal provided me a Read code list for all congenital anomalies. Dr Margaret Oates from East Midlands Perinatal Mental Health Clinical Network provided valuable insight into clinical practice and knowledge in perinatal mental illness. I sincerely thank their contributions to the studies in this thesis.

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List of Abbreviations

BDI	Beck Depression Inventroy
BMI	body mass index
BNF	British National Formulary
CAs	congenital anomalies
CES-D	Centre for Epidemiological Studies-Depression
CI	confidence interval
C/O	complain of
CSD-MR	Cegedim Strategic Data for Medical Research
DSM	Diagnostic and Statistical Manual of Mental Disorders
EUROCAT	European Surveillance of Congenital Anomalies
EPDS	Edinburgh Postnatal Depression Scale
GP	general practitioner
GPRD	General Practice Research Database
ICD	International Classification of Disease
InPS	In Practice Systems
IQR	interquartile range
NEC	not elsewhere classified
NICE	National Institute for Health and Clinical Excellence
NOS	not otherwise specified

O/E	on examination of
OR	odds ratio
QOF	Quality and Outcomes Framework
RDC	Research Diagnostic Criteria
RRR	relative risk ratio
SADS	Schedule for Affective Disorder and Schizophrenia
SCID	Structured Clinical Interview for DSM Disorders
SD	standard deviation
SSRIs	selective serotonin re-uptake inhibitors
TCAs	tricyclic antidepressants
THIN	The Health Improvement Network
UK	United Kingdom
USA	United States of America

Terminology of Time-periods Related to Pregnancy

- Antenatal (also antepartum): the period when a woman is pregnant.
- Postnatal (also postpartum): the period following delivery. Analyses in this thesis use 9 months; however, there is no strict definition and studies may use only a few weeks, 6 months, 9 months or up to a year.
- Neonatal period: the 28 days after delivery.

1 Introduction

1.1 Background

1.1.1 The current burden of mental illness

The most recent global burden of disease study from the World Health Organisation updated in 2004 reports that mental disorders, such as depression, anxiety, alcohol use disorders, bipolar disorder and schizophrenia and other related psychoses, are among the 20 leading causes of disability worldwide.[1] Particularly, unipolar depression contributes considerably to the disease burden and is the third leading cause of disability worldwide, first in middle- and high-income countries and eighth in low-income countries.[1] Mental illness has recently been estimated to cost £105 billion annually to the economy in England, of which around £30 billion is work related.[2,3] Nearly 11% of the annual secondary care health budget in England is spent on mental health[4] and the cost of treating mental health problems are expected to double before the year 2026.[5] In the United States (USA), the estimated economic burden of mental disorders from health care expenditure, loss of earnings and disability benefits was over $300 billion in 2002, equivalent to more than $1,000/year for every person in the country.[6]

Compared with men, women are particularly vulnerable to mental illness, especially common mental disorders (such as depression and anxiety).[7] Unipolar depression is estimated to be twice as common in women as in men,[8–10] and contributes the most years of healthy life lost for women aged 15-44 years in both high-income and low- and middle-income countries.[1]

In addition, it is common for women to have mental health problems, especially depression, during the perinatal period.[11] A recent systematic review of studies from across the world reported 6.5-12.9% of women had depression during pregnancy and

in the first year postpartum.[12] Although both high and low income countries have recognised the pressing need to detect and address maternal psychosocial health problems within antenatal and postnatal care pathways,[13–19] few have developed comprehensive strategies for universal screening and management.[16,17,19] Current guidance from the United Kingdom's (UK) National Institute for Health and Clinical Excellence (NICE) has emphasised that perinatal mental illness is one of the most important issues in women's health,[19] yet there are no up-to-date estimates of the current burden of these conditions available at a population level in the UK.

1.1.2 Maternal age, socioeconomic status and other factors associated with perinatal mental illness

Socio-demographic factors have a significant impact on mental illness, which is well recognised in the general population, yet there have been less studies specifically in relation to maternal mental illness. A US study published in 2010, including more than 75,000 non-pregnant women aged 18-44, found that the prevalence of major depression was greatest in women over 35 years of age, unmarried, less educated, unable to work or unemployed, and with low income.[20] In addition, the latest UK national mental illness strategy highlighted the importance of reducing health inequalities as a key objective to promote mental wellbeing in the population,[2] yet there remains a need to effectively identify and treat those who are most vulnerable. Whilst the increased risks of mental illness in people with greater socioeconomic deprivation has been well documented in the general population,[21] very few studies have assessed this in women during the perinatal period and it is unclear if this may vary by type of illness, notably depression, anxiety or more severe mental illness, such as psychosis. Previous research has shown that women with greater socioeconomic deprivation were more likely to have perinatal mental illness than those with lower socioeconomic deprivation after adjusting for other socio-

demographic factors.[22–25] The results, however, are inconsistent with other studies that did not show such associations.[22,23,26,27]

Studies of the age at which women are at greatest risk of different perinatal mental illnesses are also limited.[22,26–28] Patterns of the effect of maternal age on perinatal mental illness have been inconsistent in different studies,[22,26–28,25] showing both decreased[28] and increased[26,27] risks in older women. Whilst there is evidence that material deprivation may have varied impacts on different age groups, this has not been assessed in pregnant women.[29]

1.1.3 Impacts of perinatal mental illness and exposure to psychotropic medication

Maternal perinatal mental illness has an unfavourable impact on both the short-term and long-term physical and mental health of offspring. For common mental illnesses, such as depression and anxiety, considerable research has been conducted to examine the impact on women's pregnancies and also on neonatal health. It has been shown that women with antenatal depression and anxiety have increased risks of a range of adverse pregnancy complications including preeclampsia,[30] preterm delivery,[31] prolonged labour,[32] and caesarean delivery.[33] For severe mental illness, such as psychoses, prior studies have suggested that women with schizophrenia are more likely to have placental abruption and to have children with low birth weight and congenital heart anomalies.[34] Whether these associations are causal or due to other factors associated with mental illness is unclear, and there may be multiple mechanisms involved. Previous research has highlighted associations of mental illness with maternal smoking and other lifestyle behaviours[35], but also with abnormal endocrine and immune regulation,[36] which may directly impair growth and development of the foetus and have an adverse impact on offspring such as foetal growth retardation and low birth weight.[37]

There is increased concern over the use of psychotropic medications during pregnancy in terms of potentially increased risks of adverse pregnancy and neonatal outcomes. A recent systematic review on the safety of antipsychotic drugs in human pregnancy including papers published in English from 1966 to 2008 suggests that although there is little evidence of an important association between the use of antipsychotics during pregnancy and an increased risk of adverse pregnancy outcomes including congenital anomalies, the current evidence is insufficient to make a definitive conclusion in terms of the gestational safety of these drugs.[38] Despite this uncertainty, the use of antidepressants during pregnancy has increased dramatically in the last two decades.[39] Only from 2012 the British National Formulary (BNF) recommended that selective serotonin reuptake inhibitors (SSRIs) should not be used during pregnancy due to the potential adverse pregnancy and neonatal outcomes.[40]

Non-live pregnancy outcomes

Previous literature has indicated that mothers with mental illness during pregnancy have increased risks of stillbirth and neonatal death in their offspring.[41–44] A large population-based study in Denmark, for example, found that mothers with psychiatric disorders during pregnancy had a 42% increased risk of stillbirth (relative risk ratio [RRR]=1.42, 95% confidence interval [CI] 1.23-1.63) and a 65% increased risk of neonatal death (RRR=1.65, 95% CI 1.44-1.90) in their offspring compared with mothers without such illness during pregnancy.[43] The results however are inconsistent. A population-based study in Western Australia for instance did not find any statistically significant association of perinatal death in offspring of mothers with psychiatric disorders.[34]

In addition, women with mental illness are commonly treated with psychotropic drugs, particularly antidepressants and anti-anxiety medications. Previous research suggests that women prescribed some antidepressants during early pregnancy also

have increased risks of non-live pregnancy outcomes, including perinatal death,[45,46] miscarriage,[45,47,48] and termination.[45,49] However, the majority of these studies have been small-scale in highly selected study populations and few have considered the contribution of the underlying mental health conditions which necessitate treatment to the observed effects.[50]

Congenital anomalies in offspring

There is increased concern over the use of some SSRIs, particularly paroxetine, during early pregnancy in terms of the risk of major congenital anomalies in the offspring. In 2005, The USA Food and Drug Administration changed the pregnancy safety category for paroxetine from category C to category D with a warning of potential increased risks of congenital heart anomalies in children exposed to paroxetine in early pregnancy.[51] A recent UK national guideline on perinatal mental illness published in 2007 also highlighted the association between paroxetine taken during the first trimester with congenital heart anomalies (but not with fluoxetine).[19] However, there was very limited evidence at that time and the subsequent research findings are very controversial.[52,53] Studies on specific SSRI drugs have found increased risks of congenital heart anomalies, particularly septal heart defects and ventricular outflow tract defects, in children of women prescribed paroxetine and fluoxetine during early pregnancy,[53–55] yet these results are not consistent.[56,57] The relative safety of different antidepressants has been further clouded by a focus on studying paroxetine and SSRIs overall and publishing these data, leaving many fewer publications on the safety of other individual SSRI drugs or non-SSRI drug classes.

In addition, there is little information available on the safety of tricyclic antidepressants (TCAs) and benzodiazepines in pregnant women despite their continued use in this population and few studies have examined the effects of women's underlying mental health condition as well as the contribution of non-mental health comorbidity.

Previous studies on the safety of TCAs exclusively in pregnant women in Sweden[58] and the USA[59] have reported that children born to women prescribed TCAs during pregnancy had increased risks of heart defects,[58] limb abnormalities, and spina bifida.[59] However, no such findings have been published in other populations. In addition, some earlier studies found greater risks of congenital anomalies, particularly oral clefts and cleft palate, in children exposed to benzodiazepines during pregnancy compared with those unexposed children.[60–62] More recent studies however did not find such associations.[63–68]

1.2 Weakness of current studies in estimating pregnancy risks

Due to ethical concerns, it is impossible to conduct drug trials in pregnant women. In addition, certain rare pregnancy outcomes, such as stillbirth and specific congenital anomalies, require large study designs. However, previous studies generally use data from voluntary drug safety registers, or small highly selected groups, with potential problems of retrospective exposures and external comparison groups. Recent studies from Denmark, Sweden and Finland have overcome some of these concerns by using their large routinely-collected and national-representative databases. Although such large databases are also available in the UK, very few UK studies on pregnancy risks have been conducted using these data.

1.3 Rationale and objectives

Perinatal mental illness causes a considerable health and socioeconomic burden in high-income countries, yet in the UK there are no up-to-date estimates of this burden, especially for anxiety and serious mental illness (such as psychotic disorder) available at a population level. The most affected socio-demographic groups remain unclear.

Although previous research has suggested increased risks of adverse pregnancy and neonatal outcomes in women with mental illness, such increased risks could be attributed not only to disease itself but also to the use of psychotropic medication, such as antidepressants or anti-anxiety drugs, as well as other maternal characteristics associated with mental illness. In addition, no population-based cohort study has been carried out in the UK to investigate the effects of exposure to psychotropic medications, especially newer antidepressants, in women during early pregnancy on the risk of congenital anomalies in their offspring. It is important to use prospectively collected data on both exposures and outcomes in very large study populations to answer such questions. UK primary care data is one such available source and will provide contemporary information that is clinically relevant to the UK.

The objectives of this thesis are, therefore:

- To estimate the prevalence and overlap of different mental illnesses presenting to, diagnosed and treated in UK general practice in women of childbearing age and around the perinatal period;
- To examine the impact of maternal age, socioeconomic status and other maternal factors on the risk of maternal perinatal mental illness;

- To estimate the association between mental illness in women during pregnancy and the risk of non-live pregnancy outcomes (i.e. stillbirth and neonatal death, miscarriage and therapeutic termination);
- To examine whether the risks of adverse pregnancy outcomes differ between women with and without antenatal psychotropic drug treatment;
- To measure the association between maternal exposure to treated or untreated mental illness during early pregnancy and the risk of congenital anomalies in offspring.

1.4 Outline of the thesis

The subsequent chapters of this thesis discuss firstly the data used for the work, secondly defining and assessing maternal mental illness using primary care data, followed by three separate studies that address the main research objectives of this thesis. The outline below briefly describes the content of each chapter.

Chapter 2: Description of The Health Improvement Network (THIN) general practice database, the database of linked mother-child records extracted from THIN, and a brief description of the study ethics, the datasets extracted from the database for all analyses and statistical software used.

Chapter 3: Description of approaches of identifying maternal mental illness in UK general practice and a series of analyses to assess the recording of mental illness in the general population of women of childbearing age presenting to UK primary care.

Chapter 4*: In the first study, the prevalence and overlap of different maternal perinatal mental illnesses presenting to UK primary care are estimated and the variations by maternal age, socioeconomic status and other maternal factors are quantified.

Chapter 5*: In the second study, risks of non-live pregnancy outcomes, namely perinatal death, miscarriage and termination, in pregnant women with depression and anxiety are compared with those women without depression or anxiety. The impact of psychotropic treatment on these risks is also assessed.

Chapter 6*: In the third study, risks of congenital anomalies in live-born children are estimated and these risks are compared between women with and without antidepressant or anti-anxiety drugs in the first trimester of pregnancy.

*As three separate studies, Sections 4-6 each contain their own introduction (with a detailed literature review tailored for the study), description of methods, results, discussion and conclusion.

Chapter 7: Summary of the main findings in the thesis, suggested clinical implications and directions of future research.

1.5 Role of the candidate

The initial idea for this PhD was from my principal supervisor Dr Laila Jal Tata. The candidate continued to develop the project and each specific research question, with guidance from my supervisors Dr Laila J Tata, Dr Jack E Gibson and Dr Joe West. Data were obtained from Cegedim Strategic Data for Medical Research (CSD-MR), and were initially processed by Mr Chris JP Smith. Dr Linda Fiaschi extracted and provided a database of women of childbearing age and linked mother-and-child general practice records used for this thesis. The candidate conducted the literature review, extracted Read codes for mental illness and medication, and carried out all the data management to create individual datasets for each study and all statistical analyses. The candidate was provided with lists of Read codes for other conditions (i.e. smoking, body mass index, diabetes, hypertension, asthma, epilepsy and congenital anomalies) for the purpose of some analyses. The candidate generated all tables and figures and wrote the thesis. The final draft was read and approved by all three supervisors before submission.

2 Description of the data used for the work

This chapter describes The Health Improvement Network (THIN), a database of computerised primary health care records in the United Kingdom, which is used for all analyses in this thesis. This chapter also includes a brief description of the study ethics, datasets extracted from the database and statistical software used.

2.1 The Health Improvement Network Database (THIN)

2.1.1 Background

THIN is a large computerised database containing primary care anonymised patient medical records that are collected from UK general practice. The database was set up in 2002 through the collaboration of a medical research organisation, known as EPIC (later CSD-MR), with In Practice Systems (InPS) who provide Vision software to around 2000 general practices in the UK. InPS have written unobtrusive data collection software for Vision practices that have joined the THIN scheme and data are downloaded from general practices monthly. Although the THIN scheme started in 2003, EPIC has been collaborated with InPS in data collection much earlier and most data were collected prospectively from 1988 onwards. For this thesis, the database contained information from 429 general practices across England, Scotland, Wales and Northern Ireland, comprising a total of 7.7 million patients of which more than three million patients were actively registered with the practices (the remaining patients had prospectively collected historic data but have either left the practice or died). Most of these contributing practices had recorded over 15 years of data on their system.

2.1.2 Information contained in THIN

Upon data collection, patient identifying information such as name, address, exact date of birth and NHS number is stripped and is not exported from the computer system of THIN general practices. Although identifying information is never available

to THIN, each patient in THIN has a unique identification number for use by researchers. Additional demographic data such as age and sex are retained. Patients that live at the same address (including residential homes and flats) or are members of the same family can be linked using a household identification number provided they are registered with the same general practice. THIN patients' postcode information is also derived to measure socioeconomic status using household-level Townsend Index of Deprivation based on 2001 census data. THIN also contains patient lifestyle information, such as smoking and alcohol intake, provided these are recorded by their general practitioner (GP) in the course of clinical care.

Medical conditions and symptoms reported by patients to their GP during a consultation are recorded using Read codes, which is a very comprehensive, hierarchal clinical classification system and can be cross-referenced to the International Classification of Disease.[69] Information on referrals to secondary care is also recorded. Secondary care information, such as hospital admissions, discharge medication and diagnosis, outpatient consultation diagnosis, investigation and treatment outcomes, received by the practice should be transcribed and entered retrospectively. Although the completeness of such transcribed information is uncertain, major medical events and diagnoses are mostly likely entered the primary care records.

Compared to medical events and diagnoses, GP prescribing is particularly well recorded since the computerised system used by the GP is also used to print a copy of the prescription form for the patient to present at the pharmacy. Drug prescribing through the computerised system is recorded using the Multilex coding system,[70] linked to chapters of the BNF. Drugs prescribed by hospital doctors or other specialists will not appear in THIN data unless the treatment is continued in general practice. However, due to the constraints of specialist/hospital prescribing budgets, prescriptions issued outside of the general practice will usually only cover the first

seven days. After this time the patient will be required to get further prescriptions from their GP.

THIN data are organised by practice. The information for each patient is contained in five separate files, which can be linked by the patient and practice identification numbers. Table 2-1 shows the major information contained in THIN.

Table 2-1 The information contained in The Health Improvement Network

Files	Information contained
Patient file	Basic socio-demographic information, such as sex, registration date, date of birth/death, transfer-out date
Medical file	Medical symptoms, disease diagnoses, hospital admissions, medical procedures and investigations *(coded using Read codes)*
Therapy file	Drug prescriptions, including frequency, quantity, dose, formulation of medication *(coded using Multilex codes)*
Additional Health Data file	Additional health information, such as lifestyle and preventative health care *(coded using Read codes)*
Postcode variable indicators	Socioeconomic, ethnicity and environmental indices

2.1.3 Retrospective and prospective recording in THIN

Several dates are used in THIN to indicate when data were being prospectively recorded to a certain standard of quality and completeness. The date of computerisation is calculated by EPIC from therapy records and is the date when the practice first started issuing prescriptions from the computer every day for a certain number of consecutive months. The date for Vision is the date when the practice started using the Vision practice management software to record consultations. The acceptable mortality reporting date denotes the year from which the practice was deemed to be correctly reporting all-cause mortality rates based on predicted numbers of deaths derived from national statistics, given the practice's age/sex register.[71]

2.1.4 Justification for using THIN

One major advantage of THIN for epidemiological research is that it provides routinely, prospectively collected patient information for a large, nationally representative population.[72] THIN is a very large primary care database, making it particularly attractive for research on uncommon conditions, such as schizophrenia and other related psychotic disorders (the prevalence of which is about 1-2 per 1000 women during the perinatal period, as shown in Section 1.1.1). Although depression is relatively common in the general population, THIN provides a good opportunity to examine the impact on rare pregnancy outcomes, such as perinatal death and some specific congenital anomalies. A recent UK study published in 2010 has suggested that primary care data can be used to identify a wide range of congenital anomalies, which can be done just through the patients' computerised medical records.[73]

In addition, THIN has a high standard of validated records of medical conditions (including diagnoses and symptoms) and prescriptions.[72,74] A recent study published in 2010 has validated the depression diagnosis in THIN patients.[75] In this study, the authors sent questionnaires to GPs requesting confirmation information for a random

sample of 140 patients diagnosed with depression and found 89.6% of the patients' diagnoses were confirmed. Another similar study using THIN data conducted by the same group of authors has validated anxiety diagnoses.[76]

Whilst GPs can always enter retrospective health information, the majority of data in THIN are prospectively recorded by GPs as part of routine health care in the general practice. By comparing the date of patient's registration with a GP and the date of a medical event one can ascertain whether certain information may be retrospectively recorded. Therefore, it is less likely to have recall errors or recall bias in the recording of individual diagnoses, symptoms and other medical events in comparison with questionnaire studies of medical histories. However, as some of the data included in THIN are based on correspondence from secondary care it is possible that there is some misclassification in the recording of exact dates of events.

The quality of GP prescription recording is particularly good since the computerised system used by the GP is also used to print a copy of the prescription form. Whilst it is of course not possible to be certain that those prescribed will have definitely been exposed and exactly when, this limitation holds also for questionnaire studies that rely on patient memory and reporting of taking specific drugs.

THIN downloads data from practices every month and follows up individual patients until they or their practices exist to contribute to THIN. The data I used were collected from June 1987 to July 2009, which provides a good opportunity to investigate the potential changes of mental illness diagnoses and treatment in UK primary care over time as well as to understand the contemporary experience of women with mental illness in and around pregnancy. However since both THIN practices and patients can enter and/or exit THIN at different times, some patients may have relatively short follow-up time periods compared to others in THIN, requiring analyses that account for open cohort data.

THIN also contains basic socio-demographic and patient lifestyle information reported to the GP, such as smoking, body mass index (BMI) and socio-economic status. However, there is a potential problem regarding missing data. As the information collected in THIN is not for research purposes, but based on what was deemed important and relevant for the on-going health care of the individual patient, it is likely that there are biases in which data are missing. For example, a GP may be more likely to record a woman's smoking status during pregnancy if the woman is a regular smoker and the GP think this may adversely affect the pregnancy outcome and the health outcome of the offspring.

2.1.5 Quality and Outcomes Framework

In 2004, the Quality and Outcomes Framework (QOF) was introduced as part of the General Medical Services Contract.[77] The QOF is a voluntary incentive scheme for all general practices in the UK, which rewards GPs for how well they care for their patients. The QOF contains four main components (known as domains), including clinical, organisational, patient experience and additional service domains. A set of achievement measures, known as indicators, have been selected and developed in each domain to measure the health care quality for patients in each GP surgery. The QOF gives an indication of the overall achievement of a practice through a points system, which contains groups of indicators, against which practices score points according to their level of achievement. The higher the score, the greater the financial reward for the practice.

The clinical indicators include mainly chronic health conditions, such as coronary heart disease, hypertension, diabetes, epilepsy, and asthma. Some indicators for mental illness have also been developed. There are no specific indicators for pre-pregnancy or pregnancy care other than the offer of antenatal care and screening according to local guidelines, which is included in the additional services domain. In 2006/2007, separate indicators for smoking management were added to the QOF,

which requires GPs to record and monitor patients' smoking status if they have certain chronic conditions listed in the QOF and more recently for all registered patients. As women of childbearing age represent a relatively healthy portion of the general population, their recording will be likely less affected than other groups, such as the elderly.

Nevertheless, the development of the QOF presumably has had a substantial impact on the completeness of recording of these medical diseases and events. For example, an indicator for depression is the percentage of patients who have had an assessment of severity at the time diagnosis using an assessment tool validated for use in primary care in those patients with a new diagnosis of depression.[77] Previous research suggested that financial incentives in pay for performance schemes might not improve the quality of patient care,[78] but may result in some unintended outcomes.[79] No studies however have assessed potential impacts of the implementation of QOF on the care that patients with mental illness receive or whether this affects patients' recorded diagnoses.

2.2 Ethical approval

Ethical approval for this research was obtained from the UK Medical Research Ethics Committee (administered and approved by the National Health Service South East Research Ethics Committee) REC reference 04/MRE01/9.

THIN data are wholly and only collected and recorded for the purpose of routine management and optimal health care for patients in the UK National Health Service (NHS) general practice setting, not directly for research purposes. NHS general practices contributing data to THIN provide consent for the use of these data by researchers. Whilst ethical approval is required for each study using THIN data, direct consent from individual patients is not required under the UK Data Protection Act because all data are anonymised, such that individual patients as well as the names and specific locations of general practices cannot be identified by researchers.

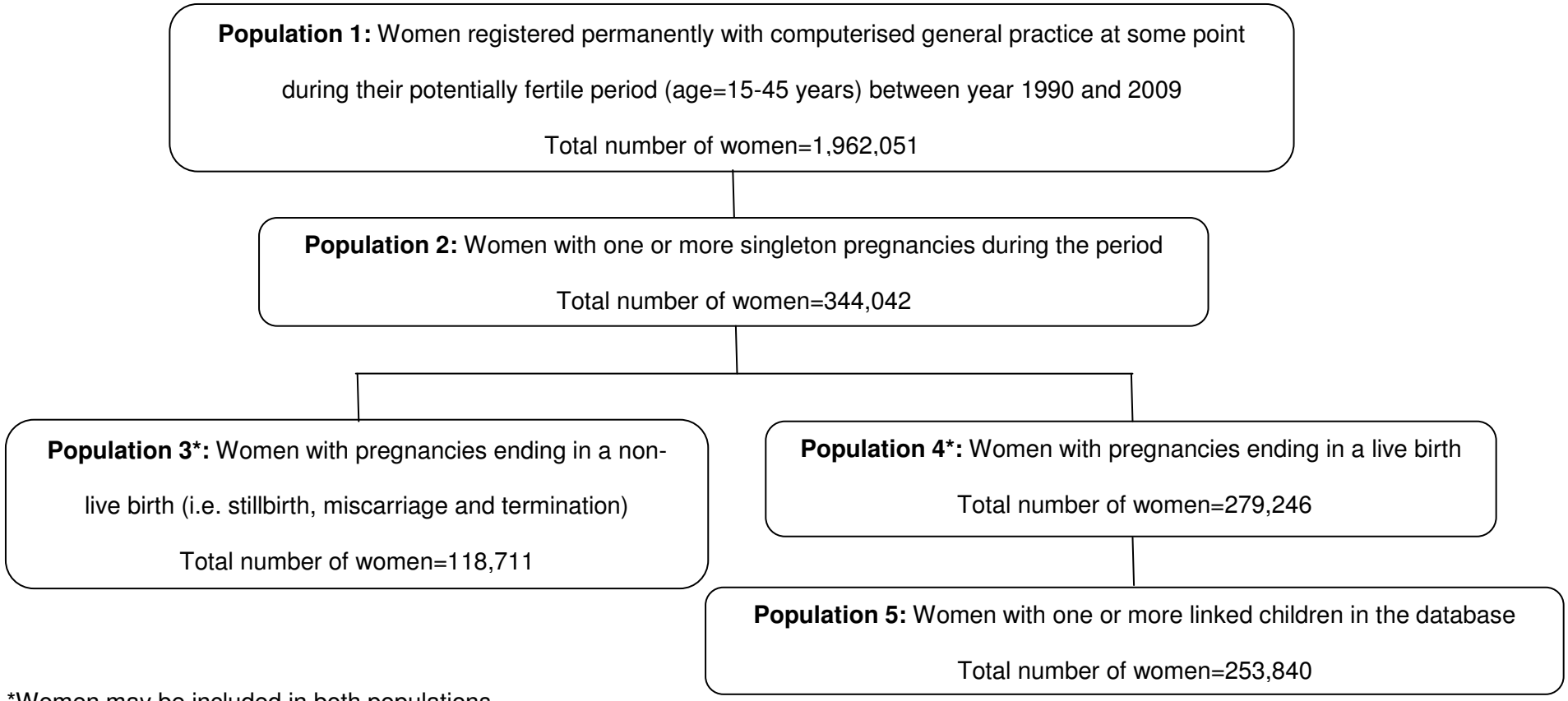
2.3 Datasets used for the work and statistical software

From THIN, several sub-set populations were extracted for the analyses in this thesis (Figure 2-1), starting with all women permanently registered with a THIN general practice using a computerised system at some point during their potentially fertile period (age 15-45 years) between 1990 and 2009 (Population 1). On average, there were 5.5-years' prospective recorded data for each woman in Population 1 (median=5.5, interquartile range [IQR] 1.9-11.6). From Population 1, all women with at least one singleton pregnancy during the study period were included as Population 2, thus women were excluded if they only had multiple pregnancies during the study period or only had pregnancies started before they registered with a GP. Women were then separated according to whether they had pregnancies ending in a live or non-live birth (Populations 3 and 4) and women may be included in both populations if they had both live and non-live births during the study period. From women with a live birth, those women with one or more children linked in THIN were then extracted (Population 5).

The linkage between women and their children was done by using delivery details and unique household identification number in both women's and children's medical records. Dates of conception were estimated based on a range of recordings relating to pregnancy, including last menstrual period dates, expected delivery dates, maturity estimates (e.g. codes for post-term or preterm deliveries), timing of routine monitoring events and recorded weeks of gestation at birth in children's records, and where no information was available, live births were assumed to take place at 40 weeks and miscarriage and termination at 10 weeks.

For the studies in Chapters 4-6, based on the populations in Figure 2-1, slight changes were also made to accommodate some specific criteria for different studies (please see the methods part for each individual study). All data management and

statistical analyses were carried out using Stata SE 11.0 (Stata Corp., TX, USA) for Windows 2007 Enterprise Edition (Microsoft Corporation, Seattle, USA).



*Women may be included in both populations.

Figure 2-1 Sub-datasets extracted from THIN for all analyses in this thesis

3 Defining and assessing mental illness in primary care data

This chapter describes the process of identifying different mental illnesses in women of childbearing age in UK general practice by extracting recording of medical diagnoses, symptoms and prescriptions of psychotropic drugs from the primary care database. This includes a series of analyses to assess the recording of maternal mental illness in the general population presenting to primary care using Population 1 in Figure 2-1.

3.1 Background

3.1.1 Identification and diagnosis of mental illness

Although psychiatric disorders are increasingly recognised as one of the most common human disorders which cause great morbidity worldwide, the information about aetiology and treatment in psychiatric disorders is vague, compared with other specialties of medicine.[80] Psychiatric disorders are predominantly disorders of brain functions. Currently, there are no gold standard diagnostic tests for psychiatric disorders. Physical examination or other investigations (e.g. blood tests) are more likely to be investigations of exclusion and some functional mental illnesses are presumably defined by a failure to locate a physical cause. Psychiatrists and other clinicians therefore commonly base diagnosis and treatment on symptom clusters alone.[80] Since people with mental illnesses may not be willing to disclose their feelings to doctors or other health professionals, under-diagnosis of mental illness could be fairly common in the general population,[81] yet it is also possible that there is over-diagnosis in the medical setting for some people.

Psychiatric research generally classifies psychiatric disorders according to defined criteria. There are two main medically accepted systems of psychiatric classification: the World Health Organisation's International Classification of Disease (ICD);[82] and

the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM).[83] Although the two systems of classification are fairly similar and generally correspond with each other well, there is considerable uncertainty and controversy around diagnosis and classification of different types of mental illnesses, much of which stems from a lack of accurate measurements to validate the diagnoses,[84] given considerable variation between people's symptoms and presentation as well as possible comorbidity of different mental illnesses within individuals.

3.1.2 Issues and concerns using general practice records

In daily practice the concept of mental illness is increasingly questioned. Mental illness especially depression and anxiety may be described as an everyday problem rather than as an objective diagnostic category by the GP and standardised diagnostic interviews are not, and cannot at present, be used in primary care.[85] Although a systematic review found low accuracy of depression recognition by non-psychiatrist physicians,[86] prior research has suggested that GPs are able to recognise more severe depression,[87,88] and try to avoid labelling people with mild symptoms as being mentally ill.[89] A recent study in general practice data found that whilst recording of depression diagnoses had decreased over the period 1996-2006, symptom recording of depression increased substantially and the combined total varied minimally over time.[89]

In addition, in UK general practice it is common for patients to be prescribed psychotropic drugs without direct recording of the diagnostic indication for the prescription, which likely reflects both the diagnostic pathway (e.g. prescriptions of psychotropic drugs as part of diagnostic procedure) and routine clinical practice (e.g. a GP with knowledge of his or her patient's clinical history will not need to record a new diagnosis of depression with each prescription for effective clinical care). Previous studies of mental illness using primary care data typically define mental

disorders using recordings of both diagnoses and psychotropic drug prescriptions.[76,89–94]

In addition, previous research in the General Practice Research Database (GPRD), a large general practice database similar to THIN, has reported exceptionally high incidence rates of various diseases in the period shortly after registration.[95] This likely means that the diagnoses within the first few months after registration are more often prevalent or past diagnoses recorded as part of a patient's initial important medical history when they join a new practice. However, this research only examined specific morbidities (e.g. heart disease and cancer) and did not include any mental illness, nor did it examine the pattern of drug prescriptions. Since about half of the general practices in GPRD also contribute to THIN, a similar finding would be expected in studies using data from THIN, in which case the post-registration period needs to be separately examined.

3.2 Defining mental illness in primary care data

For this PhD I focused on clinically recognised mental illness presenting to and/or treated in UK general practice. Depression, anxiety, bipolar disorder and schizophrenia and other related psychotic disorders which are not due to known organic illness or substance misuse (based on the two classification systems) were investigated. I categorised these mental health conditions as *common mental illness* (depression and anxiety) and rarer but more severe disorders, as *serious mental illness* (bipolar disorder, schizophrenia and other related psychotic disorders).

I extracted Read codes for both diagnoses and symptoms of each mental illness. I also extracted prescriptions for some psychotropic drugs, which included antidepressants, antipsychotics, anti-anxiety drugs, and anti-manic drugs including lithium and mood stabilisers (valproate acid and carbamazepine). A series of analyses were carried out to examine the recording of these mental illnesses and related prescribing in women of childbearing age in UK general practice.

3.2.1 Extracting Read codes for diagnoses and symptoms

Most diagnostic Read codes for psychiatric disorders are under chapter heading 'E- Mental Disorders'. The command 'searchrc' [96] in Stata SE 11 was also used to extract both diagnostic and symptom codes from the Read code dictionary. Table 3-1 summarises the search terms used for each mental illness. The category retention option of the command was also used to extract codes in the same Read code categories as the matched codes.

Using the command 'searchrc' and the search terms in Table 3-1, more than 10,000 codes were initially extracted. By comparing with previous research of which Read codes were used to define different mental illnesses in general practice,[89,97] exclusive code-lists were created for depression, anxiety, bipolar disorder and schizophrenia and other related psychotic disorders (Appendix I), separately.

Table 3-1 Search terms for different mental illnesses

Mental illness	Search terms
Depression	*depress*, *dythami*, *mood*, *affect*, *tired*, *sad*, *blunt* or *stupor*
Anxiety	*anxi*, *phobi*, *panic*, *fear*, *stress*, *traumatic* or *obsessive*
Bipolar disorder	*bipolar*, *manic depress*, *manic-depress*, *cyclothymi*, *mood* or *affect*
Schizophrenia and other psychoses	*schizo*, *psycho*, *delusion*, *hallucina*, *diaorgani*, *amusia* or *oneirophreni*

3.2.2 Extracting Multilex codes for drug prescriptions

BNF 57 (2009)[98] and key UK psychiatry handbooks[80,99] were used to help identify psychotropic medicines that were normally used for treating depression, anxiety, bipolar disorder, and schizophrenia and other related psychotropic disorders in the UK. Since the same drug can be used to treat different mental illnesses (e.g. citalopram for both depressive disorders and anxiety) and the same mental illness can be treated by drugs from different drug classes (e.g. bipolar disorders treated by both anti-mantic and antipsychotic drugs), instead of making drug code-lists for each mental illness, four drug code-lists based on the BNF drug classification were extracted. These are anti-anxiety drugs (including hypnotics in BNF chapter 4.1.1 and anxiolytics in BNF chapter 4.1.2), antipsychotic drugs in BNF chapter 4.2.1 and chapter 4.2.2, anti-manic drugs (lithium and mood stabilisers) in BNF chapter 4.2.3 and chapter 4.8.1, and antidepressants in BNF chapter 4.3. All Multilex codes, linked to these chapters of the BNF, were extracted from the drug code dictionary of THIN. Please see Appendix II for the lists of drugs from the BNF that were used in this thesis.

3.3 Assessing recordings of mental illness

3.3.1 Frequency of Read codes used for each mental illness

For Population 1 in Figure 2-1, all recording for depression, anxiety, bipolar disorder, schizophrenia and other related psychotic disorders were extracted using Read codes identified in Section 3.2.1. Of the 1,962,051 women in Population 1, more than 26% had some kind of recording for these mental conditions, of whom 63.5% had at least two recordings in their medical records. Overall, over two-million mental illness related recordings were extracted and about three out of four were diagnostic records. Table 3-2 shows the frequency of mental illness overall for the recording of diagnoses and symptoms separately and the top 10 most common codes which accounted for 89.3% of the recorded diagnoses and 96.1% of the recorded symptoms. The following tables show the frequency results for depression (Table 3-3), anxiety (Table 3-4), bipolar disorder (Table 3-5) and schizophrenia and other related psychotropic disorders (Table 3-6) separately.

Overall, for diagnostic codes, nearly one third of the recordings were coded with 'Depressive disorder not elsewhere classified (NEC)' and 19.4% was the code 'Anxiety state' (Table 3-2). The most frequently used symptomatic code was `Low mood' followed by the code `Depressed' (Table 3-2). For depression, more than half of the recordings for diagnoses used non-specific codes, such as 'Depressive disorder NEC' and `Depression not otherwise specified (NOS)' (Table 3-3). For anxiety, over half of the diagnostic recordings used the two codes `Anxiety state' and `Anxiety with depression' and nearly 60% of the recordings for symptoms used the codes `Anxiousness – symptom' and `Anxiousness' (Table 3-4). There were far fewer women with recordings of bipolar disorder (Table 3-5) or schizophrenia and other related psychotic disorders (Table 3-6) and the vast majority were recorded using diagnostic codes rather than recordings of symptoms.

Table 3-2 Top 10 most frequently used Read codes for recording of diagnoses and symptoms separately in women of childbearing age (N=1,962,051)

	All diagnostic codes (1,451,878)			All symptom codes (664,617)		
	Read code description	**n**	**%***	**Read code description**	**n**	**%***
1	Depressive disorder NEC	443,239	30.5	Low mood	134,332	20.2
2	Anxiety states	183,041	19.4	Depressed	97,502	14.7
3	[X]Depression NOS	154,977	12.6	C/O - feeling depressed	78,345	11.8
4	Anxiety with depression	141,075	10.7	Anxiousness - symptom	73,615	11.1
5	Postnatal depression	57,653	4.0	Anxiousness	72,457	10.9
6	[X]Depressive episode	51,520	3.5	Panic attack	57,142	8.6
7	Neurotic depression reactive type	48,774	3.4	Depressed mood	37,587	5.7
8	Panic disorder	30,752	2.1	Stress related problem	31,989	4.8
9	Endogenous depression - recurrent	24,136	1.7	Symptoms of depression	31,402	4.7
10	Endogenous depression first episode	20,779	1.4	O/E - depressed	23,783	3.6

* 11% other codes of diagnoses and 4% other symptom codes
NEC=not elsewhere classified
NOS=not otherwise specified
C/O=complain of
O/E=on examination of
[X]: These Read codes have been added to ensure mapping to all ICD codes

Table 3-3 Top 10 most frequently used Read codes for recording of depression (N=417,048)

	Diagnostic codes (1,123,529)			Symptom codes (409,083)		
	Read code description	**n**	**%**	**Read code description**	**n**	**%**
1	Depressive disorder NEC	443,239	39.5	Low mood	134,332	32.8
2	[X]Depression NOS	154,977	13.8	Depressed	97,502	23.8
3	Anxiety with depression	141,075	12.6	C/O - feeling depressed	78,345	19.2
4	Postnatal depression	57,653	5.1	Depressed mood	37,587	9.2
5	[X]Depressive episode	51,520	4.6	Symptoms of depression	31,402	7.7
6	Neurotic depression reactive type	48,774	4.3	O/E - depressed	23,783	5.8
7	Endogenous depression - recurrent	24,136	2.1	Depressive symptoms	6,132	1.5
8	Endogenous depression first episode	20,779	1.8	---		
9	[X]Moderate depressive episode	19,750	1.8	---		
10	[X]Depressive episode, unspecified	18,512	1.6	---		

NEC=not elsewhere classified
NOS=not otherwise specified
C/O=complain of
O/E=on examination of
[X]: These Read codes have been added to ensure mapping to all ICD codes

Table 3-4 Top 10 most frequently used Read codes for recording of anxiety (N=267,483)

	Diagnostic codes (545,926)			Symptom codes (251,472)		
	Read code description	**n**	**%**	**Read code description**	**n**	**%**
1	Anxiety states	183,041	33.5	Anxiousness - symptom	73,615	29.3
2	Anxiety with depression	141,075	25.8	Anxiousness	72,457	28.8
3	Panic disorder	30,752	10.5	Panic attack	57,142	22.7
4	Anxiety state NOS	14,430	5.6	Stress related problem	31,989	12.7
5	[X]Obsessive - compulsive disorder	7,869	2.6	C/O - panic attack	9,553	3.8
6	Generalised anxiety disorder	6,665	1.4	Feeling stressed	5,183	2.1
7	[X]Mixed anxiety and depressive disorder	6,590	1.2	O/E - anxious	979	0.4
8	[X]Post - traumatic stress disorder	5,874	1.2	Obsessional thoughts	554	0.2
9	Chronic anxiety	4,703	1.1	---		
10	Obsessive-compulsive disorders	3,867	0.9	---		

NOS=not otherwise specified
C/O=complain of
O/E=on examination of
[X]: These Read codes have been added to ensure mapping to all ICD codes

Table 3-5 Top 10 most frequently used Read codes for recording of bipolar disorder (N=5,168)

	Diagnostic codes (15,115)			Symptom codes (214)		
	Read code description	**n**	**%**	**Read code description**	**n**	**%**
1	[X]Bipolar affective disorder	5,846	38.7	Elevated mood	158	73.8
2	[X]Hypomania	2,236	14.8	O/E - elated	56	26.2
3	[X]Manic-depressive illness	1,344	8.9	---		
4	Bipolar psychoses	1,045	6.9	---		
5	Unspecified bipolar affective disorder	821	5.4	---		
6	Single manic episode, mild	609	4.0	---		
7	[X]Mania NOS	338	2.2	---		
8	[X]Manic episode	262	1.7	---		
9	Manic disorder, single episode	237	1.6	---		
10	[X]Cyclothymia	210	1.4	---		

O/E=on examination of
[X]: These Read codes have been added to ensure mapping to all ICD codes

Table 3-6 Top 10 most frequently used Read codes for recording of schizophrenia and other related psychotic disorders (N=12,335)

	Diagnostic codes (29,257)			Symptom codes (3,848)		
	Read code description	**n**	**%**	**Read code description**	**n**	**%**
1	Schizophrenic disorders	5,991	20.5	Hallucinations	2,900	75.4
2	[X]Psychosis NOS	2,629	9.0	Delusions	788	20.5
3	Paranoid schizophrenia	1,781	6.1	Delusion	160	4.2
4	Psychotic episode NOS	1,602	5.5	---		
5	Nonorganic psychosis NOS	1,556	5.3	---		
6	[X]Schizoaffective disorders	1,101	3.8	---		
7	Bipolar psychoses	1,045	3.6	---		
8	[D]Hallucinations, auditory	1,011	3.5	---		
9	Paranoid states	1,000	3.4	---		
10	[X]Paranoid psychosis	966	3.3	---		

NOS=not otherwise specified
[D]: Working diagnosis
[X]: These Read codes have been added to ensure mapping to all ICD codes

3.3.2 Recording of each mental illness over time

To investigate whether the recording of mental illness changed during the study period and how, yearly prevalence figures of clinically recognised depression, anxiety, bipolar disorder and schizophrenia and other related psychotropic disorders from 1990 to 2008 were calculated as the number of women with recordings of each type of mental illnesses during each year among all women who remained registered on the first day of July of that year. Recording for diagnoses and symptoms were examined separately for each mental illness. Data from 2009 were excluded since data were only collected up to July and were thus incomplete for that year.

Figure 3-1 shows proportions of women with one or more recordings of clinically recognised depression by diagnoses and symptoms separately during each year from 1990 to 2008. From 1990 to 2003, the prevalence of recording of both diagnoses and symptoms generally increased but overall was approximately 2-4.5% annually. Recording of depressive diagnoses however decreased after 2004 but recording of symptoms continued to increase (Figure 3-1). Similar patterns were also found in women with recording of anxiety (Figure 3-2) with overall 1-2.5% annually, bipolar disorder (Figure 3-3) with overall 0.03-0.06% annually and schizophrenia and other related psychotic disorders (Figure 3-4) with overall 0.07-0.10% annually, although the trend was less marked for these conditions.

My results show that before 2004, recording of diagnostic codes for depression, anxiety and serious mental illness in THIN general practices increased steadily. Prior research on diagnoses in THIN data[100] have also shown increases over time and this may partially be due to more complete recording especially after the mid-1990s, by which time most of the THIN general practices had started using Vision system. Compared with recording of diagnoses, recording of mental illness symptoms was rare in early 1990s, though it increased slightly afterwards, especially for depressive

symptoms. However, the recording of diagnostic codes for all mental illnesses was decreasing after the year 2004 but the recording of symptoms continued to increase. The reasons for these changes are unclear. One potential explanation is that the introduction of QOF payments after 2004 had an effect on the specificity of GP's diagnostic coding, such that they were less willing to assign more definitive diagnoses in uncertain or borderline cases of mental illness in their patients. Several studies have found unintended effects of performance-based contracting on clinical practice in primary care.[79,101,102] The QOF incentive may produce changes in documentation rather than changes in the actual diagnosis or health care treatment delivered to patients. Our findings may be an example of this behaviour; however, the inclusion of both diagnosis and symptom records show that there is some but not considerable variation over time. The overall increase in recording may also be due to a general increase in awareness of mental illness by doctors and the general population over the past two decades.

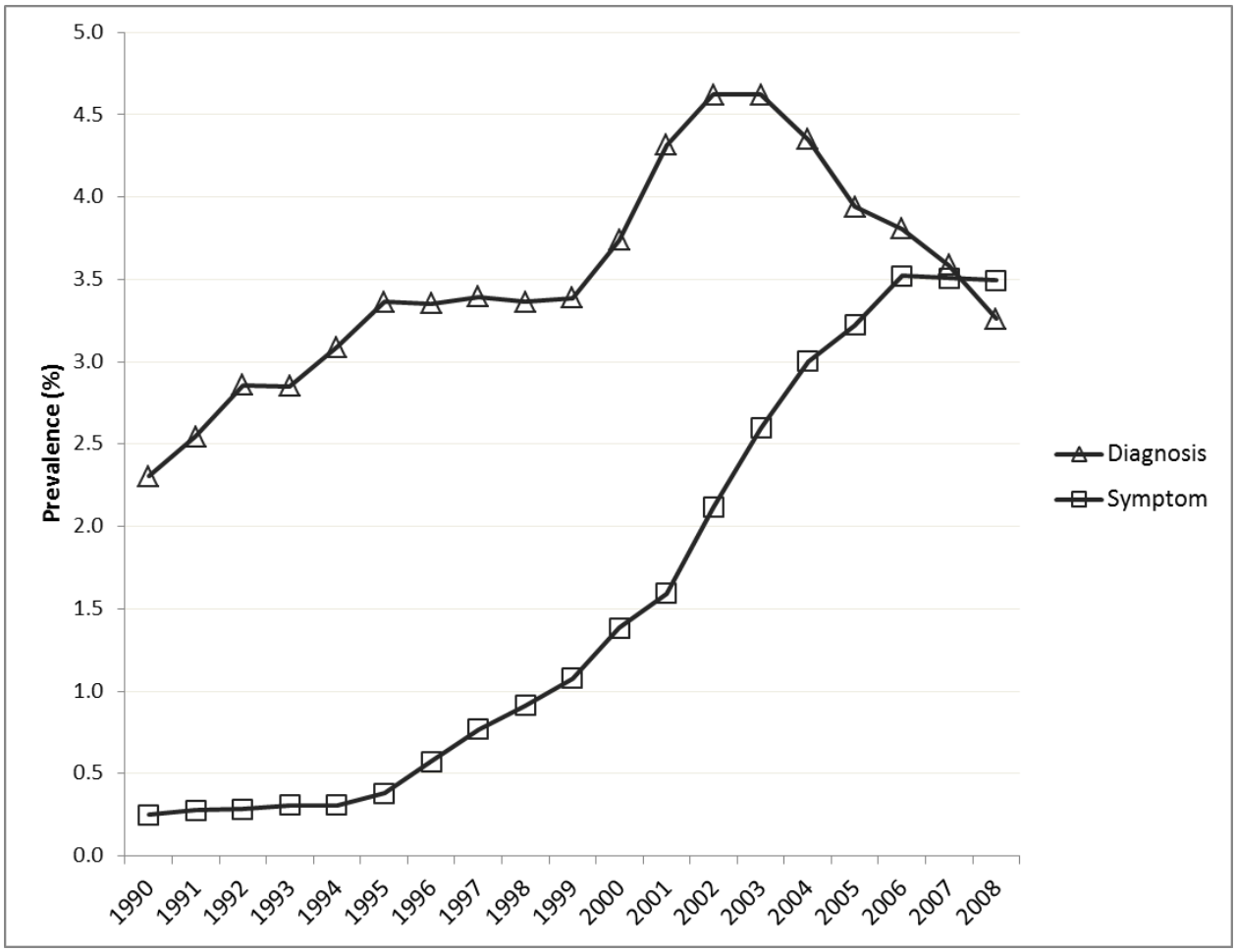


Figure 3-1 Proportions of women with one or more recordings of clinically recognised depression by diagnoses and symptoms separately each year from 1990 to 2008

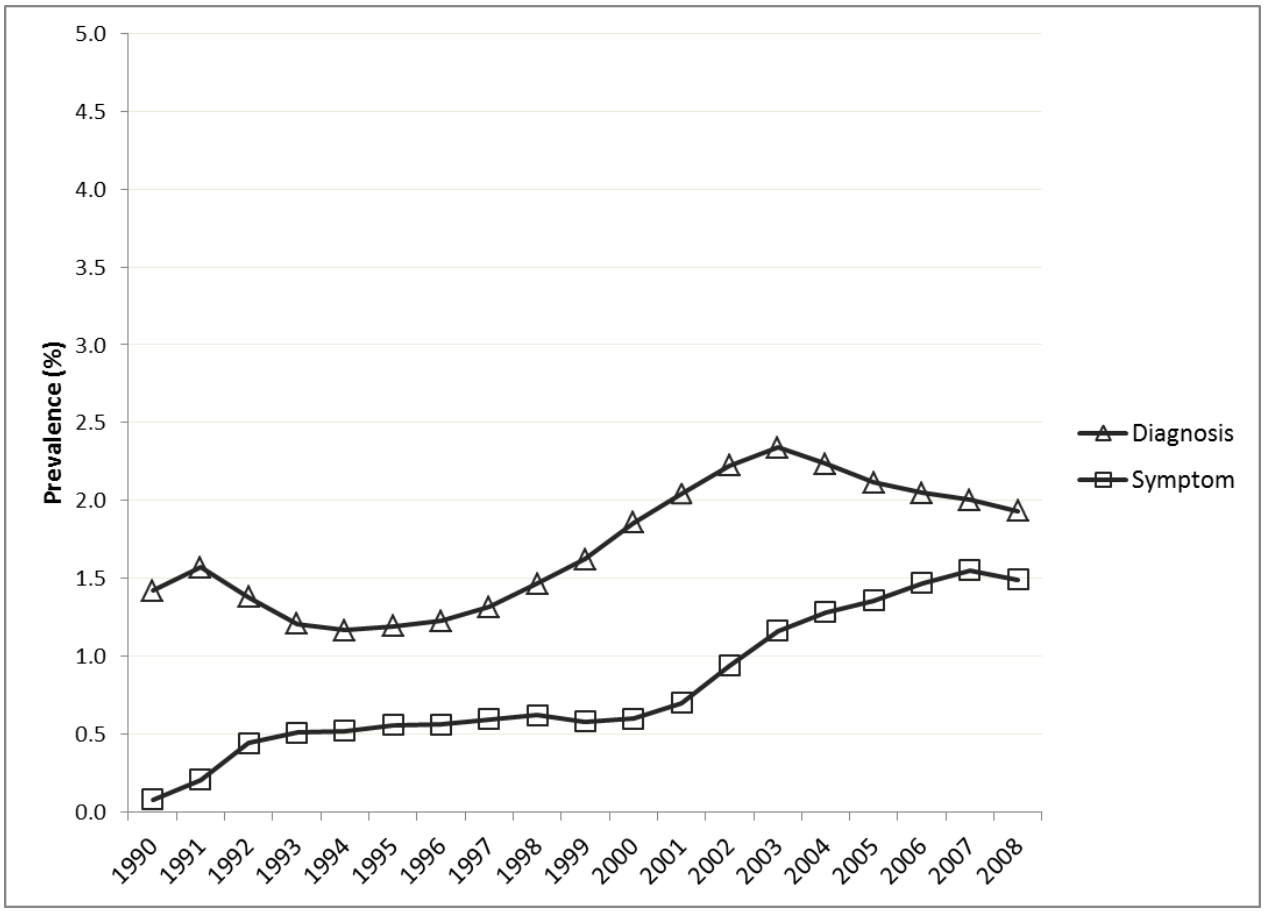


Figure 3-2 Proportions of women with one or more recordings of clinically recognised anxiety by diagnoses and symptoms separately each year from 1990 to 2008

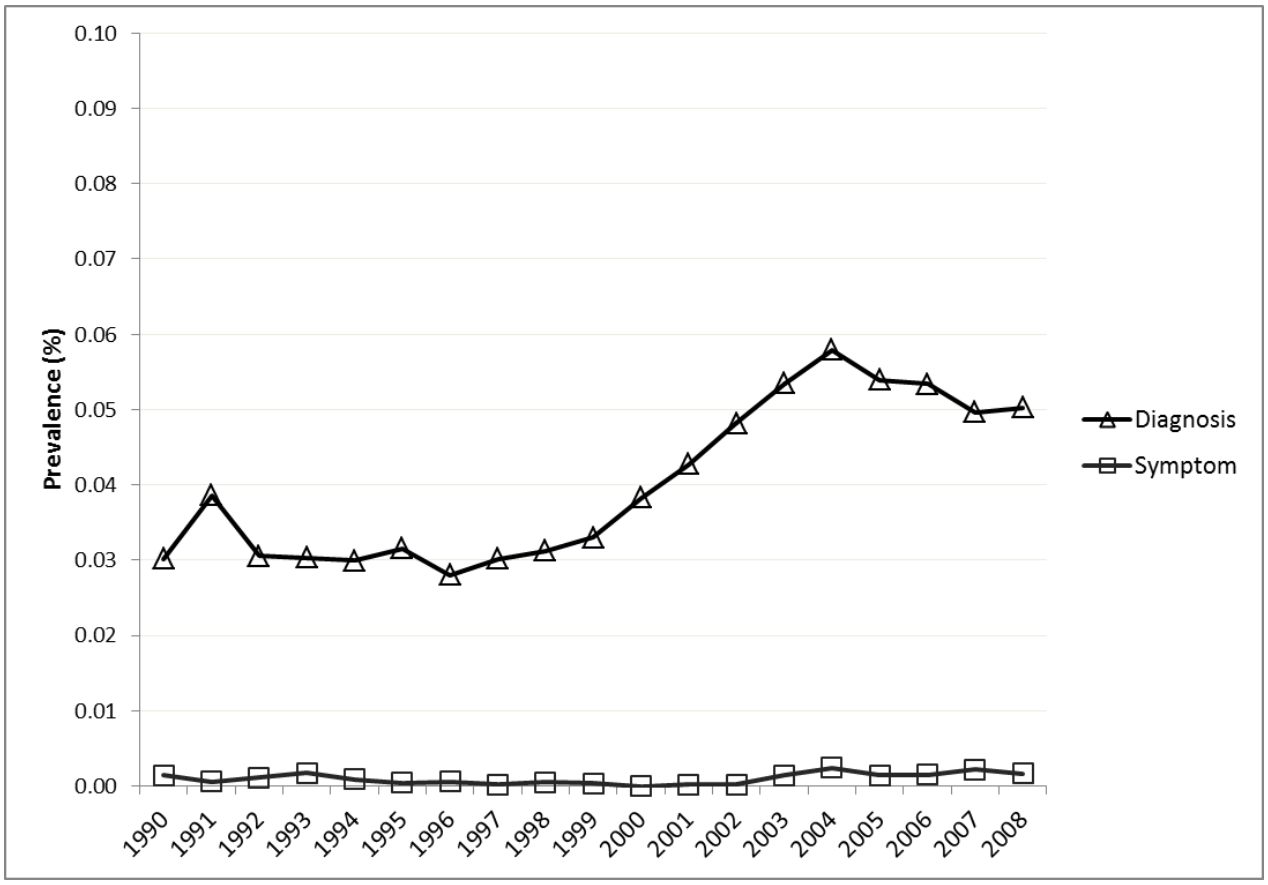


Figure 3-3 Proportions of women with one or more recordings of clinically recognised bipolar disorder by diagnoses and symptoms separately each year from 1990 to 2008

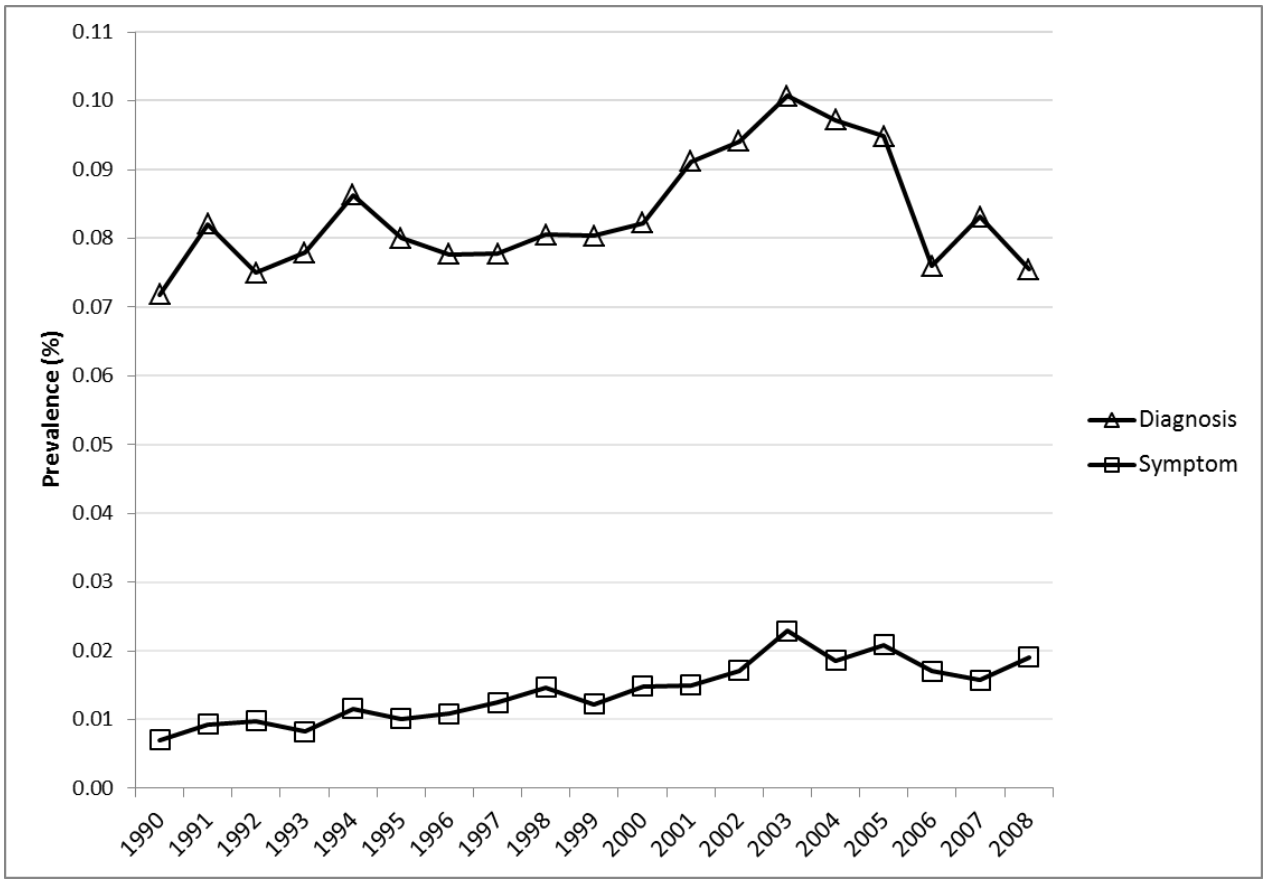


Figure 3-4 Proportions of women with one or more recordings of clinically recognised schizophrenia and other related psychotic disorders by diagnoses and symptoms separately each year from 1990 to 2008

3.3.3 Length of psychotropic drug prescriptions

The duration of prescriptions was calculated by using three variables in the Therapy table of THIN. These are variable 'rxdays' which is the duration of the prescription in days, variable 'rxqty' which is quantity prescribed in the prescription and variable 'dosgval' which is the daily dosage of the prescription. If the duration of a prescription (variable `rxdays') was missing, the length of the prescriptions was calculated by using quantity prescribed in that prescription (variable 'rxqty') divided by the daily dosage (variable 'dosgval'), when such information was available. It was assumed that the maximum of duration of a single prescription was no more than 6 months (24 weeks, 168 days). Extreme values (more than 168 days) therefore were excluded and treated as missing data in the estimation. In addition, since women may have more than one psychotropic drug prescription recorded in the same day, it was assumed that these prescriptions would be taken around the same time and only the prescription with the longest duration was included in the estimation. The results from the descriptive analyses show that overall approximately one third of the prescriptions had missing value on duration of prescriptions and the median time of prescriptions was 28 days (IQR 28-30).

3.3.4 Prescriptions of psychotropic medication over time

To investigate whether the recording of prescriptions of psychotropic drugs changed over the study period and how it changed, I calculated the yearly prevalence of prescriptions of antidepressants, anti-anxiety drugs, anti-manic drugs, and antipsychotic drugs from 1990 to 2008 as a proportion of women with recordings of each type of psychotropic drugs during each year in women who remained registered on the first day of July of that year. Information from 2009 was excluded since the data were incomplete for that year.

Figure 3-5 shows the prevalence of drug prescriptions during each year over time. There was an increase in prevalence of all psychotropic drugs, but this was most evident for prescriptions of antidepressants. Prescriptions of antidepressants increased dramatically in the last two decades from about 3% in 1990 to 12% in 2008, and became the most frequently prescribed class of psychotropic drugs in women of childbearing age (Figure 3-5). The increasing trend for prescriptions of antidepressants and anti-anxiety drugs was clearly larger than the increases observed in the medical recording of mental illness. Previous UK studies using primary care data also report a substantial increase in the prevalence of antidepressant prescribing from the early 1990s,[103–105] especially in women.[103]

No clear explanations however have been given for such remarkable increases.[106–109] Moore *et al.* conducted a study attempting to explain the rise in antidepressant prescribing by using GPRD,[108] and suggested that the dramatic change in antidepressant prescribing was largely due to the increased proportion of patients remaining on long term antidepressant treatment (at least five years), who were also prescribed the most antidepressants in the primary care. However, another study focused on the GP's perspectives argued that the increased prescribing of antidepressants could be simply because more attention to mental illness has been

paid by both doctors and patients which could be due to increased awareness of its high social and economic burden and decreased discrimination related to it.[109]

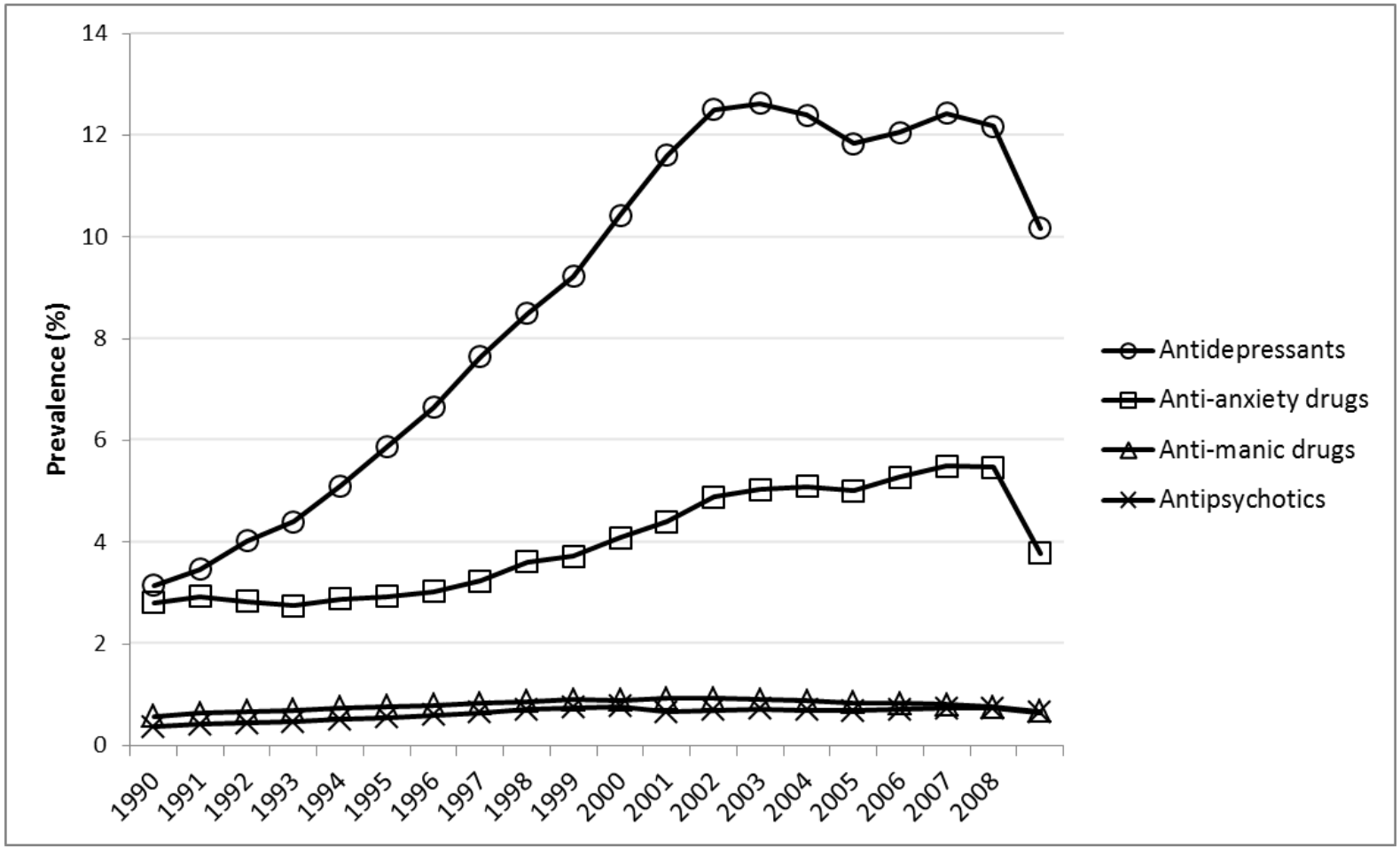


Figure 3-5 Proportions of women with one or more prescriptions of different psychotropic drugs during each year from 1990 to 2008

3.3.5 The pattern of antidepressant prescribing and switching

Since antidepressants were becoming the most frequently prescribed psychotropic medication, I additionally investigated the prevalence by different types of antidepressants separately, namely selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and other antidepressants which are not included as SSRIs or TCAs (i.e. venlafaxine, reboxetine, mirtazapine, tryptophan, duloxetine, flupentixol, and monoamine-oxidase inhibitors).

Figure 3-6 shows the changes in proportions of different classes of antidepressants prescribed to women as their first ever antidepressant during each year from 1990 to 2009 (the denominator was the number of women with a first ever antidepressant prescription during each year). The proportion of TCAs as first prescriptions decreased steadily from nearly 90% in 1990 to just about 20% in 2009 in contrast with a substantial increase in prescriptions of SSRIs (less than 10% in 1990 but more than 70% in 2009). There were no remarkable changes for other antidepressants (7% and 5% in 1990 and 2009, respectively).

Figure 3-7 shows the changes in proportions of women prescribed the same class of antidepressants for their first three antidepressant prescriptions for women initially prescribed TCAs, SSRIs or other antidepressants separately during each year from 1990 to 2009 (the denominators were the numbers of women with the first ever TCA, SSRI or other antidepressant who had at least three prescriptions). In 1990, women were most likely to stay in the same drug class for the next two prescriptions if they were prescribed a TCA as the first-line antidepressant, compared with those prescribed a SSRI or other antidepressant. This however changed over the next decade, during which time the proportions of women prescribed the same drug class for their first three prescriptions steadily increased for those initially prescribed an SSRI (67% in 1990 and 88% in 2000) but decreased for those prescribed a TCA (85%

and 64%, respectively). After 2000, the figure for TCAs also increased along with those for SSRIs (84% for TCAs and 96% for SSRIs in 2009). For women initially prescribed other antidepressants, the proportion of women prescribed the same drug class for their first three prescriptions was lowest in 1990 (45%) among all three type of antidepressants and continued to decrease to 35% in 1993; however, this figure increased dramatically afterwards to 86% in 2009 (Figure 3-7).

My results from examining antidepressant prescribing show that antidepressant prescribing and switching of drug classes has changed remarkably since 1990s. In THIN general practices, women are increasingly prescribed SSRIs as the first choice antidepressant in contrast to a considerable decreased use of TCAs. Subsequent drug switching within the same drug class rather than to a different class progressively happens in women initially prescribed an SSRI and other antidepressants but not in those with a TCA which is in accordance with the current guidelines.[110,111]

During the study period, several guidelines have been published to regulate antidepressant prescribing and switching in the UK primary care.[110,112–114] In general, the guidelines emphasised that GPs should choose relatively safe and tolerable antidepressants (mainly newly developed antidepressants, such as SSRIs) as the first-line antidepressants. More recent guidelines also suggested that switching of antidepressants should be first within the same drug class, especially when SSRIs were initially prescribed.[98]

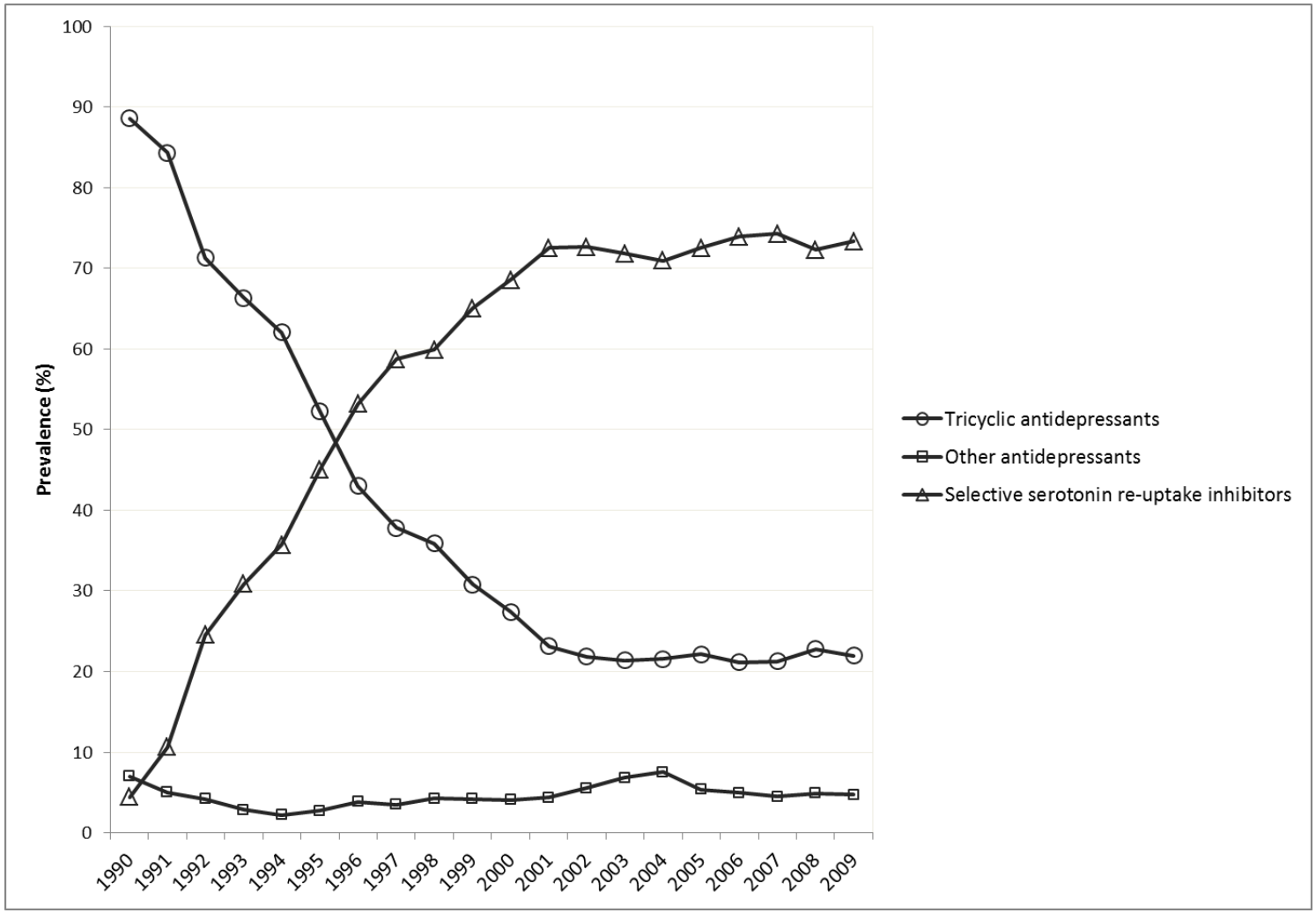


Figure 3-6 Proportions of different antidepressants prescribed as the first-line drug treatment during each year from 1990 to 2009

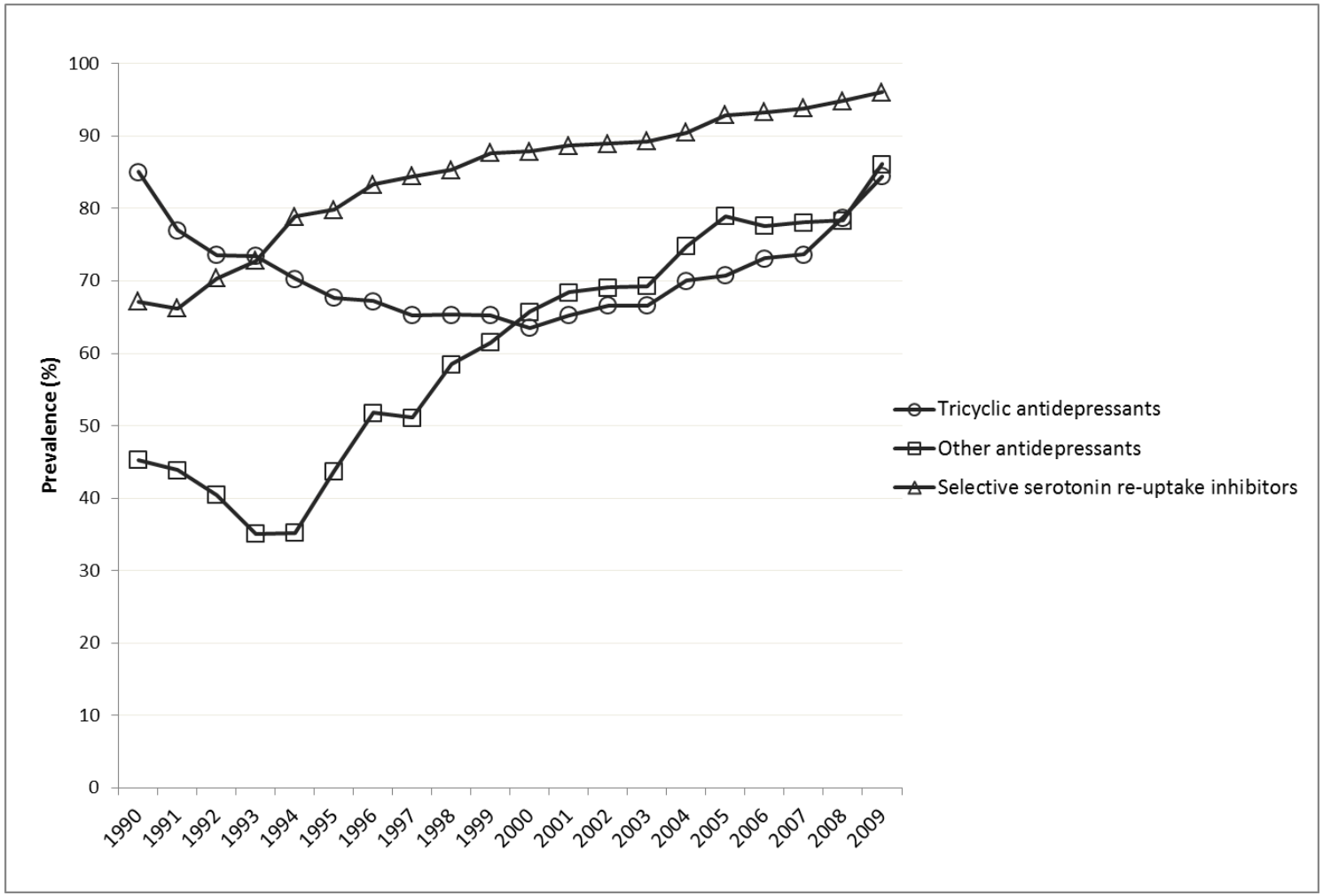


Figure 3-7 Proportions of women prescribed the same class of antidepressants for the first three prescriptions from 1990 to 2009

3.3.6 First recording of mental illness and psychotropic drug prescriptions in the early period following registration: incident or prevalent illness?

To assess the extent of mental illness recording as a medical history, I calculated the rate of first recorded mental illness (including recording of diagnoses and/or symptoms) for women newly registering with a computerised general practice (registered after general practice computerisation date), every three months for the first four years following registration, for each type of mental illness. The results are shown separately for depression (Figure 3-8), anxiety (Figure 3-9), bipolar disorder (Figure 3-10) and schizophrenia and other related psychotic disorders (Figure 3-11) since registration. For all mental illnesses, the incidence was much higher in the first three months following registration and then plateaued in the remaining period.

I also repeated the same analyses for first recorded prescriptions of each type of psychotropic drugs since women registered with a general practice using a computerised system. The results are shown for antidepressants (Figure 3-12), anti-anxiety drugs (Figure 3-13), anti-manic drugs (Figure 3-14), and antipsychotics (Figure 3-15) separately. For all psychotropic drug prescriptions, the incidence of was highest in the first three months following women's registration and then plateaued in the remaining period.

My results show that there was increased recording of mental illness in the first three months following women' registration with a computerised general practice. Lewis *et al.*, who used data from GPRD, examined several acute and chronic conditions, but did not include mental illness, and found increased recording during the early period of registration.[95] This may suggest that the cases identified in the period immediately following registration could be those patients with existing mental illness actively seeking medication or those with a history of mental illness. The increased recording of psychotropic drug prescriptions in the first three months after registration

suggested these patients were likely to have active illness and need medical treatment. My analysis suggested that at least the first three months should be excluded when attempting to identify cases of patients with a new incident episode of mental illness. It is also possible, however, that some patients were suffering from a new episode of illness, which prompted them to register with a GP so than they could receive medical care.

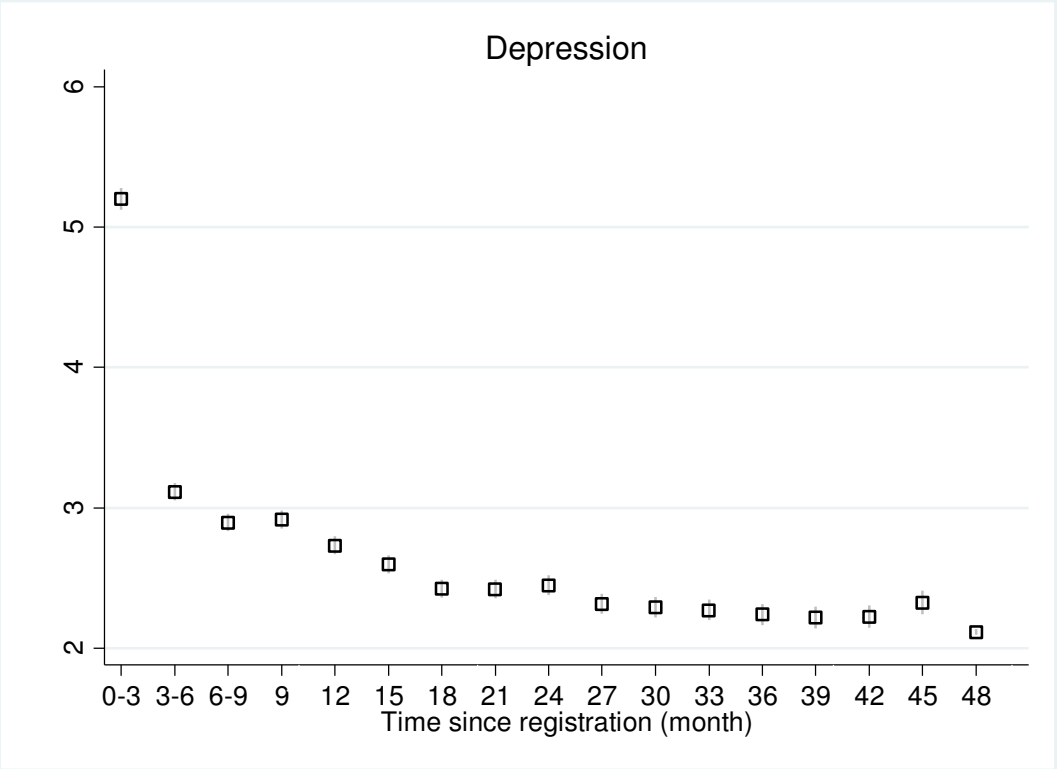


Figure 3-8 Rate of first recorded depression in women registered with a computerised general practice

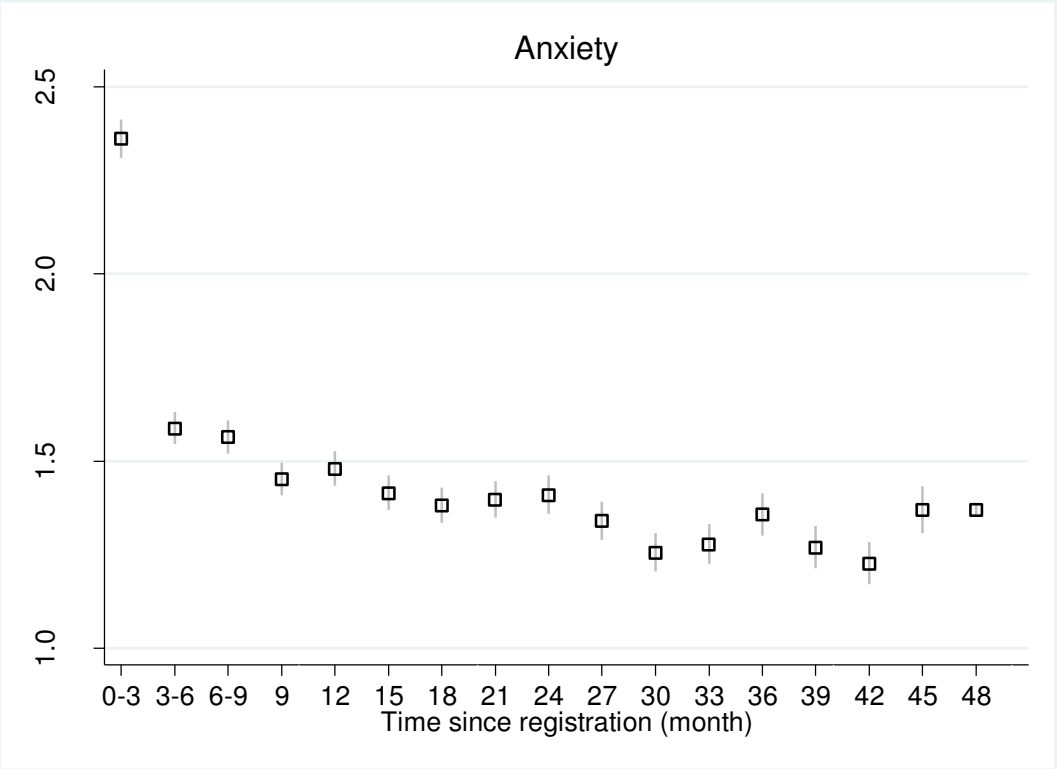


Figure 3-9 Rate of first recorded anxiety in women registered with a computerised general practice

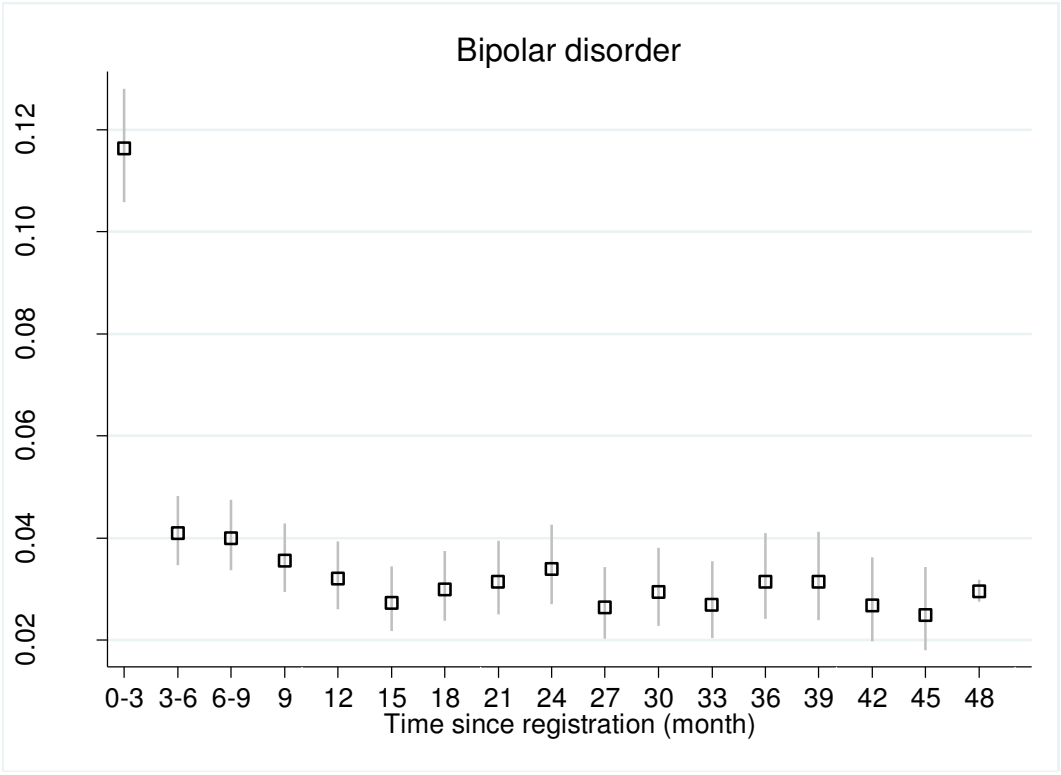


Figure 3-10 Rate of first recorded bipolar disorder in women registered with a computerised general practice

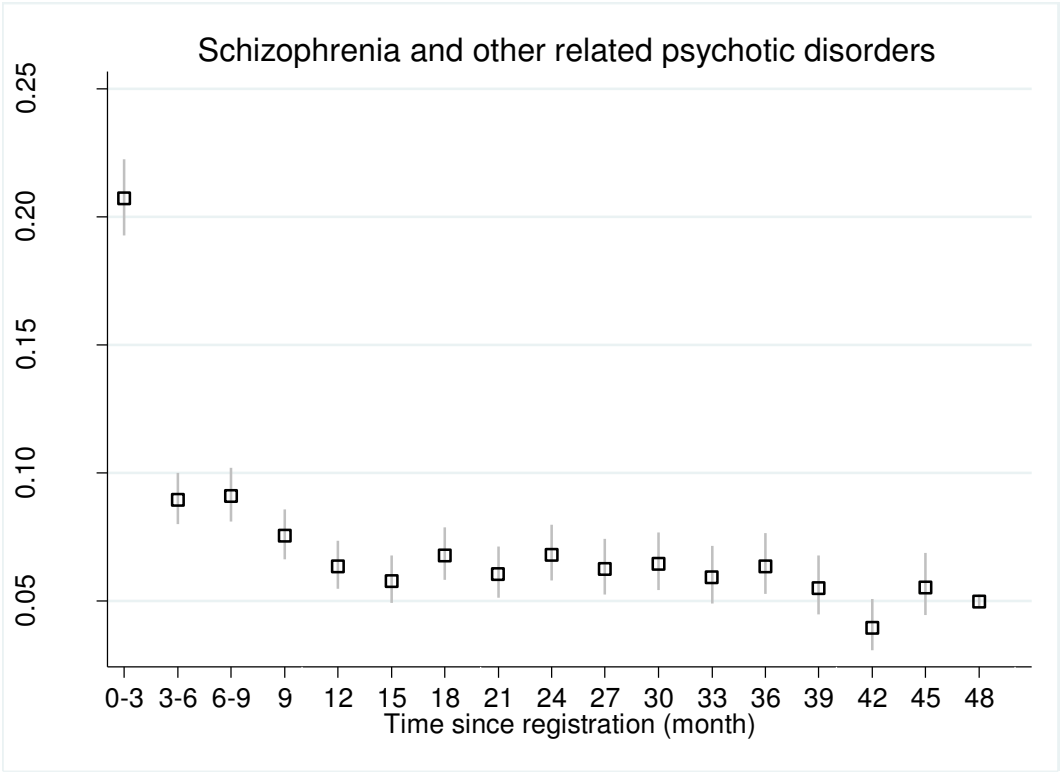


Figure 3-11 Rate of first recorded schizophrenia and other related psychotic disorders in women registered with a computerised general practice

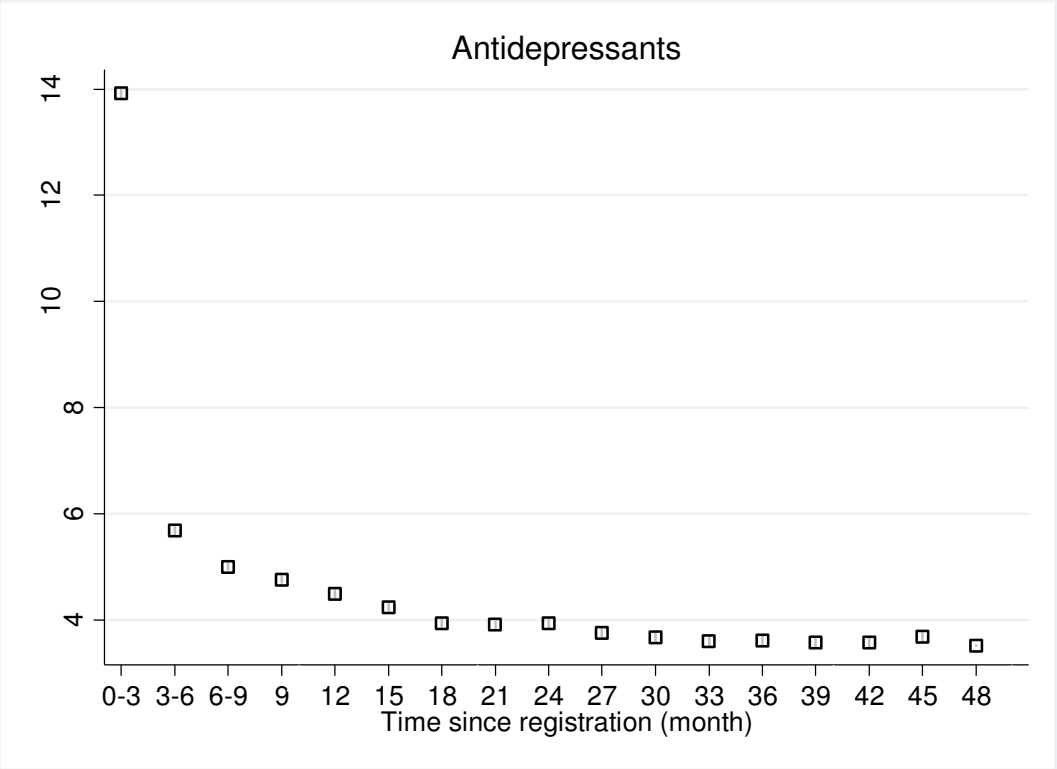


Figure 3-12 Rate of first recorded antidepressants prescriptions in women registered with a computerised general practice

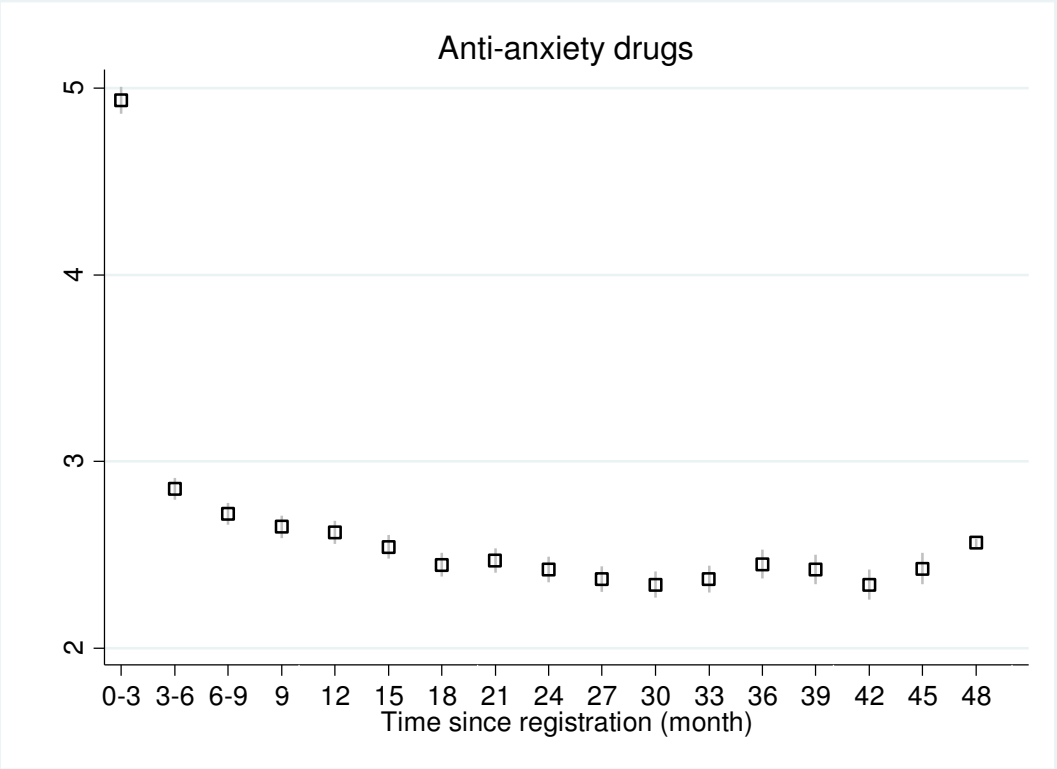


Figure 3-13 Rate of first recorded anti-anxiety drug prescriptions in women registered with a computerised general practice

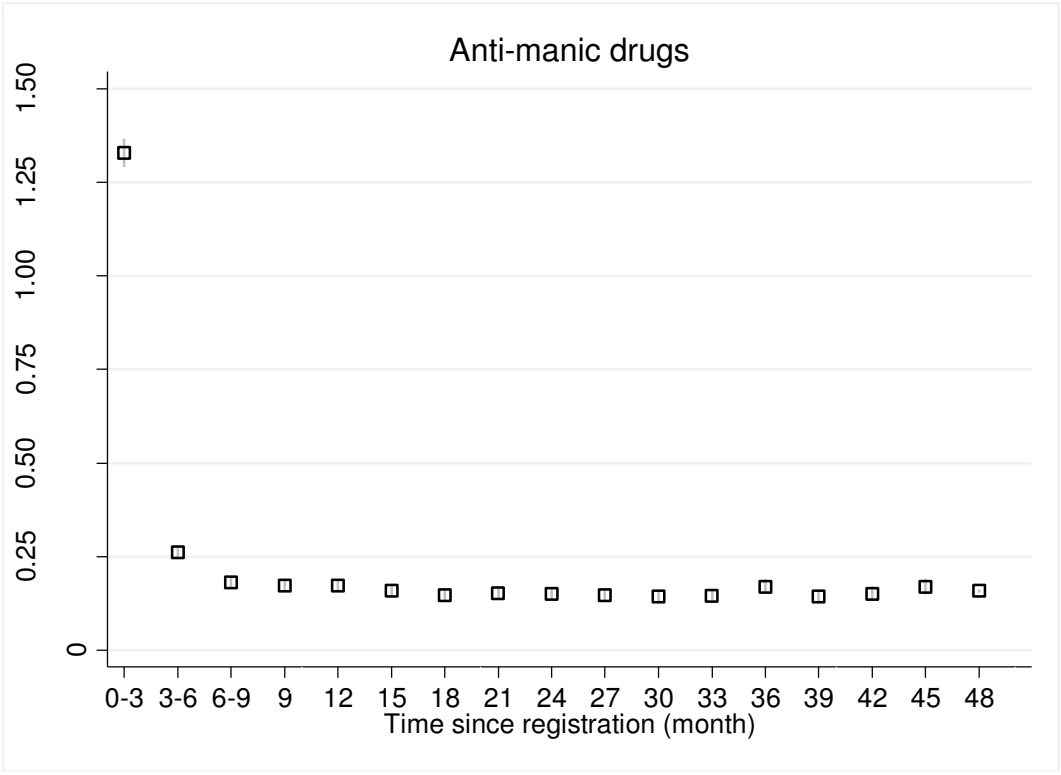


Figure 3-14 Rate of first recorded anti-manic drug prescriptions in women registered with a computerised general practice

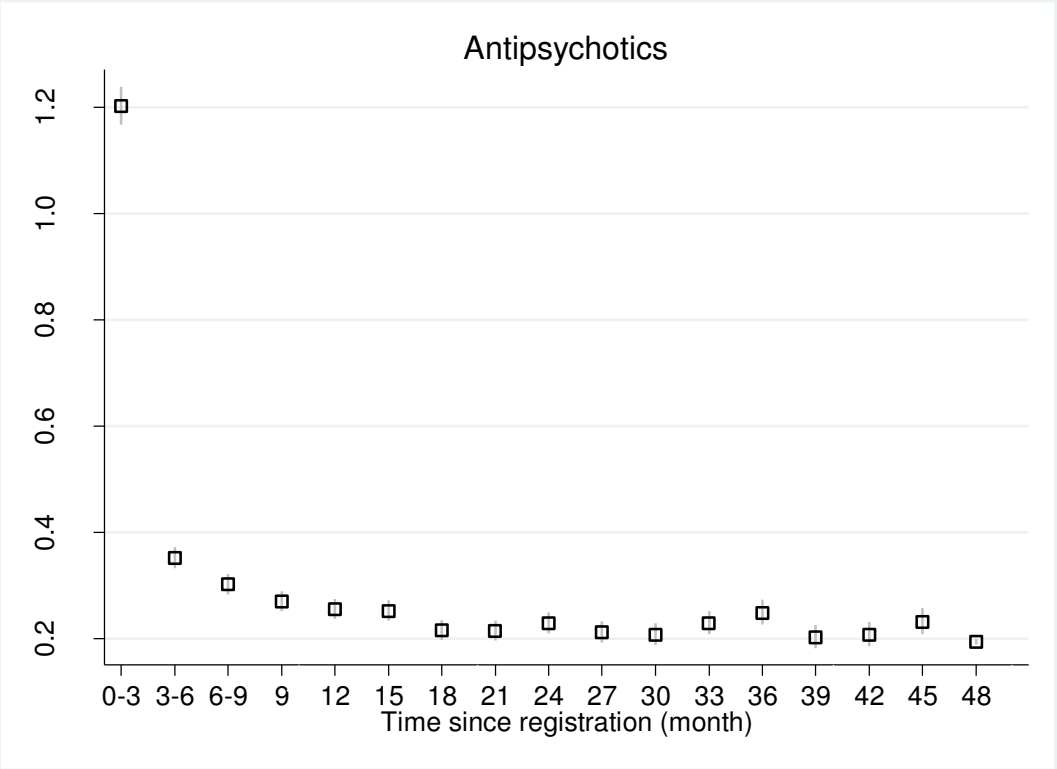


Figure 3-15 Rate of first recorded antipsychotic prescriptions in women registered with a computerised general practice

3.4 Discussion and conclusion

My results on assessing recordings of mental illness in THIN are generally consistent with general practice guidelines and results from previous studies using other primary care data and reflect current GP clinical practice. The THIN data I have used are therefore appropriate for assessing the clinical burden and the health care needs of the women with mental illness in UK primary care.

To define women with mental illness, alongside recording of diagnoses, recordings of psychotropic drug prescriptions and mental illness symptoms should also be considered to reflect the on-going health care management for patients with mental health problems in UK primary care and the changes in its clinical practices adopted by GPs. I have therefore attempted to identify patients with mental illness presenting to and/or treated in UK general practice by using combinations of recordings of mental illness diagnoses, symptoms and drug prescriptions as described later (please see Section 4.3.2 for the details). However, I will have missed women with mental illness who did not report their symptoms to their GPs or health care workers. Since all pregnant women must be registered with GPs in order to benefit from antenatal checks, free medications, hospital antenatal and postnatal care, and health services provided by midwives or health visitors, it is unlikely that a high proportion of women with significant mental illness, especially those with psychotropic drug prescriptions, would be misclassified. The results however are more likely to reflect patients' health seeking behaviours rather than the true disease activity. My approaches to identify women with mental illness therefore is likely to be pragmatic rather than exhaustive and the population identified by such approaches represents those presenting to and/or clinically treated in UK primary care which will be relevant for public health planning and policy making.

4 Clinical burden of maternal perinatal mental illness in United Kingdom primary care and its associated factors

This chapter describes a cross-sectional study conducted to estimate the current clinical burden of maternal depression, anxiety and serious mental illness (bipolar disorder, schizophrenia and other related psychotropic disorders) presenting to UK primary care in women in and around pregnancy, and the associations with age, socioeconomic status, and other maternal factors.

4.1 Introduction

4.1.1 Occurrence of depression and associated factors

Prevalence and incidence of maternal depression

There have been a great number of studies estimating the prevalence and incidence of maternal depression during and after pregnancy in the literature. Previous work however commonly focuses on subgroups and few general population based estimates are available. A meta-analysis of maternal depression in high-income countries found the prevalence of major depressive disorder in women during pregnancy and in the first year postpartum was approximately 6.5% to 12.9%, yet individual study estimates have varied very widely.[12] Table 4-1 summaries all systematic reviews (and/or meta-analyses) published on estimating prevalence and/or incidence of depression in women in and around pregnancy in English language journals.

Table 4-1 Systematic reviews and/or meta-analyses on estimating prevalence and/or incidence of maternal depression in and around pregnancy

Author(s), publication year	Study type and period	Interested outcome	Inclusion criteria		Number of studies initially identified	Number of studies finally included	Total population	Prevalence (95% CI)
			Study population	Diagnosis method				
Gavin et al., 2005[12]	Systematic review from January 1980 to March 2004	Prenatal and/or postnatal depression	Women recruited during pregnancy or the first year postpartum	Clinical assessment or structured clinical interview (i.e. RDC, DSM and ICD)	109	28	54 to 4,964 women per study (median sample size=202)	During pregnancy and in the first postpartum year: 6.5% to 12.9%
Bennett et al., 2004[115]	Meta-analysis from 1966	Prenatal depression by different trimester	Pregnant women aged over 17 years recruited from general obstetric and prenatal units or from population surveys	Self-report questionnaire (i.e. BDI and EPDS) or structured clinical interview (i.e. SADS, SCID and RDC)	714	21	19,284	First trimester: 7.4% (2.2-12.6) Second trimester: 12.8% (10.7-14.8) Third trimester: 12.0% (7.4-16.7)
O'Hara et al., 1996[25]	Meta-analysis	Postnatal depression by different diagnosis method	Pregnant women recruited through random or quasi-random techniques and assessed after at least two weeks postpartum	Self-report questionnaire or structured clinical interview	Not reported	59	12,810	Overall:12.8% (12.3-13.4) BDI:11.6% (9.7-13.5) CES-D:18.0% (16.1-19.9) EPDS:12% (10.9-13.1) RDC:10.5% (9.7-11.3) DSM:7.2% (3.7-10.7)

BDI=Beck Depression Inventory
CES-D=Centre for Epidemiological Studies-Depression
CI=confidence interval
DSM=Diagnostic and Statistical Manual III, III-R
DSM-IV=Diagnostic and Statistical Manual of Mental Disorders, IV
EPDS=Edinburgh Postnatal Depression Score
RDC=Research Diagnostic Criteria
SADS=Schedule for Affective Disorders and Schizophrenia
SCID=Structured Clinical Interview for DSM Disorders

While previous studies have generally found that depression is highly prevalent in women during the perinatal period, the estimates have varied considerably based on different study population and assessment methods. Most previous research has assessed depression by, often study-specific, screening with self-administered questionnaires, such as the Edinburgh Postnatal Depression Scale (EPDS, Appendix III). The EPDS questionnaire was designed to assess how a pregnant woman or a new mother felt in the past seven days.[116] It contains 10 single-choice questions and the maximum score is 30. Although a score above 12 or 13 is widely used to indicate that mothers are likely to be suffering from depressive symptoms of varying severity, a score above certain threshold cannot in itself confirm a diagnosis of depression and such thresholds may over- or under-estimate depression during pregnancy or postpartum.[117–119] Therefore, the EPDS score should not override clinical judgement.

For example, a previous cohort study in south-west England assessed 12,000 women using the EPDS and found that at 32 weeks of pregnancy 13.5% of women scored equal or over 12 on EPDS for probable depression and 9.1% at eight weeks postpartum.[120] The study found a similar risk pattern after the researchers used a higher EPDS threshold (a score equal or over 13) in pregnancy. This study found that overall depression scores (measured by the EPDS) were also higher at 32 weeks of pregnancy than eight weeks postpartum (mean difference=0.88, 95% confidence interval [CI] 0.79-0.97) and concluded that symptoms of depression are not more common or severe after childbirth than during pregnancy. In addition, an Australian study retrospectively assessed women for symptoms of depression using the Delusions-Symptoms-States Inventory (similar to EPDS) during the perinatal period and found that the risk of depression at 6-month postpartum was lower compared with shortly after childbirth.[121]

In contrast to studies using various questionnaires to measure depression, by using a structured clinical interview a UK study examining nearly 5,000 women found 15% of

women had depression in the early postpartum period.[122] Another fairly recent UK study using routine primary health care data from general practice records found the incidence of new maternal depression, defined as first depression diagnosis or antidepressant prescription after at least 12 months with neither, was 14/100 person-years at the time of the birth and then decreased to 10/100 person years at 6 months after birth.[91]

Very few studies have compared the burden of maternal depression in women during the perinatal period with those in non-childbearing periods. Previous studies in high-income countries comparing women before or after pregnancy with similar age groups of women during non-childbearing periods found slightly higher, but not statistically significant, prevalence of non-psychotic psychiatric illness (mainly depression) in women during the perinatal period.[123–125] These studies however had very small sample sizes and all dated back to the early 1990s. In addition, after restricting to new onset of depression, one of the studies conducted in UK found a 3-fold increased incidence of postpartum depression in women within five weeks of delivery compared to women during non-childbearing periods.[124]

Factors associated with maternal depression in and around pregnancy

Previous research suggests that the prevalence and/or incidence of maternal depression may vary substantially by different maternal socio-demographic and lifestyle factors. For instance, a recent American study of more than 75,000 non-pregnant women aged 18-44 years found that the prevalence of major depression was greatest in women who were over 35 years of age, unmarried, less educated, unable to work or unemployed or with low income.[20]

For maternal depression in and around pregnancy, most studies have focused on women during the postpartum period. O'Hara and Swain conducted a meta-analysis to identify risk factors associated with postpartum depression, which included 59

studies from high-income countries.[25] This study found that the prevalence of postpartum depression was 13% and was highest in women with a history of psychological disorder during pregnancy, poor marital relationship and low social support, and stressful life events. Particularly, this study showed that women with higher income had a lower score of depression (measured by various self-administrated questionnaires, such as the EPDS) than women with low income (mean difference=-0.14, 95% CI -0.21 to -0.08). In addition, it only found a marginally increased, but not statistically significant, score for depression with increased age (mean difference=0.04, 95% CI 0.00 to 0.09).[25]

Rich-Edwards and colleagues in America investigated whether socio-demographic factors were associated with antenatal or postnatal depression measured using EPDS (EPDS>12 defined as having probable depression).[22] They examined 1,662 women during and after pregnancy prospectively and found that the strongest risk factor for maternal depression in mid-pregnancy was a history of depression (odds ratio [OR] =4.07, 95% CI 3.76 to 4.40), and the strongest risk for depression at six weeks postpartum was depressive symptoms during pregnancy (OR=6.78, 95% CI 4.07 to 11.31) or a history of depression before pregnancy (OR=3.82, 95% CI 2.31 to 6.31).

In addition, the American study found an increased odds of postpartum depression in women with financial hardship (OR=3.6, 95% CI 1.9-6.7) after adjusting for maternal age, race/ethnicity, immigration status, parity and annual household income.[22] Although women aged less than 23 years had two to three times the odds of having maternal depression during or after pregnancy as those aged 30-34 (OR=2.71, 95% CI 1.4-5.2 in mid-pregnancy and OR=2.37, 95% CI 1.05-5.38 at six months postpartum after adjusting for race/ethnicity), after adjusting for household income, the association of maternal age with depression was decreased and was not statistically significant (e.g. OR=1.87, 95% CI 0.93-3.74 for antenatal depression),

suggesting that the effect of maternal age was largely driven by different financial circumstances.[22]

Likewise, Warner *et al.* carried out a study in the south Manchester area of England to identify the risk factors of postnatal depression.[24] They examined 2,375 women at six weeks postpartum and found unplanned pregnancy (OR=1.44, 95% CI 1.10-1.89), not breast feeding (OR=1.52, 95% CI 1.12-2.06), maternal unemployment (OR=1.56, 95% CI 1.14-2.12) and head of household unemployed (OR=1.50, 95% CI 1.10-2.04) were associated with an increased risk of postpartum depression after they mutually adjusted for each other. This study also found a slightly decreased risk of postpartum depression in women with increased age (unadjusted OR=0.94, 95% CI 0.92-0.96). This association however disappeared after adjusting for other socio-demographic factors.

A more recent American study recruited nearly 2,000 women during pregnancy and depression was assessed using criteria from the DSM-IV based on the Patient Health Questionnaire.[126] About 10% of women had antenatal depression and half had major depression. After mutual adjustment, psychosocial stress, domestic violence, chronic medical conditions and ethnicity were associated with an increased odds of both antenatal and postpartum depression, whereas older age was associated with a decreased odds. No association however was found between depression and years of education.

4.1.2 Occurrence of anxiety and associated factors

Compared with depression, far fewer studies have been conducted to estimate the prevalence and/or incidence of maternal anxiety during the perinatal period. To my best knowledge, there has been only one systematic review on maternal anxiety. Based on three small studies, this systematic-review however reported that the prevalence of generalised anxiety disorder ranged from 4.4-8.2% postpartum.[127] It concluded that there were too few studies to obtain adequate estimates around pregnancy.

In addition, studies that have estimated the burden of maternal anxiety so far have been on a much smaller scale. For example, a previous US study interviewed 68 women and found 4.4% of them had generalized anxiety disorder during the early postnatal period.[128] Another more recent French study assessing 497 women using a structured diagnostic interview found that nearly 25% of women suffered from anxiety during the third trimester of pregnancy.[129]

Very few studies have been conducted to examine factors associated with the occurrence of maternal anxiety. Wenzel *et al.* interviewed 174 women at approximately eight weeks after childbirth and found that personal psychiatric history, family psychiatric history, and socioeconomic status were significantly associated with increased risks of anxiety symptoms measured using the Beck Anxiety Inventory.[130] In addition, research has shown that a history of previous mental illness, and particularly a history of major depression or generalised anxiety disorder, is associated with increased risks of post-traumatic stress disorder following childbirth.[131–133]

4.1.3 Occurrence of serious mental illness and associated factors

Whilst relatively few studies have estimated prevalence and/or incidence of less common but more severe psychiatric illness (i.e. bipolar affective disorder and

schizophrenia and other related psychotic disorders), their estimates are fairly consistent at about 1 per 1,000 women during the perinatal period.[26,134–136] Two previous large population studies in Denmark found the prevalence of first-time severe mental disorders was 0.45-1.03 per 1000 births within the first three months after delivery.[134,135] Nager *et al.* examining half a million Swedish first-time mothers found that during the postpartum period, 0.07% of them had their first hospitalisation due to psychotic disorders.[26]

Kendell *et al.* carried out a large population-based study in Edinburgh, Scotland in 1987 and found a higher proportion of psychiatric admission in women, mainly diagnosed with severe depression and psychotic disorder, after childbirth than during pregnancy.[136] This higher risk postpartum was particularly evident in first-time mothers with a history of mental illness. In Denmark, Munk-Olsen and colleagues examined more than one million first-time parents between 1973 and 2005 and found that compared with 6-11 months after childbirth, there was an increased risk of hospital admission or outpatient contact for any mental disorder in women during the first month postpartum (relative risk ratio [RRR] =3.49, 95% CI 3.01-4.04), but a decreased risk during pregnancy (RRR=0.72, 95% CI 0.63-0.81).[134] However, a more recent study in the same population conducted by the same researchers reported that compared with women without children, hospital readmission rate was in fact lower in new mothers within the two months after childbirth.[137]

In addition, a very large population-based study in Sweden examined the association between first hospital admissions due to postpartum psychosis within the first year after childbirth and socio-demographic factors in first-time mothers from 1986 to 1997. This study found there was an increased risk of having first hospital admission in mothers with increased age (e.g. adjusted hazard ratio=6.6, 95% CI 3.1-13.8 in women aged 40-44 years compared with women aged 20-24 years after adjusting for maternal education level, marital status and year of delivery).[26] This Swedish study

used education level as a measure of socioeconomic status and found there was no association between education level and first hospital admission due to postpartum psychosis in first-time mothers. In contrast, a later study using the same population cohort found that women with less years of education were more likely to have postpartum psychosis.[27]

4.1.4 Overlap or concurrent diagnoses of different mental illnesses

Although co-morbidity of different mental illnesses, especially between depression and anxiety, is fairly common, few studies have estimated the degree of overlap in women during the perinatal period.[138–143] An Australian study assessing both depression (including major or minor depression) and anxiety (including panic, phobia and generalised anxiety disorders) found 3.2% of women had both depression and anxiety at 6-8 weeks postpartum.[139] Lee *et al.* studied 357 women in an antenatal clinic in Hong Kong and found 39-47% of women with common mental disorders had both anxiety and depressive symptoms when individually assessed at 6-8 weeks postpartum.[139] Two previous cross-sectional studies using self-reported patient questionnaires in high-income countries found that nearly one third of patients with anxiety and/or depression had both conditions.[141,143]

4.2 Rationale and objectives

Although maternal mental illness during and after pregnancy commonly presents to and is primarily treated in general practice, there were no up-to-date estimates of these conditions, especially for anxiety and serious mental illness, and hardly any estimates of concurrent diagnoses of different mental illnesses in women in and around pregnancy at primary care level. In addition, the most affected groups of pregnant women in focus of age and socio-demographics remain unclear.

The objectives of this large population-based study therefore were to provide current estimates of maternal perinatal depression, anxiety and serious mental illness identified in UK general practice and its variations by different maternal factors, including age, socioeconomic status, lifestyle characteristics, history of previous pregnancy and maternal chronic comorbidities.

4.3 Methods

4.3.1 Study population

From Population 4 in Figure 2-1, I identified women of childbearing age with at least one recorded pregnancy ending in live birth between April 1994 and July 2009, and with at least 15 months of prospectively recorded data preceding conception and nine months following childbirth. To remove any clustering effects, I randomly selected one pregnancy for each woman.

4.3.2 Measuring perinatal mental illness

As shown in the previous chapter, recording of diagnoses of mental illness was decreasing substantially after 2003 whereas the recording of symptoms was increasing, which likely reflected shifting of how GPs label their patients rather than decrease of actual disease prevalence. Both diagnostic and symptom records were therefore used to identify women with mental illness. In addition, in UK general practice it is common for patients to be prescribed psychotropic drugs without direct recording of the diagnostic indication for the prescription, which likely reflects both the diagnostic pathway (e.g. prescriptions of psychotropic drugs as part of diagnostic procedure) and routine clinical practice (e.g. a doctor with knowledge of his or her patient's clinical history will not need to record a new diagnosis of depression with each prescription for effective clinical care). Furthermore, individuals may receive more than one type of diagnosis, concurrently or at different times during their life.

A comprehensive approach therefore was adopted to define and distinguish between different types of mental illness in women's records by using a combination of medical diagnoses and psychotropic drug prescriptions. Maternal mental illness was defined during the 9 months before pregnancy, during pregnancy (antenatal period) and during the 9 months after pregnancy (postnatal period). Periods of 9-months were used as they were similar in length to the average pregnancy, minimising potential

effects of different period lengths on prevalence estimates. Definitions of how clinically recognised depression, anxiety and serious mental illness (bipolar disorder, schizophrenia, other psychotic disorders) were measured in and around pregnancy are shown below:

- Depression

  I identified women as having clinically recognised depression in each period if they had records of depression and/or antidepressant prescriptions during that time. Because antidepressants are also commonly prescribed for other mental illnesses (e.g. anxiety), women who had been prescribed antidepressants but had no diagnosis of depression in their entire medical records were excluded.

- Anxiety

  I firstly identified women as having clinically recognised anxiety if they had records of anxiety and/or anxiolytic prescriptions during each period, excluding women who were prescribed anxiolytics with no diagnosis of anxiety throughout their medical record. Secondly, since anxiety is commonly treated using antidepressants, we identified women with antidepressant prescriptions during the period and a diagnosis of anxiety at any time but without records of depression.

- Serious mental illness

  Although serious mental illnesses are considered clinically to have life-long impact and NICE guidelines indicate the importance of knowing a woman's history of psychotic illness, I focused on evidence of currently recognised illness. Women were considered to have clinically recognised bipolar disorder during each period if they had medical records of the illness

and/or prescriptions of lithium or mood stabilisers during that time. Since mood stabilisers are also used for other conditions (e.g. epilepsy), women prescribed mood stabilisers but with no diagnoses of bipolar disorder in their medical records were excluded. We identified women with schizophrenia and other psychotic disorders in the same way and, as these are rare conditions, grouped them together as 'serious mental illness'.

4.3.3 Extracting maternal age, socioeconomic status and other factors

From women's medical records, I extracted data on the following characteristics of women: maternal age at the end of pregnancy (categorised as 15-24, 25-34, and 35-45 years), year of childbirth (categorised as 1994-1999, 2000-2004, and 2005-2009), household socioeconomic status, maternal body mass index (BMI, kg/m^2) before pregnancy and most recent smoking status before delivery. I also extracted data on women's pregnancy history (i.e. number of previous known live births as a proxy of parity) and other known important maternal comorbidities which might complicate the pregnancy, including maternal pre-existing diabetes and hypertension and maternal asthma and epilepsy. Definitions of how these factors were measured are shown below:

- Socioeconomic status

  Socioeconomic status was measured using postcode-level Townsend Index of Deprivation.[144] To maintain anonymity in THIN, patients' home postcodes are assigned a quintile of Townsend Index before data leave the general practice. As quintiles are based on census data distribution, they are representative of women's relative socioeconomic position at UK national level.

- Pre-gestational diabetes (pre-existing diabetes before pregnancy)

  Records of diagnosed diabetes were extracted from both Medical and Additional Health Data files and records for anti-diabetic drug prescriptions were extracted from Therapy file, according to BNF (Chapter 6.1.1, 6.1.2, and 6.1.3). Women were defined as having pre-existing diabetes if they ever had a clinical record of diabetes (except gestational diabetes) before the expected date of conception or ever had a prescription of either insulin or oral hypoglycaemic agents during or before pregnancy but without diagnoses of diabetes.

- Pre-gestational hypertension (pre-existing hypertension before pregnancy)

  Records of diagnosed hypertension and prescriptions of anti-hypertensive drugs were extracted. Women were identified as having pre-existing hypertension if they had records of either diagnoses or drug prescriptions before pregnancy. Women with records of drug prescriptions during pregnancy but no diagnostic records either before or during pregnancy were also included.

- Asthma

  Records of diagnosed asthma and prescriptions of anti-asthmatic medication were extracted. Women were defined with asthma if they had an asthma diagnosis ever before the end of the first trimester and had a recording of asthma exacerbation or prescriptions of any anti-asthmatic drugs within one year before and during pregnancy.

- Epilepsy

  Records of diagnosed epilepsy were extracted from both Medical and Additional Health Data files and epilepsy medication prescriptions were

extracted from Therapy file. Women were defined as having epilepsy if they had diagnostic recording of epilepsy ever and had a recording of prescriptions from one year before or during pregnancy.

4.3.4 Statistical analyses

Prevalence and overlap of perinatal mental illness

The prevalence of clinically recognised depression, anxiety and serious mental illness with or without treatment in women presenting to UK primary care was calculated as the proportions (with 95% confidence intervals [CI]) of all women during the periods before, in and after pregnancy using a combination of medical records of mental illness and psychotropic drug prescriptions. I also estimated the prevalence of each mental illness by only using recordings of diagnoses/symptoms (but not drug prescriptions). In addition, I restricted prevalence estimates to women whose first ever recording of each mental illness fell in each 9-months period to estimate newly-recognised mental illness before, during and after pregnancy. The period of 9-months before pregnancy was used as a reference period as an indication of baseline prevalence in women during childbearing, but not the perinatal, period.

In addition, the overall prevalence of each mental illness measured by combination of diagnoses/symptoms and psychotropic drug prescriptions was assessed by maternal age, year of childbirth, socioeconomic status, maternal smoking history, maternal BMI before pregnancy, pregnancy history and maternal comorbidity (including maternal pre-existing diabetes and hypertension and asthma and epilepsy). To provide estimates of concurrent diagnoses (overlapping illness), proportions of women with two or more different diagnoses were also calculated.

Impact of socioeconomic status stratified by age

Logistic regression was used to calculate odds ratios (ORs) for the association of each maternal mental illness during and after pregnancy with socioeconomic

deprivation. Given that the effect of socioeconomic deprivation on mental illness could vary substantially by age, I assessed effect modification using the likelihood ratio test and presented prevalence estimates to show absolute risks of clinically recognised mental illness in each deprivation quintile, stratified by maternal age alongside odds ratios adjusted for calendar period and the number of women's previously recorded live births. I also conducted a sensitivity analysis and assessed the impact of socioeconomic status using women's first clinically recognised mental illnesses.

4.4 Results

4.4.1 Prevalence and overlap of perinatal mental illness

I identified 116,457 women with at least one pregnancy ending in a live birth. The median age at the end of pregnancy was 31 years (IQR 26-35) and the numbers (proportions) of pregnant women aged 15-24, 25-35 and 35-44 years were 21,341 (18.3%), 64,214 (55.1%) and 30,902 (26.5%) respectively. Of all women, 23.2% (26,984) were from the least socioeconomically deprived group whereas 14.2% (16,524) were from the most socioeconomically deprived group (5.3% (6,172) had no socioeconomic group recorded).

Table 4-2 shows the clinical presentation of depression, anxiety and serious mental illness in and around pregnancy. Compared with maternal depression in the period before pregnancy (9.3%), prevalence was lower during pregnancy (5.1%) and higher postpartum (13.3%). For anxiety and serious mental illness, prevalence before pregnancy was similar to after, although clinical recording for both was lower during pregnancy (2.6% and 0.09% respectively). Compared with all clinical presentations, first presentations were less common but had similar prevalence patterns over the three periods, such that they were still lowest in the antenatal period. When restricting to mental illness defined by clinical diagnoses/symptoms only during each period, the prevalence was as expected decreased for all mental illnesses but the similar pattern that the prevalence was lower during pregnancy was observed again.

Figure 4-1 shows the overlap of different mental illnesses in women in and around pregnancy. Majority women with serious mental illness also had depression or anxiety, yet most diagnostic overlap was between common mental illnesses with about 20% of women with depression also having anxiety in and around pregnancy (Figure 4-1).

Table 4-2 Prevalence of maternal depression, anxiety and serious mental illnesses† presenting to UK general practice in and around pregnancy (N=116,457)

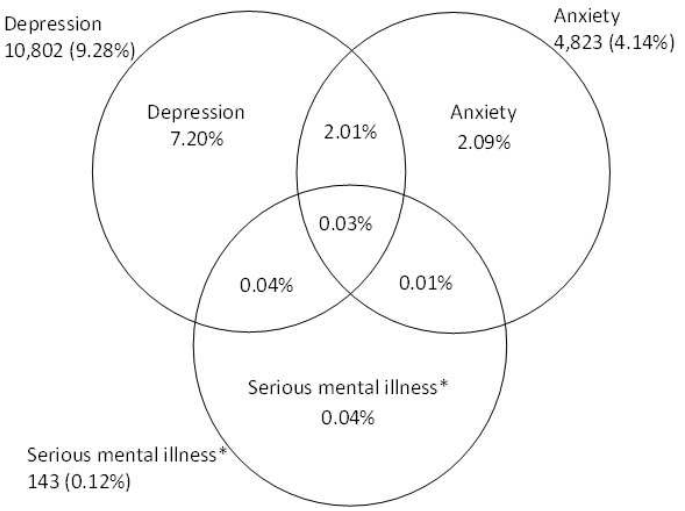
	Depression	Anxiety	Serious mental illness†
	n (%; 95% CI)	n (%; 95% CI)	n (%; 95% CI)
Combination of diagnoses/symptoms and psychotropic drug prescriptions			
Any presentation or treatment			
During 9-month before pregnancy	10,802 (9.3; 9.1-9.4)	4,823 (4.1; 4.0-4.3)	143 (0.12; 0.11-0.14)
During pregnancy	5,926 (5.1; 5.0-5.2)	3,084 (2.6; 2.6-2.7)	110 (0.09; 0.08-0.11)
During 9-month after pregnancy	15,454 (13.3; 13.1-13.5)	4,325 (3.7; 3.6-3.8)	176 (0.15; 0.13-0.18)
First presentation or treatment*			
During 9-month before pregnancy	3,482 (3.0; 2.9-3.1)	2,253 (1.9; 1.9-2.0)	30 (0.03; 0.02-0.04)
During pregnancy	975 (0.8; 0.8-0.9)	1,196 (1.0; 1.0-1.1)	14 (0.01; 0.01-0.02)
During 9-month after pregnancy	5,814 (5.0; 4.9-5.1)	1,621 (1.4; 1.3-1.5)	56 (0.05; 0.04-0.06)
Clinical diagnoses/symptoms only			
Any presentation			
During 9-month before pregnancy	6,481 (5.6; 5.4-5.7)	3,073 (2.6; 2.5-2.7)	61 (0.05; 0.04-0.07)
During pregnancy	3,333 (2.9; 2.8-3.0)	2,244 (1.9; 1.8-2.1)	45 (0.04; 0.03-0.05)
During 9-month after pregnancy	12,590 (10.8; 10.6-11.0)	3,024 (2.6; 2.5-2.7)	97 (0.08; 0.07-0.10)
First presentation*			
During 9-month before pregnancy	2,578 (2.2; 2.1-2.3)	1,741 (1.5; 1.4-1.6)	34 (0.03; 0.02-0.04)
During pregnancy	979 (0.8; 0.8-0.9)	1,216 (1.0; 1.0-1.1)	21 (0.02; 0.01-0.03)
During 9-month after pregnancy	5,900 (5.1; 4.9-5.2)	1,576 (1.4; 1.3-1.4)	60 (0.05; 0.04-0.07)

†Serious mental illness includes bipolar disorder (including mania and hypomania), schizophrenia or other related psychotic disorders

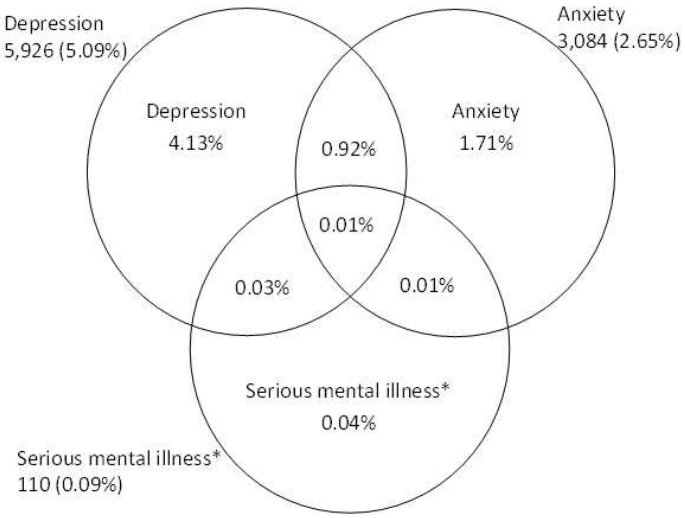
*Prevalence estimates are for presentation or treatment only when it first appeared in a woman's record during the respective 9-month period, excluding any women with a history of the relevant mental illness

CI=confidence interval

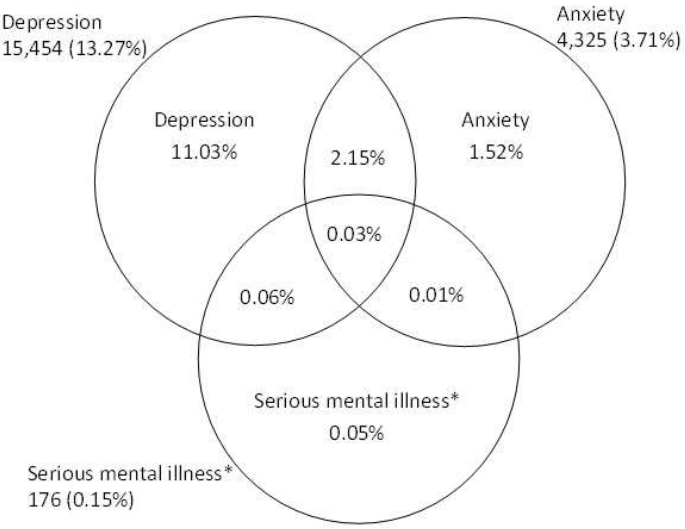
9-month before pregnancy



During pregnancy



9-month after childbirth



* Serious mental illness includes bipolar disorder, schizophrenia or other related psychotic disorders

Figure 4-1 Venn diagrams of prevalence of maternal perinatal mental illnesses and overlap shown as proportions of all pregnant women (N=116,457)

4.4.2 Prevalence estimates by different maternal factors

The prevalence estimates varied considerably by maternal age, socioeconomic status, smoking history, maternal BMI and maternal comorbidities. The results are shown in following tables for depression (Table 4-3), anxiety (Table 4-4), and serious mental illness (Table 4-5), separately. Overall, younger women were more likely to have depression in and around pregnancy and older women were more likely to have serious mental illness whilst anxiety showed less age variation. Women from groups with greater socioeconomic deprivation were more likely to have all three mental illnesses compared with groups with less socioeconomic deprivation during the same period. Women who had a history of smoking, abnormal BMI before pregnancy or other chronic conditions were also more likely to have a record of the three mental illnesses.

Figure 4-2 shows the prevalence ($\log_{10}$ scale) of clinically recognised depression, anxiety and serious mental illness in women in and around pregnancy in three different calendar periods. The prevalence estimates of each mental illness across the different time periods generally remain consistent during the study period. The estimates for depression before and during pregnancy however were slightly higher after year 2000.

Figure 4-3 shows the prevalence ($\log_{10}$ scale) of clinically recognised depression, anxiety and serious mental illness in women in and around pregnancy by the number of previous known live births. In general, women with higher parity had higher prevalence of depression in and around pregnancy. For anxiety and serious mental illness, the prevalence trend however was more stable.

Table 4-3 Prevalence of perinatal depression varied by different maternal factors (N=116,457)

	During 9-month before pregnancy		During pregnancy		During 9-month after pregnancy	
	n	%	n	%	n	%
Maternal age at the end of pregnancy, years						
15=<age<25 (n=21,341)	2,209	10.4	1,300	6.1	3,762	17.6
25=<age<35 (n=64,214)	5,910	9.2	3,127	4.9	8,305	12.9
35=<age<=45 (n=30,902)	2,683	8.7	1,499	4.9	3,387	11.0
Townsend deprivation index						
1 (least deprivation) (n=26,984)	1,706	6.3	911	3.4	2,648	9.8
2 (n=21,978)	1,671	7.6	869	4.0	2,450	11.2
3 (n=23,028)	2,190	9.5	1,188	5.2	3,056	13.3
4 (n=21,771)	2,449	11.2	1,347	6.2	3,445	15.8
5 (most deprivation) (n=16,524)	2,203	13.3	1,276	7.7	3,026	18.3
Missing (n=6,172)	583	9.4	335	5.4	829	13.4
Maternal smoking history						
No (n=62,867)	4,172	6.6	2,169	3.5	6,490	10.3
Yes (n=53,590)	6,630	12.4	3,757	7.0	8,964	16.7
Maternal BMI before pregnancy (kg/m^2)						
Under-weight (<18.5) (n=4,023)	4,51	11.2	241	6.0	574	14.3
Normal (18.5-24.9) (n=53,365)	4,636	8.7	2,532	4.7	6,509	12.2
Over-weight(25-29.9) (n=22,822)	2,269	9.9	1,193	5.2	3,172	13.9
Obese (30-39.9) (n=13,667)	1,701	12.4	970	7.1	2,339	17.1
Missing (n=22,580)	1,745	7.7	990	4.4	2,860	12.7
Maternal comorbidity						
No (n=113,786)	10,441	9.2	5,710	5.0	14,980	13.2
Yes (n=2,671)	361	13.5	216	8.1	474	17.7

Table 4-4 Prevalence of perinatal anxiety varied by different maternal factors (N=116,457)

	During 9-month before pregnancy		During pregnancy		During 9-month after pregnancy	
	n	%	n	%	n	%
Maternal age at the end of pregnancy, years						
15=<age<25 (n=21,341)	891	4.2	606	2.8	842	3.9
25=<age<35 (n=64,214)	2,754	4.3	1,680	2.6	2,462	3.8
35=<age<=45 (n=30,902)	1,178	3.8	798	2.6	1,021	3.3
Townsend deprivation index						
1 (least deprivation) (n=26,984)	892	3.3	532	2.0	800	3.0
2 (n=21,978)	779	3.5	498	2.3	707	3.2
3 (n=23,028)	921	4.0	619	2.7	851	3.7
4 (n=21,771)	1,037	4.8	633	2.9	930	4.3
5 (most deprivation) (n=16,524)	939	5.7	637	3.9	820	5.0
Missing (n=6,172)	255	4.1	165	2.7	217	3.5
Maternal smoking history						
No (n=62,867)	1,875	3.0	1,279	2.0	1,800	2.9
Yes (n=53,590)	2,948	5.5	1,805	3.4	2,525	4.7
Maternal BMI before pregnancy (kg/m^2)						
Under-weight (<18.5) (n=4,023)	244	6.1	119	3.0	188	4.7
Normal (18.5-24.9) (n=53,365)	2,226	4.2	1,375	2.6	2,001	3.7
Over-weight(25-29.9) (n=22,822)	968	4.2	634	2.8	851	3.7
Obese (30-39.9) (n=13,667)	669	4.9	450	3.3	595	4.4
Missing (n=22,580)	716	3.2	506	2.2	690	3.1
Maternal comorbidity						
No (n=113,786)	4,672	4.1	2,975	2.6	4,180	3.7
Yes (n=2,671)	151	5.6	109	4.1	145	5.4

Table 4-5 Prevalence of perinatal serious mental illness* varied by different maternal factors (N=116,457)

	During 9-month before pregnancy		During pregnancy		During 9-month after pregnancy	
	n	%	n	%	n	%
Maternal age at the end of pregnancy, years						
15=<age<25 (n=21,341)	23	0.11	13	0.06	25	0.12
25=<age<35 (n=64,214)	63	0.10	53	0.08	86	0.13
35=<age<=45 (n=30,902)	57	0.18	44	0.14	65	0.21
Townsend deprivation index						
1 (least deprivation) (n=26,984)	20	0.07	14	0.05	29	0.11
2 (n=21,978)	15	0.07	12	0.05	27	0.12
3 (n=23,028)	26	0.11	19	0.08	27	0.12
4 (n=21,771)	41	0.19	30	0.14	52	0.24
5 (most deprivation) (n=16,524)	35	0.21	30	0.18	35	0.21
Missing (n=6,172)	6	0.10	5	0.08	6	0.10
Maternal smoking history						
No (n=62,867)	49	0.08	35	0.06	67	0.11
Yes (n=53,590)	94	0.18	75	0.14	109	0.20
Maternal BMI before pregnancy (kg/m^2)						
Under-weight (<18.5) (n=4,023)	3	0.07	6	0.15	5	0.12
Normal (18.5-24.9) (n=53,365)	58	0.11	47	0.09	84	0.16
Over-weight(25-29.9) (n=22,822)	30	0.13	19	0.08	36	0.16
Obese (30-39.9) (n=13,667)	29	0.21	22	0.16	27	0.20
Missing (n=22,580)	23	0.10	16	0.07	24	0.11
Maternal comorbidity						
No (n=113,786)	132	0.12	101	0.09	167	0.15
Yes (n=2,671)	11	0.41	9	0.34	9	0.34

*Severe mental illnesses including bipolar disorder, schizophrenia or other related psychotic disorders

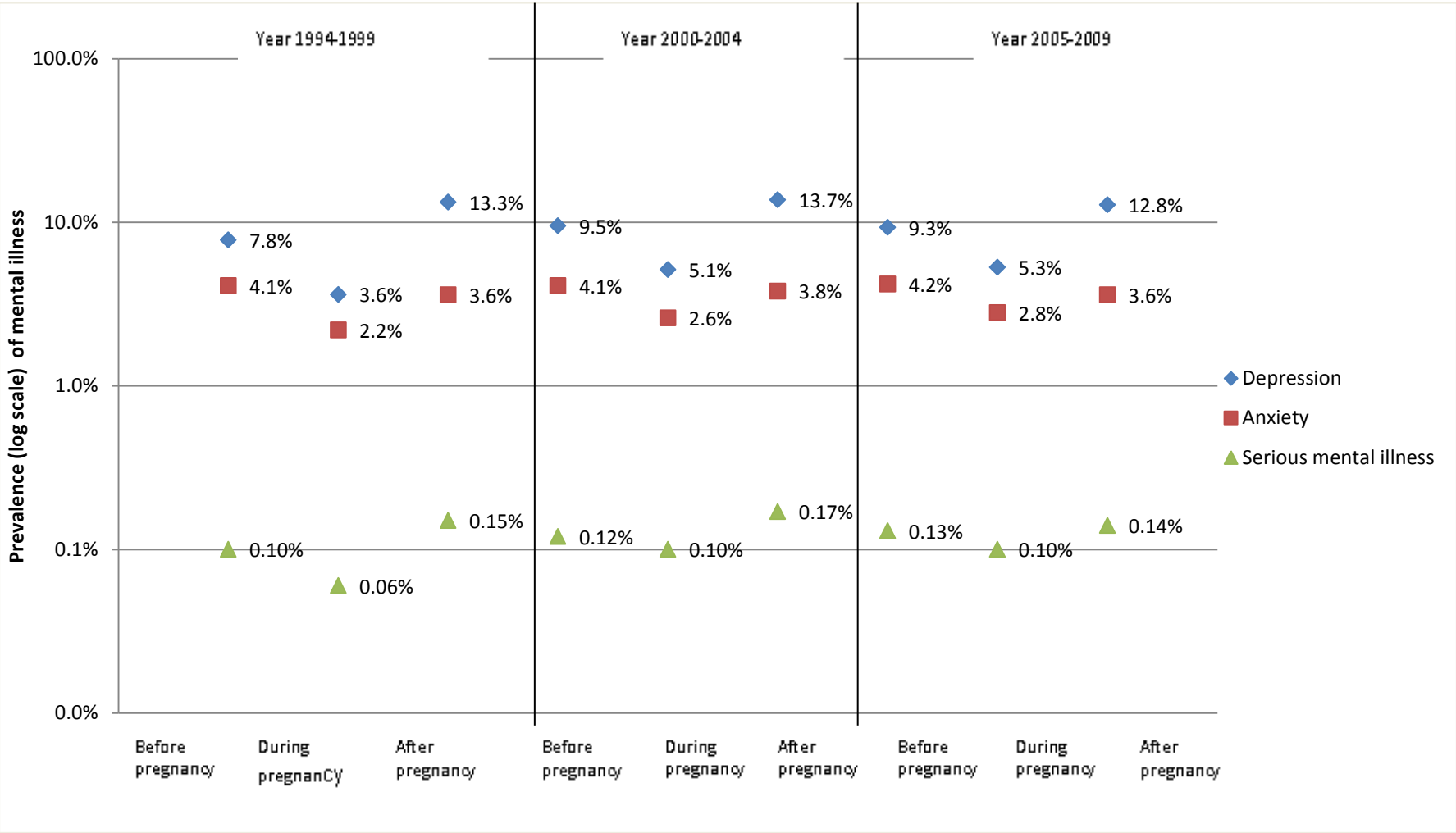


Figure 4-2 Prevalence (log_{10} scale) of depression, anxiety and serious mental illness in and around pregnancy by calendar period

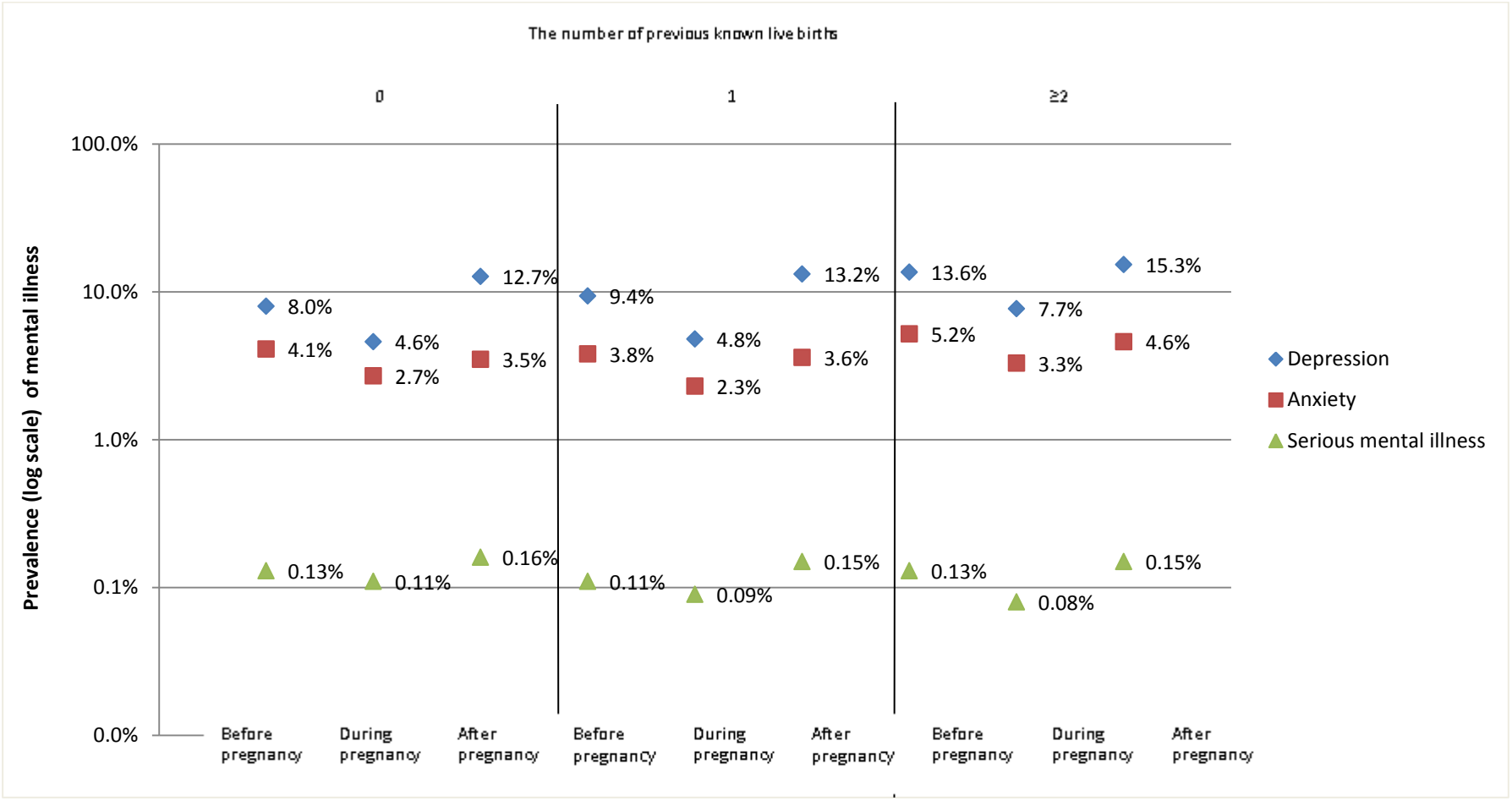


Figure 4-3 Prevalence (log_{10} scale) of depression, anxiety and serious mental illness in and around pregnancy by the number of previous known live births

4.4.3 Impact of socioeconomic status stratified by age

The following tables show absolute risks and adjusted ORs of clinically recognised depression (Table 4-6), anxiety (Table 4-7) and serious mental illness (Table 4-8) with socioeconomic deprivation, stratified by maternal age. The prevalence of maternal depression and anxiety was highest in the youngest women and lowest in the oldest women, although this pattern varied considerably by socioeconomic group. For women of all ages, the prevalence of all three mental illnesses during and after pregnancy increased with greater socioeconomic deprivation.

After adjusting for calendar time and number of previously recorded live births, the odds of perinatal mental illness increased with each deprivation quintile, compared to women in the least socioeconomically deprived quintile. In the youngest age group, several 95% confidence intervals included unity, however, tests for trend with increasing socioeconomic deprivation were $p<0.001$ for depression during and after pregnancy (Table 4-6), $p=0.06$ for anxiety (Table 4-7), and $p=0.33$ and 0.10 for serious mental illness (Table 4-8), which affected very few women.

In older women, the degree of increase in odds of all three clinical mental illnesses with greater socioeconomic deprivation was more marked. For example, women aged 35-45 years from the most socioeconomically deprived quintile had 2.6 times the odds of antenatal depression (OR=2.63, 95%CI 2.22-3.13), 2.5 times the odds of anxiety (OR=2.48, 95%CI 1.98-3.11) and 7.7 times the odds of serious mental illness (OR=7.68, 95%CI 2.92-20.24) as those from the least socioeconomically deprived quintile whereas in women aged 15-24, the equivalent ORs were 1.35 (95%CI 1.07-1.70), 1.49 (95%CI 1.06-2.09) and 1.59 (95%CI 0.19-13.64) respectively.

Similar patterns of risks were found postnatally. The p-values from the likelihood ratio tests for interaction between socioeconomic deprivation quintile and maternal age group were less than 0.001 for antenatal depression, postnatal depression and

antenatal anxiety, and 0.09 for postnatal anxiety; however there was weak statistical evidence for such interaction in serious mental illness (0.79 antenatal and 0.39 postnatal) with fairly small numbers of women in each age group.

After restricting to women's first clinical recording of mental illness, prevalence estimates of all three mental illnesses presenting initially during or after pregnancy were substantially reduced across all age and socioeconomic groups, which are shown in Table 4-9 for depression, Table 4-10 for anxiety, and Table 4-11 for serious mental illness. The impact of socioeconomic deprivation also reduced, yet patterns of increasing odds ratios with greater deprivation generally persisted. The degree of increase with deprivation quintile was again greatest in women aged 35-45 for antenatal depression (Table 4-9), antenatal and postnatal anxiety (Table 4-10), but not for postnatal depression (Table 4-9) which was instead greatest in women aged 15-24. Since very few women had a first clinical recording of serious mental illness during or after pregnancy, we were not able to stratify by age. Although adjusted odds ratios showed an association with deprivation, 95% confidence intervals were extremely wide (Table 4-11).

Table 4-6 Absolute risks and adjusted odds ratios for maternal depression associated with socioeconomic status, stratified by maternal age (N=110,285*)

Socioeconomic status (deprivation quintile)	Maternal age											
	15-24 years				25-34 years				35-45 years			
	N[†]	n[‡]	%	AOR[a] (95% CI)	N[†]	n[‡]	%	AOR[a] (95% CI)	N[†]	n[‡]	%	AOR[a] (95% CI)
Antenatal period[c]	**20,176**	**1,223**	**6.1**		**60,722**	**2,952**	**4.9**		**29,387**	**1,416**	**4.8**	
1 (least deprivation) (N=26,984)	1,843	94	5.1	1.00	15,732	492	3.1	1.00	9,409	325	3.5	1.00
2 (N=21,978)	2,479	109	4.4	0.85 (0.64-1.13)	12,655	482	3.8	1.22 (1.07-1.38)	6,844	278	4.1	1.18 (1.00-1.39)
3 (N=23,028)	4,052	240	5.9	1.15 (0.90-1.47)	13,069	661	5.1	1.61 (1.43-1.82)	5,907	287	4.9	1.41 (1.20-1.66)
4 (N=21,771)	5,838	364	6.2	1.21 (0.95-1.52)	11,452	707	6.2	1.93 (1.72-2.17)	4,481	276	6.2	1.77 (1.50-2.09)
5 (most deprivation) (N=16,524)	5,964	416	7.0	1.35 (1.07-1.70)	7,814	610	7.8	2.39 (2.11-2.70)	2,746	250	9.1	2.63 (2.22-3.13)
p value for trend				p<0.001[#]				p<0.001[#]				p<0.001[#]
Postnatal period[c]	**20,176**	**3,550**	**17.6**		**60,722**	**7,840**	**12.9**		**29,387**	**3,235**	**11.0**	
1 (least deprivation) (N=26,984)	1,843	236	12.8	1.00	15,732	1,576	10.0	1.00	9,409	836	8.9	1.00
2 (N=21,978)	2,479	368	14.8	1.19 (1.00-1.41)	12,655	1,401	11.1	1.12 (1.04-1.21)	6,844	681	10.0	1.14 (1.02-1.27)
3 (N=23,028)	4,052	708	17.5	1.44 (1.23-1.69)	13,069	1,708	13.1	1.35 (1.25-1.45)	5,907	640	10.8	1.25 (1.12-1.39)
4 (N=21,771)	5,838	1,100	18.8	1.56 (1.34-1.82)	11,452	1,766	15.4	1.62 (1.50-1.74)	4,481	579	12.9	1.51 (1.35-1.69)
5 (most deprivation) (N=16,524)	5,964	1,138	19.1	1.58 (1.36-1.84)	7,814	1,389	17.8	1.88 (1.74-2.03)	2,746	499	18.2	2.25 (1.99-2.53)
p value for trend				p<0.001[#]				p<0.001[#]				p<0.001[#]

* 5.3% (6,172) of the original population (116,457) had no socioeconomic status recorded
[c] Likelihood ratio test for interaction between deprivation quintile and age group: during pregnancy p<0.001; after pregnancy p<0.001
[†] Number of women in each deprivation quintile
[‡] Number of women with depression
[a] Odds ratio and 95% confidence interval adjusted for calendar time and number of previous known live births
[#] p value for trend from least to greatest deprivation excluding women with missing information for socioeconomic status
CI=confidence interval

Table 4-7 Absolute risks and adjusted odds ratios for maternal anxiety associated with socioeconomic status, stratified by maternal age (N=110,285*)

Socioeconomic status (deprivation quintile)	Maternal age											
	15-24 years				25-34 years				35-45 years			
	N[†]	n[‡]	%	AOR[a] (95% CI)	N[†]	n[‡]	%	AOR[a] (95% CI)	N[†]	n[‡]	%	AOR[a] (95% CI)
Antenatal period[c]	**20,176**	**559**	**2.8**		**60,722**	**1,593**	**2.6**		**29,387**	**767**	**2.6**	
1 (least deprivation) (N=26,984)	1,843	41	2.2	1.00	15,732	302	1.9	1.00	9,409	189	2.0	1.00
2 (N=21,978)	2,479	70	2.8	1.27 (0.86-1.88)	12,655	293	2.3	1.21 (1.03-1.42)	6,844	135	2.0	0.98 (0.78-1.23)
3 (N=23,028)	4,052	116	2.9	1.29 (0.90-1.85)	13,069	348	2.7	1.39 (1.19-1.62)	5,907	155	2.6	1.31 (1.06-1.62)
4 (N=21,771)	5,838	135	2.3	1.03 (0.72-1.47)	11,452	345	3.0	1.56 (1.33-1.83)	4,481	153	3.4	1.71 (1.38-2.12)
5 (most deprivation) (N=16,524)	5,964	197	3.3	1.49 (1.06-2.09)	7,814	305	3.9	2.02 (1.72-2.38)	2,746	135	4.9	2.48 (1.98-3.11)
p value for trend				p=0.06[#]				p<0.001[#]				p<0.001[#]
Postnatal period[c]	**20,176**	**804**	**4.0**		**60,722**	**2,330**	**3.8**		**29,387**	**974**	**3.3**	
1 (least deprivation) (N=26,984)	1,843	65	3.5	1.00	15,732	477	3.0	1.00	9,409	258	2.7	1.00
2 (N=21,978)	2,479	82	3.3	0.93 (0.67-1.30)	12,655	425	3.4	1.11 (0.97-1.27)	6,844	200	2.9	1.07 (0.88-1.29)
3 (N=23,028)	4,052	165	4.1	1.16 (0.86-1.55)	13,069	502	3.8	1.27 (1.12-1.44)	5,907	184	3.1	1.14 (0.94-1.38)
4 (N=21,771)	5,838	230	3.9	1.11 (0.84-1.47)	11,452	521	4.6	1.50 (1.32-1.70)	4,481	179	4.0	1.46 (1.20-1.77)
5 (most deprivation) (N=16,524)	5,964	262	4.4	1.24 (0.94-1.63)	7,814	405	5.2	1.69 (1.47-1.94)	2,746	153	5.6	2.06 (1.68-2.53)
p value for trend				p=0.06[#]				p<0.001[#]				p<0.001[#]

* 5.3% (6,172) of the original population (116,457) had no socioeconomic status recorded
[c] Likelihood ratio test for interaction between deprivation quintile and age group: during pregnancy p<0.001; after pregnancy p=0.09
[†] Number of women in each deprivation quintile
[‡] Number of women with anxiety
[a] Odds ratio and 95% confidence interval adjusted for calendar time and number of previous known live births
[#] p value for trend from least to greatest deprivation excluding women with missing information for socioeconomic status
CI=confidence interval

Table 4-8 Absolute risks and adjusted odds ratios for serious mental illness[β] associated with socioeconomic status, stratified by maternal age (N=110,285*)

Socioeconomic status (deprivation quintile)	Maternal age											
	15-24 years				25-34 years				35-45 years			
	N[†]	n[‡]	%	AOR[a] (95% CI)	N[†]	n[‡]	%	AOR[a] (95% CI)	N[†]	n[‡]	%	AOR[a] (95% CI)
Antenatal period[c]	**20,176**	**13**	**0.06**		**60,722**	**48**	**0.08**		**29,387**	**44**	**0.15**	
1 (least deprivation) (N=26,984)	1,843	1	0.05	1.00	15,732	7	0.04	1.00	9,409	6	0.06	1.00
2 (N=21,978)	2,479	0	---	---	12,655	7	0.06	1.24 (0.44-3.55)	6,844	5	0.07	1.15 (0.35-3.76)
3 (N=23,028)	4,052	3	0.07	1.36 (0.14-13.13)	13,069	8	0.06	1.38 (0.50-3.80)	5,907	8	0.14	2.13 (0.74-6.13)
4 (N=21,771)	5,838	4	0.07	1.26 (0.14-11.31)	11,452	14	0.12	2.75 (1.11-6.81)	4,481	12	0.27	4.21 (1.58-11.22)
5 (most deprivation) (N=16,524)	5,964	5	0.08	1.55 (0.18-13.24)	7,814	12	0.15	3.46 (1.36-8.78)	2,746	13	0.47	7.45 (2.83-19.63)
p value for trend				p=0.33[#]				p<0.01[#]				p<0.001[#]
Postnatal period[c]	**20,176**	**25**	**0.12**		**60,722**	**81**	**0.13**		**29,387**	**64**	**0.22**	
1 (least deprivation) (N=26,984)	1,843	1	0.05	1.00	15,732	15	0.10	1.00	9,409	13	0.14	1.00
2 (N=21,978)	2,479	1	0.04	0.74 (0.05-11.89)	12,655	17	0.13	1.41 (0.70-2.82)	6,844	9	0.13	0.95 (0.41-2.22)
3 (N=23,028)	4,052	3	0.07	1.36 (0.14-13.13)	13,069	13	0.10	1.04 (0.50-2.19)	5,907	11	0.19	1.35 (0.60-3.01)
4 (N=21,771)	5,838	12	0.21	3.79 (0.49-29.20)	11,452	25	0.22	2.29 (1.21-4.35)	4,481	15	0.33	2.43 (1.15-5.11)
5 (most deprivation) (N=16,524)	5,964	8	0.13	2.47 (0.31-19.79)	7,814	11	0.14	1.48 (0.68-3.22)	2,746	16	0.58	4.24 (2.04-8.82)
p value for trend				p=0.10[#]				p=0.07[#]				p<0.001[#]

* 5.3% (6,172) of the original population (116,457) had no socioeconomic status recorded
[c] Likelihood ratio test for interaction between deprivation quintile and age group: during pregnancy p=0.79; after pregnancy p=0.39
[β] Serious mental illness includes bipolar disorder, schizophrenia or other related psychotic disorders
[†] Number of women in each deprivation quintile
[‡] Number of women with serious mental illness
[a] Odds ratio and 95% confidence interval adjusted for calendar time and number of previous known live births
[#]p value for trend from least to most deprivation excluding women with missing information for socioeconomic status (5.3% missing overall)
CI=confidence interval

Table 4-9 Absolute risks and adjusted odds ratios for first clinically recognised depression associated with socioeconomic status, stratified by maternal age (N=110,285*)

Socioeconomic status (deprivation quintile)	Maternal age											
	15-24 years				25-34 years				35-45 years			
	N[†]	n[‡]	%	AOR[a] (95% CI)	N[†]	n[‡]	%	AOR[a] (95% CI)	N[†]	n[‡]	%	AOR[a] (95% CI)
Antenatal period[c]	**20,176**	**336**	**1.7**		**60,722**	**426**	**0.7**		**29,387**	**164**	**0.6**	
1 (least deprivation) (N=26,984)	1,843	32	1.7	1.00	15,732	80	0.5	1.00	9,409	45	0.5	1.00
2 (N=21,978)	2,479	34	1.4	0.79 (0.49-1.29)	12,655	75	0.6	1.17 (0.85-1.60)	6,844	31	0.5	0.94 (0.60-1.49)
3 (N=23,028)	4,052	74	1.8	1.05 (0.69-1.60)	13,069	104	0.8	1.56 (1.16-2.09)	5,907	29	0.5	1.03 (0.64-1.64)
4 (N=21,771)	5,838	90	1.5	0.89 (0.59-1.33)	11,452	87	0.8	1.48 (1.09-2.01)	4,481	31	0.7	1.42 (0.90-2.26)
5 (most deprivation) (N=16,524)	5,964	106	1.8	1.02 (0.69-1.53)	7,814	80	1.0	1.98 (1.45-2.71)	2,746	28	1.0	2.09 (1.30-3.37)
p value for trend				p=0.64[#]				p<0.001[#]				p=0.004[#]
Postnatal period[c]	**20,176**	**1,823**	**9.0**		**60,722**	**2,931**	**4.8**		**29,387**	**1,083**	**3.7**	
1 (least deprivation) (N=26,984)	1,843	124	6.7	1.00	15,732	692	4.4	1.00	9,409	360	3.8	1.00
2 (N=21,978)	2,479	199	8.0	1.22 (0.96-1.56)	12,655	590	4.7	1.08 (0.96-1.21)	6,844	223	3.3	0.83 (0.70-0.99)
3 (N=23,028)	4,052	377	9.3	1.42 (1.15-1.77)	13,069	650	5.0	1.16 (1.04-1.30)	5,907	224	3.8	0.98 (0.83-1.17)
4 (N=21,771)	5,838	566	9.7	1.52 (1.24-1.88)	11,452	603	5.3	1.25 (1.11-1.40)	4,481	154	3.4	0.88 (0.72-1.07)
5 (most deprivation) (N=16,524)	5,964	557	9.3	1.45 (1.18-1.79)	7,814	396	5.1	1.18 (1.03-1.34)	2,746	122	4.4	1.12 (0.90-1.39)
p value for trend				p<0.001[#]				p=0.001[#]				p=0.62[#]

* 5.3% (6,172) of the original population (116,457) had no socioeconomic status recorded
[c] Likelihood ratio test for interaction between deprivation quintile and age group: during pregnancy p=0.21; after pregnancy p<0.001
[†] Number of women in each deprivation quintile
[‡] Number of women with first clinically diagnosed depression
[a] Odds ratio and 95% confidence interval adjusted for calendar time and number of previous known live births
[#] p value for trend from least to greatest deprivation excluding women with missing information for socioeconomic status
CI=confidence interval

Table 4-10 Absolute risks and adjusted odds ratios for first clinically recognised anxiety associated with socioeconomic status, stratified by maternal age (N=110,285*)

Socioeconomic status (deprivation quintile)	Maternal age											
	15-24 years				25-34 years				35-45 years			
	N[†]	n[‡]	%	AOR[a] (95% CI)	N[†]	n[‡]	%	AOR[a] (95% CI)	N[†]	n[‡]	%	AOR[a] (95% CI)
Antenatal period[c]	**21,341**	**276**	**1.3**		**64,214**	**648**	**1.0**		**30,902**	**272**	**0.9**	
1 (least deprivation) (N=26,984)	1,843	25	1.4	1.00	15,732	136	0.9	1.00	9,409	69	0.7	1.00
2 (N=21,978)	2,479	33	1.3	0.98 (0.58-1.66)	12,655	114	0.9	1.04 (0.81-1.34)	6,844	52	0.8	1.04 (0.72-1.49)
3 (N=23,028)	4,052	55	1.4	1.00 (0.62-1.61)	13,069	147	1.1	1.30 (1.03-1.65)	5,907	61	1.0	1.41 (1.00-2.00)
4 (N=21,771)	5,838	53	0.9	0.67 (0.41-1.08)	11,452	131	1.1	1.33 (1.04-1.69)	4,481	33	0.7	1.00 (0.66-1.52)
5 (most deprivation) (N=16,524)	5,964	88	1.5	1.09 (0.70-1.70)	7,814	95	1.2	1.41 (1.08-1.84)	2,746	45	1.6	2.26 (1.55-3.29)
p value for trend				p=1.00[#]				p<0.01[#]				p<0.01[#]
Postnatal period[c]	**21,341**	**392**	**1.8**		**64,214**	**874**	**1.4**		**30,902**	**355**	**1.2**	
1 (least deprivation) (N=26,984)	1,843	36	2.0	1.00	15,732	202	1.3	1.00	9,409	95	1.0	1.00
2 (N=21,978)	2,479	39	1.6	0.80 (0.51-1.27)	12,655	171	1.4	1.05 (0.86-1.29)	6,844	74	1.1	1.07 (0.79-1.45)
3 (N=23,028)	4,052	76	1.9	0.96 (0.64-1.43)	13,069	175	1.3	1.04 (0.85-1.28)	5,907	72	1.2	1.21 (0.89-1.65)
4 (N=21,771)	5,838	103	1.8	0.90 (0.61-1.32)	11,452	151	1.3	1.03 (0.83-1.27)	4,481	55	1.2	1.22 (0.87-1.70)
5 (most deprivation) (N=16,524)	5,964	120	2.0	1.03 (0.71-1.50)	7,814	127	1.6	1.27 (1.02-1.59)	2,746	44	1.6	1.60 (1.11-2.29)
p value for trend				p=0.49[#]				p=0.11[#]				p=0.01[#]

* 5.3% (6,172) of the original population (116,457) had no socioeconomic status recorded
[c] Likelihood ratio test for interaction between deprivation quintile and age group: during pregnancy p<0.01; after pregnancy p=0.93
[†] Number of women in each deprivation quintile
[‡] Number of women with first clinically diagnosed anxiety
[a] Odds ratio and 95% confidence interval adjusted for calendar time and number of previous known live births
[#] p value for trend from least to greatest deprivation excluding women with missing information for socioeconomic status
CI=confidence interval

Table 4-11 Absolute risks of adjusted odds ratios for first clinically diagnosed serious mental illness[β] associated with socioeconomic status (N=110,285*)

Socioeconomic status (deprivation quintile)	N[†]	n[‡]	%	AOR[a] (95% CI)
Antenatal period	**110,285**	**14**	**0.01**	
1 (least deprivation)	26,984	1	---	1.00
2	21,978	1	<0.01	1.22 (0.08-19.55)
3	23,028	2	0.01	2.36 (0.21-26.14)
4	21,771	3	0.01	3.97 (0.41-38.63)
5 (most deprivation)	16,524	7	0.04	13.15 (1.57-110.01)
p value for trend				p=0.002[#]
Postnatal period	**110,285**	**55**	**0.05**	
1 (least deprivation) (N=26,984)	26,984	14	0.05	1.00
2 (N=21,978)	21,978	8	0.04	0.71 (0.30-1.69)
3 (N=23,028)	23,028	5	0.02	0.42 (0.15-1.17)
4 (N=21,771)	21,771	17	0.08	1.51 (0.73-3.12)
5 (most deprivation) (N=16,524)	16,524	11	0.07	1.28 (0.56-2.93)
p value for trend				p=0.23[#]

* 5.3% (6,172) of the original population (116,457) had no socioeconomic status recorded
[β] Serious mental illness includes bipolar disorder, schizophrenia or other related psychotic disorders
[†] Number of women in each deprivation quintile
[‡] Number of women with serious mental illness
[a] Odds ratio and 95% confidence interval adjusted for calendar time and number of previous known live births
[#] p value for trend from least to most deprivation excluding women with missing information for socioeconomic status
CI=confidence interval

4.5 Discussion

4.5.1 Principal findings

A substantial burden of depression, anxiety and serious mental illness during the perinatal period presents and is managed in UK general practice among women with pregnancies ending in live births, although there are considerable variations by different maternal characteristics in terms of the absolute risk. Higher risks of mental illness in mothers in more socioeconomically deprived areas compared with those in less deprived areas persist with increasing maternal age. When women's initial clinical presentation of mental illness was during or after pregnancy, the impact of socioeconomic deprivation remained yet was reduced, indicating that this was partially due to a history of mental illness commonly recurring in the perinatal period.

4.5.2 Strengths and limitations

This is the largest study to examine the clinical prevalence and overlap of maternal depression, anxiety and serious mental illness presenting to general practice in and around pregnancy. It is also the first to assess the joint effect of maternal age and socioeconomic status on the clinical burden of maternal perinatal mental illness in the UK. The considerable sample size means that our findings are unlikely to be due to chance. Equally as data were obtained from a large general practice database with prospectively recording, the potential for recall bias of mental illness was excluded.

The definition of maternal mental illness relies on women presenting to and being correctly identified by practitioners. Such estimates quantify the primary care burden in pregnancy, thus excluding undiagnosed illness in women not disclosing feelings to their doctor or health visitor.[81] A range of diagnostic tools (e.g. EPDS) has been used in cohort studies of selected populations, yet there is no universal agreement that these are advantageous in a routine clinical setting (or for screening) and as such there are no widely applied cut-offs used in practice to diagnose mental illness.[145,146] I

based case identification on medical diagnostic and prescribing records to reflect routine practice, similar to methods used by the Office for National Statistics and other published studies of mental illness in general practice databases.[76,89–91] Since GPs occupy a gate-keeper role to health care in the UK, and are normally the first point of contact for non-emergency services, referred via midwives and health visitors, I believe that these data are an ideal source for estimating the prevalence of mental illness presenting to general practice nationally. The similarity of my prevalence estimates to studies restricting to diagnosed postpartum depression using standardized interviewing schedules[25,124] and anxiety[127] is reassuring.

The decreased prevalence observed during pregnancy may reflect NICE guidelines to reduce psychotropic drug treatment during pregnancy which has been observed elsewhere. However, after estimating the prevalence based on recording of medical diagnoses regardless of drug prescriptions, a similar pattern of lower prevalence estimates during pregnancy was again observed. This could also be due to greater midwifery antenatal care or diagnostic bias if general practitioners remain more likely to diagnose and treat mental illness postpartum.

4.5.3 Interpretation in context of previous studies

Although numerous studies have estimated the prevalence of maternal depression, fewer have assessed anxiety and serious mental illness and ours is the first to compare prospectively all clinically recognised mental illnesses (depression, anxiety and serious mental illness) and their overlap before, during and after pregnancy in UK general practice. A systematic review of studies in high-income countries found the prevalence of maternal postpartum depression was 13% however individual study estimates varied widely.[25] A systematic review of maternal anxiety concluded that there were too few studies to obtain adequate estimates around pregnancy, however, based on three small studies, generalised anxiety disorder ranged from 4.4-8.2% postpartum.[127] Most previous studies assessed mental illness by, often study-specific,

screening with self-administered questionnaires (e.g. Edinburgh postnatal depression scale),[120] which means they are not directly comparable with this study, which represents disease identified through health service use or primary care attendance.

Previous studies on serious mental illness primarily rely on medical admissions and our similar estimates indicate these diagnoses are reasonably captured among women registered in general practice. Nager and colleagues examined Swedish first-time mothers (n=502,767) and found about 0.07% of mothers had their first hospital admission for psychosis postpartum, which is very similar to my estimate of first recorded serious mental illness.[26] Our estimates also concur with a 1987 Edinburgh registry study in which a higher proportion of psychiatric admissions presented in women after childbirth than during pregnancy.[136] In Denmark, Munk-Olsen and colleagues examined over a million first-time parents between 1973 and 2005 and found that compared with 6-11 months postpartum, medical contact for any mental disorder was more likely during the first month postpartum (relative risk=3.49), and less likely during pregnancy (relative risk=0.72), which is consistent with our findings.[147]

Few studies have estimated the degree of overlap between depression, anxiety and serious mental illness in women in and around pregnancy. Studying 357 women in an antenatal clinic in Hong Kong, Lee *et al.* found 39-47% of women with common mental disorders had both anxiety and depressive symptoms when individually assessed.[138] Two previous cross-sectional studies using self-reported patient questionnaires in high-income countries reported an equivalent figure of 28% in the general population.[141,143]

Socio-demographic factors have an important impact on maternal mental illness yet the joint effects of maternal age and socioeconomic deprivation among pregnant women and new mothers as predictors of important health burden in the population

have not been adequately assessed. A recent American study of more than 75,000 non-pregnant women aged 18-44 found that the prevalence of major depression was greater in women over 35 years, unmarried, less educated, unable to work or unemployed or with low income than in women without such risk factors.[20]

Previous studies show that women with greater socioeconomic deprivation were more likely to have perinatal mental illness than those with lower socioeconomic deprivation after adjusting for other socio-demographic factors.[22–25] A Swedish birth cohort study found that in first time mothers fewer years of maternal education was not associated with the increased risk of postpartum psychosis[26] but did appear to have an effect in a later study of the same population cohort.[27] Patterns of the effect of maternal age on perinatal mental illness have been inconsistent in different studies,[22,26,28,25] showing both decreased[28] and increased[26,27] risks in older women.

Rich-Edwards and colleagues investigated whether socio-demographic factors were associated with antenatal or postnatal depression.[22] They interviewed 1,662 women from Boston in the United States of America and found an increased odds of postnatal depression in those with financial hardship (OR=3.6, 95%CI 1.9-6.7 after adjusting for maternal age, race/ethnicity, immigration status, parity and income). Since patients with depression are more likely to have another episode in the later stage of their life, this US study also found that a history of depression was the strongest risk factor for perinatal depression. However, similar to my study, the effect of financial hardship remained when the authors excluded women with a history of depression. In addition, women under age 23 years had more maternal depression during and after pregnancy than women aged 30-34 (OR=2.7, 95%CI 1.4-5.2 mid-pregnancy and OR=2.4, 95%CI 1.1-5.4 six months postpartum after adjusting for race/ethnicity); however effects reduced and were not statistically significant after adjusting for household income, suggesting that effect of maternal age was largely driven by different financial circumstances.

4.5.4 Conclusion and implications

This study shows that there is considerable primary care burden of maternal perinatal mental illness and women in more socioeconomically deprived circumstances are at high risk. This highlights that greater recognition is needed at policy level. As there is currently not enough evidence that perinatal screening tools are advantageous over clinical assessment in routine practice,[145,146] this should emphasise the need for trials of methods to effectively identify women and interventions to prevent and treat perinatal mental illness among high-risk women in the primary care setting.

5 Live and non-live pregnancy outcomes in women with antenatal mental illness with and without psychotropic medication

Since there is a considerable clinical burden of maternal perinatal mental illness presenting to and/or treated in UK general practice, this section describes a prospective cross-sectional study conducted to examine the risks of non-live pregnancy outcomes in pregnant women with history of mental illness with or without psychotropic drug prescriptions compared with those women without mental illness.

5.1 Introduction

5.1.1 Non-live pregnancy outcomes in women with antenatal mental illness

Perinatal death

Previous research has suggested that women with mental illness (including affective disorder, such as depression, and schizophrenia and other related psychotic disorders) have increased risks of stillbirth[41,43,44,148,149] and neonatal death.[43,44,150] For instance, Webb *et al.* conducted a prospective population-based study in Denmark including all singleton live births and stillbirths (nearly 1.5 million in total) identified using Danish population and birth registers during 1973-1998 and found that after adjustment for offspring age and calendar year, women with a history of hospitalisation for affective disorder before childbirth (not limited to antenatal mental illness only) had a 66% increased risk of stillbirth (OR=1.66, 95% CI 1.29-2.19) and a 2.5-fold increased risk of neonatal death (OR=2.5, 95% CI 1.93-3.13) compared with women with no such history.[43] Some other studies however did not find increased risks of stillbirth or neonatal death in women with mental health problems.[32,34,151]

Miscarriage

In contrast, few large population-based studies have been conducted to examine the risks of miscarriage in women with mental illness with or without psychotropic medication. Sugiura-Ogasawara and colleagues carried out a study in Japan from April 1995 to August 1997 and recruited 45 women with a history of two consecutive first-trimester miscarriages, but with no live birth, before the third pregnancy from Nagoya City University Hospital.[152] After controlling for maternal age and occupation, they found that pre-existing depression, but not anxiety, was associated with an increased risk of miscarriage in the following pregnancy (p-value=0.04; no measures of effects were presented). A later study from the same cohort also found that scores for psychological symptoms of both depression and anxiety (measured by using self-reported questionnaires administrated both before and within two weeks of pregnancy) were higher, especially before pregnancy, in women with subsequent miscarriage than in women with normal delivery.[153] However, these two studies focused on a subset population of women with a history of miscarriage only and no information is available for the general population.

A prospective study in the USA examining 1,186 women in early pregnancy from 1999 to 2001 found no association of depressive symptoms with the risk of miscarriage (OR=0.75, 95% CI 0.47-1.19) after adjusting for maternal and gestational age, social support, prior spontaneous abortion, education level and cigarette and cocaine use.[154] The women were, however, recruited at an emergency department with nine weeks of mean gestational age and depressive symptoms were measured using self-reported questionnaires at recruitment only.

Potential explanations

There are several potential explanations to suggest that there might be increased risks of miscarriage and perinatal death in women with mental illness. Previous

research has suggested that poor lifestyle choices (such as smoking) and antenatal care could potentially contribute to such raised risks seen across various maternal mental illnesses.[44] There are also associations between mental illness and maternal smoking[35] and abnormal endocrine and immune regulation,[36] which may directly impair the development of the foetus lead to foetal growth retardation and low birth weight.[37] In addition, women with mental illness are more likely to be from relatively socioeconomically deprived groups and receive inadequate antenatal care.[155,156]

Pregnant women with mental illness are also more likely to be exposed to psychotropic medications. Although there have been considerable studies examining the risks of non-live pregnancy outcomes in women exposed to psychotropic drugs, most did not directly compare women with depression or anxiety taking medication with those not. A recent study of only 90 women in the USA showed that among women with major depressive disorders, women taking antidepressants during pregnancy had shorter gestational age at birth and increased risks of preterm delivery than those not exposed to antidepressants.[157]

5.1.2 Impact of psychotropic medication during pregnancy

Many previous studies have been conducted to examine the potential adverse effects of exposure to psychotropic medication, particularly antidepressants, in women during early pregnancy on the pregnancy outcomes. Previous research suggests that women exposed to antidepressants during early pregnancy have increased risks of perinatal death[45,46] and miscarriage.[45,47,48,158] It has also been suggested that women taking antidepressants antenatally are more likely to choose to terminate their pregnancy.[45,49,159] Table 5-1 (for cohort studies) and Table 5-2 (for case-control studies) summarise all such studies published in English language journals since 1960 until June 2012 through searching PubMed and references of individual papers relevant to the study question.

Table 5-1 Cohort studies for the impact of depression and/or anxiety on non-live pregnancy outcomes

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (and/or %) of mothers exposed	Outcome(s)	Any co-variables considered	Findings (measure of effects with 95% confidence interval, if not otherwise specified)
Depression and/or anxiety										
Hanlon et al., 2009[32]	Ethiopia	Jul 2005 to Feb 2006	Health programme	1,046	Common mental disorders during the third trimester of pregnancy	Y	128+634	Stillbirth and neonatal death (28 days of birth)	Y	No association
Wisborg et al., 2008[148]	Denmark	Sep 1989 to Aug 98	Maternity unit in hospital	19,282	Psychological stress (measure by GHQ) during pregnancy	Y	Not reported	Stillbirth	Y	High psychological stress: OR=1.9 (1.1-3.2)
Antidepressants										
Einarson et al., 2009[159]	Canada	Not reported	Teratology information service	1,874	Antidepressants prior to and during the first trimester of pregnancy	Y	937	Miscarriage and termination	Y (matched by age, smoking and alcohol consumption)	Miscarriage: relative risk ratio=1.63 (1.24-2.14); Termination: relative risk ratio=3.25 (1.48-7.14)
Diav-Citrin et al., 2008[45]	Israel, Italy and Germany	1994-2002 and 2002-05	Teratology information service	2,191	Paroxetine and fluoxetine during the first trimester of pregnancy	Y	410 (paroxetine) and 314 (fluoxetine)	Non-live born pregnancies	Y	Fluoxetine: increased risk of miscarriage and termination; Paroxetine: increased risk of stillbirth
Lennestål and Källén, 2007[160]	Sweden	Up to 2004	Medical birth registry data	860,215	SSRIs and SNRI/NRI in early pregnancy	Y	6,481+732	Stillbirth and infant death	Y	No association

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (and/or %) of mothers exposed	Outcome(s)	Any co-variables considered	Findings (measure of effects with 95% confidence interval, if not otherwise specified)
Djulus et al., 2006[161]	Worldwide (incl. UK)	Jun 2002 to Aug 2005	Teratogen information services/drug safety research unit	312	Mirtazapine during pregnancy	Y	104	Non-live birth outcomes	N	Higher prevalence of miscarriage but not statistically significant
Wen et al., 2006[46]	Canada	1990-2000	Database	4,850 (matched)	SSRIs in the year before delivery	Y	972	Stillbirth and infant death (less than 1 year of age)	Y (matched)	Stillbirth: OR=2.23 (1.01-4.93); Infant death: OR=1.96 (0.97-3.94)
Chun-Fai-Chan et al., 2005[158]	Canada and UK	Not reported	Teratogenic information service and drug safety research unit	269 (matched)	Bupropion during the first trimester of pregnancy	Y	136	Non-live birth outcomes	Y	Miscarriage: p=0.009
Sivojelezova et al., 2005[162]	Canada	Not reported	Teratogen information centre	396 (matched)	Citalopram during early pregnancy	Y	132	Non-live birth outcomes	Y	No association
Einarson et al., 2003[163]	Canada	Not reported	Teratogenic information service	441 (matched)	Trazodone or nefazodone during the first trimester of pregnancy	Y	147	Non-live birth outcomes	Y	No association
Einarson et al., 2001[164]	Canada	Not reported	Teratogenic information service	450 (matched)	Venlafaxine during 4th to 14th week gestation	Y	150	Miscarriage and termination	Y	No association
Ericson et al., 1999[165]	Sweden	1995-97	Birth registry data	281,728	Antidepressants during pregnancy	Y	969 (0.3)	Infant death	N	No association

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (and/or %) of mothers exposed	Outcome(s)	Any co-variables considered	Findings (measure of effects with 95% confidence interval, if not otherwise specified)
Kulin et al., 1998[166]	North America	Not reported	Teratogenic information service	534 (matched)	SSRIs during the first trimester of pregnancy	Y	267	Non-live birth outcomes	Y	No association
Johnson, 1997[167]	USA	Not reported	Teratogen information service	482 (matched)	Fluoxetine during pregnancy	Y	228	Miscarriage	N	No association
Chamber et al., 1996[49]	USA	1989-95	Teratogenic information service	482 (matched)	Fluoxetine during pregnancy	Y	228	Non-live birth outcomes	N	Higher rate of termination: 9.6 vs. 2.7% (p=0.002)
McElhatton et al., 1996[168]	Europe	Not reported	Teratology information services	689 exposed only	Tricyclic and nontricyclic antidepressants	Y	689	Non-live birth outcomes	N	Higher rate of termination in multidrug groups than in mono-therapy groups
Pastuszak et al., 1993[48]	Canada	Not reported	Teratogenic information service	256 (matched)	Fluoxetine during the first trimester of pregnancy	Y	128	Miscarriage and termination	Y (matched)	Increased risk of miscarriage: p=0.03
Anxiolytics										
Ornoy et al., 1998[66]	Israel	1988 to Jul 1996	Teratogenic information service	884 (matched)	Benzodiazepines during pregnancy	Y	460	Miscarriage and termination	N	Miscarriage: 8.7 vs. 5.2% (P=0.01); Termination: 14.1 vs. 4.7% (P<0.01)
Hartz et al., 1975[169]	USA	1958-1966	Hospital records	50,282	Meprobamate and chlordiazeproxide in the first 16 weeks of pregnancy	Y	356 meprobamate and 257 chlordiazeproxide	Stillbirth/death to the fourth birth day	Y	No association

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (and/or %) of mothers exposed	Outcome(s)	Any co-variables considered	Findings (measure of effects with 95% confidence interval, if not otherwise specified)
Milkovich and van den Berg, 1974[170]	USA	1959-1966	Health registry data	19,044	Meprobamate and chlordiazeproxide in the first six weeks of pregnancy	Y	395 meprobamate and 172 chlordiazeproxide	Perinatal death	N	Higher rate of perinatal death but not statistically significant

SNRI/NRI included mianserin, mirtazapine, venlafaxine and reboxetine
GHQ=general health questionnaires
USA=United States of America; UK=United Kingdom

Table 5-2 Case-control studies for the impact of depression and/or anxiety on non-live pregnancy outcomes

Author(s), year	Country	Study period	Source of study population	Number of cases/controls	Outcome(s)	Number (and/or %) of offspring exposed in cases	Exposed	Other co-variables considered and/or adjusted	Major findings
Depression and/or anxiety									
Gold et al., 2007[171]	USA	Early 1990s	National comorbidity survey data	606/1,354*	Miscarriage and stillbirth	(41)	Any mental health disorder diagnosed before 1st birth	Y	OR=1.80 (1.35-2.41) mainly in affective disorder and substance use disorder, but not in anxiety disorder
Nelson et al., 2003[154]	USA	Jan 1999 to Aug 2001	Emergency department in hospital	174/798	Miscarriage	(47)	Depressive symptoms measured by self-report questionnaires (CES-D)	Y	No difference
Antidepressants									
Nakhai-Pour et al., 2010[47]	Canada	1998-2003	Pregnancy registry data	5,124/51,240*	Miscarriage	284 (5.5)	Antidepressants during pregnancy	Y	OR=1.68 (1.38-2.06); SSRIs alone (esp. paroxetine) and venlafaxine
Anxiolytics									
Laegreid, 1992[172]	Sweden	1985-86	Maternal health clinics in hospital	73/73	Stillbirth and early neonatal death	18	Benzodiazepines during pregnancy	N	OR=4.0 (2.0-7.9)

* Retrospective cohort study/nested case control study
CES-D=Centre for Epidemiologic Studies Depression Scale; USA=United States of America

Few studies have examined the effects of exposure to multiple psychotropic drug classes. Previous research found a higher proportion of elective termination in mothers with multiple drugs than in those with single drug only (17.6% vs. 10.0%),[168] and a 3-fold increased risk of miscarriage in women with multiple classes of antidepressants than those with one class of antidepressants alone (e.g. OR=3.51, 95% CI 2.20-5.61 for at least 2 different classes of antidepressants).[47] Such studies however have not been widely repeated and the results are inconsistent. For example, another study including women identified through teratology information service found no increased risks of miscarriage in women exposed to both SSRIs and benzodiazepines compared with those exposed to SSRIs alone.[45]

Miscarriage and perinatal death

A Swedish population-based study examining all singleton and twin births from 1995 to 1997 using national birth registry data found a slightly higher proportion of infant deaths (within the first year after delivery) in mothers exposed to antidepressants during early pregnancy than mothers unexposed (0.7% vs. 0.6% for any antidepressants and 0.8% vs. 0.5% for SSRIs only).[165] This Swedish study however only identified seven infant deaths in women taking antidepressants and no formal statistical analyses were carried out due to the very small numbers of the adverse outcome.

A more recent Swedish study in the same population examined the association between exposure to newer antidepressants (i.e. venlafaxine, mirtazapine, miaserin and reboxetine) during early pregnancy and the risk of stillbirth.[160] After adjusting for maternal age, year of birth, parity, maternal smoking and maternal BMI, this study found a 70% increased risk, though not statistically significant (OR=1.70, 95% CI 0.6-3.6), of stillbirth in women exposed to newer antidepressants during the first trimester of pregnancy compared with women without exposure to such drugs. By linking with

another similar study from the same cohort, the Swedish study found no increased risk of stillbirth in mothers exposed to SSRIs (adjusted risk ratio=0.8, 95% CI 0.5-1.2). However, fewer than 1% of women had received SSRIs, much less than other European or North American populations,[173] which limited statistical power and suggested different clinical practice of treating maternal mental illness in Sweden.

Very few studies have tried to examine the effects of psychotropic medication with consideration of past and/or current mental illness. A case-control study using pregnancy registry data in Canada identified nearly 70,000 pregnant women and found a 68% (OR=1.68, 95% CI 1.38-2.06) increased risk of miscarriage in women with exposure to antidepressants even after adjusting for depression, anxiety, history of medication use during one year before pregnancy and the severity of the illness (defined as the number of days antidepressants were prescribed and the number of visits to a psychiatrist in the year before pregnancy).[47] Specifically, this Canadian study observed a higher risk of miscarriage in women exposed to SSRIs, but not to TCAs (ORs=1.61 and 1.27, 95% CIs 1.28-2.04 and 0.85-1.91, respectively).

Four very similar prospective cohort studies including mothers consulting the same teratology information service (before their pregnancy outcome occurred) in Canada found on average 1.5-2 fold increased risks of miscarriage in women taking TCAs, SSRIs and newer antidepressants (e.g. venlafaxine) during the first trimester of pregnancy compared with women exposed to non-teratogenic drugs (such as acetaminophen).[48,163,164,166] Nevertheless, all had relatively small sample sizes and there was considerable uncertainty in the estimates. In contrast, a European observational study conducted by McElhatton and colleagues in 1996 examined 689 pregnancies with exposure to antidepressants throughout pregnancy and found a similar risk of miscarriage between women exposed to tricyclic and non-tricyclic antidepressants in pregnancy (11.5% vs. 11.3%).[168]

By pooling the results from the six cohort studies,[48,49,163,164,166,168] Hemels and colleagues found a 45% (relative risk ratio [RRR]=1.45, 95% CI 1.19-1.77) increased risk of miscarriage in women with antidepressants during early pregnancy compared with women unexposed.[174] They also examined individual drug classes and found an increased risk of miscarriage in all antidepressant classes (RRR=1.23, 1.52, and 1.65, 95% CIs 0.84-1.78, 1.17-1.98, and 1.02-2.69 for TCAs, SSRIs, and new antidepressants, respectively).

The results are less consistent for specific drugs. A Canadian study including 5,124 women entered in the Quebec Pregnancy Registry database between 1998 and 2003 found increased risks of miscarriage in women with paroxetine and venlafaxine (ORs=1.75 and 2.11, 95% CIs 1.28-2.04 and 1.34-3.30, respectively) compared with women taking other SSRI drugs.[47] In contrast, a multi-centre prospective study conducted by Diav-Citrin *et al.* in high-income countries between 1994 and 2005 found significantly higher proportions of miscarriage in women with fluoxetine (11.8% vs. 6.6% for miscarriage compared with the control group, $p<0.05$), but not in paroxetine, by comparing women with exposures to paroxetine and fluoxetine during pregnancy with women exposed to substances known not to be teratogenic, such as antibiotics, oral contraceptives and paracetamol.[45] After adjusting for maternal age, smoking and previous miscarriage history, and prescriptions of other concomitant psychotropic medication, the association between exposures to fluoxetine and the risk of miscarriage reduced (adjusted OR=1.27, 95% CI 0.76-2.13 for miscarriage).[45]

Termination

Very few studies have been published to examine the risk of termination in women exposed to psychotropic drugs during pregnancy. Unlike miscarriage and perinatal death which mostly occurred due to some potential biological mechanism, most therapeutic terminations in the UK are voluntary and not for reasons of medical

problems for the mother or the child. Terminations are occasionally done because of a known chromosomal or congenital anomaly, yet this is uncommon.[175] Discovery of pregnancy when taking psychotropic drugs could also contribute to such decisions, since women may worry about the potential adverse impact on the health of their offspring.[159] Women with psychotropic medication may also have more severe symptoms of depression and may feel unable to continue the pregnancy. Findings from previous studies have suggested that the increased risk of termination in women with psychotropic medication during pregnancy is more evident than the risk of miscarriage or perinatal death.[49,159]

For example, Chambers *et al.* conducted a cohort study in 408 American women who contacted a teratology information service before pregnancy outcome occurred from 1989 to 1995 and found a significantly higher proportion of termination (p=0.002), but not miscarriage or stillbirth, in pregnant women taking fluoxetine during the first trimester.[49] Einarson *et al.* carried out a study in Canada including 937 women taking antidepressants during early pregnancy found three-fold increased risk of termination in exposed women compared with those unexposed (OR=3.25, 95% CI 1.48-7.14).[159] This study also found an increased, but much less evident, risk of miscarriage (OR=1.63, 95% CI 1.24-2.14).

5.2 Rationale and objectives

Although the impact of maternal exposure to psychotropic medication, especially antidepressants, during early pregnancy on the risks of non-live pregnancy outcomes have been investigated in previous literature, no large population-based studies have attempted to differentiate between the effects of psycho-pharmaceutical treatment of mental illness and those of maternal mental illness itself, and the contribution of the underlying illnesses to these risks remains unclear. In addition, few studies have been conducted to investigate the safety of anti-anxiety drugs (mainly benzodiazepines) in pregnant women and to comprehensively examine individual classes of psychotropic drugs exclusively. No studies have been done to assess the impact of discontinuing psychotropic medication after women with mental illnesses become pregnant, on their pregnancy outcomes.

The objectives of this study were to examine the impacts of maternal antenatal mental illness with and without drug treatments on the risks of non-live pregnancy outcomes, and to investigate the risks of each drug class separately. I also assessed whether there was any risk modification after discontinuation of specific drug classes when pregnant.

5.3 Methods

5.3.1 Study population

From Populations 3 and 4 in Figure 2-1, I identified all clinically recognised singleton pregnancies among women aged 15-45 years between 1990 and 2009 that ended in live birth, stillbirth, termination or miscarriage. For pregnancies ending in a live birth, I searched the records of both mothers and their children, if linked, for recordings of infant death within 28 days postpartum, and combined these with stillbirths as a measure of perinatal death. Since the legislation on termination of pregnancy in Northern Ireland is more restrictive than that in other parts of the UK, I excluded women registered at general practices in this area. Since there were very few women with serious mental illness, I excluded all women with evidence of serious mental illnesses (bipolar disorder, schizophrenia and other related psychotic disorders), comprising less than 0.5% of the original study population.

5.3.2 Definition of exposures

As described in Section 4.3.2, depression and anxiety, and exposure to medication were defined according to the presence or absence of a relevant medical record in the women's primary care electronic health records within the first 90 days following the estimated date of conception (the first trimester of pregnancy). Dates of conception were estimated based on a range of recordings relating to pregnancy (including expected delivery dates, maturity estimates and timing of routine monitoring events), and where no information was available, live births were assumed to take place at 40 weeks and miscarriage and termination at 10 weeks. I extracted records of prescriptions of all antidepressants, hypnotics, and anxiolytics that were primarily indicated for the treatment of depression or anxiety according to British national guidelines.[98] To minimise the risk of detecting reverse-causal effects (where a non-live outcome may be the trigger for depression or anxiety and its treatment), I

excluded prescriptions and diagnoses within the last seven days of pregnancies which ended within the first trimester.

I grouped mothers into eight mutually exclusive categories according to their diagnostic and treatment status:

Group 0: No history of anxiety or depression (non-exposed group).

Group 1: History of anxiety or depression before pregnancy but no diagnostic recordings during the first trimester.

Group 2: Diagnostic records of anxiety or depression but no prescriptions of interest during the first trimester.

Group 3: Prescriptions for any tricyclic antidepressants (TCAs) (alone - i.e. no other psychotropic medication of interest) during the first trimester

Group 4: Prescriptions for any SSRIs (alone) during the first trimester.

Group 5: Prescriptions for any benzodiazepines (alone) during the first trimester.

Group 6: Prescriptions for any other single class of drug from the following groups during the first trimester

1. Other sedative medications: buspirone, meprobamate, zaleplon, zolpidem tartrate, zopliclone, chloral hydrate, triclofos sodium;
2. Monoamine oxidase inhibitors: phenelzine, isocarboxazid, tranylcypromine and moclobemide;
3. Other antidepressants: duloxetine, mirtazapine, reboxetine, tryptophan and venlafaxine;

Group 7: Prescriptions for two or more classes of psychotropic drug (mentioned above) during the first trimester.

5.3.3 Co-variables (maternal socio-demographic and lifestyle factors)

I identified potential confounders by extracting information on the following characteristics of women: maternal age at the end of pregnancy, the most recent recording of smoking status before delivery, body mass index (BMI, kg/m^2) before pregnancy and quintiles of Townsend's Index of Deprivation[176] for each woman's postcode of residence. Since women aged 15-17 may have different risks of non-live pregnancy outcomes from older women,[177] we categorised maternal age as follows: 15-17 years, 18-24 years, 25-34 years, and 35-45 years. In addition, since women's prior pregnancy history could affect the risk of subsequent pregnancy loss, or of developing mental illness during later pregnancies,[178,179] for each pregnancy, I also extracted information on the number of previous known live births (a proxy of parity) and the number of prior pregnancy losses, which included clinically recognised pregnancy losses occurring during women's general practice registration and clinical records of pregnancy history where available (e.g. Read medical code: 1542200 H/O: 1 miscarriage).

5.3.4 Statistical analyses

Multinomial logistic regression models (for study outcomes with more than two values) were used to obtain relative risk ratios (RRRs) for perinatal death, miscarriage and termination relative to live births in each of the seven exposure groups compared with women without any indication of current or prior depression or anxiety. I included more than one pregnancy for some women and a cluster correction on the women's unique identification codes was applied.

To identify potential confounders, chi-squared tests were used to determine whether maternal age, Townsend deprivation index (in quintiles), maternal smoking history or BMI were associated with each exposure, or with any adverse pregnancy outcome among women in the referent group. Co-variables with statistically significant associations at the 5% level with both were included in multivariable models to obtain

adjusted RRRs. Missing values for co-variables were fitted as a separate category in the analyses to provide an implicit adjustment for any dissimilarity between women associated with differential recording.

In addition, sensitivity analyses were conducted to assess the effects of prior pregnancy history. By using chi-squared tests, the association of prior pregnancy history with exposures or with current adverse pregnancy outcomes was examined and the variable of previous live births or prior pregnancy losses was added into the main multivariable model separately. The data were open cohort data that included all prospectively recorded pregnancy outcomes from the point at which women registered with their general practitioners, which could be at any age during the potentially fertile period. Although all women in the UK must be registered with a general practitioner to receive obstetric care, people do change general practitioners, often because they move home. I therefore did not have certainty of complete pregnancy history for all women, particularly for older women. I also adjusted for previous pregnancy history in a further multivariable model restricted to women who were registered by the age of 20 in an attempt to minimise misclassification due to unrecorded prior pregnancies. In addition, to reduce any potential effects of pregnancy history, I excluded women with evidence of prior pregnancy losses from the main multivariable model, both for the whole population and in women registered by age 20 to assess the effects on the main RRR estimates.

To determine whether the use of psychotropic medication was associated with an excess risk of each adverse pregnancy outcome compared with un-medicated depression or anxiety, I repeated the main analyses excluding women without current depression or anxiety (i.e. excluding the original referent group and group 1), so that RRRs were in reference to group 2 (a recording of depression or anxiety, but no prescription during the first trimester).

Another sensitivity analysis was carried out to investigate whether the risks of adverse pregnancy outcomes in women who continued to receive psychotropic medications after conception were greater among those who discontinued their use. All women exclusively prescribed any TCAs, SSRIs or benzodiazepines (the three most common medication classes) within 90 days before pregnancy were identified. For each drug class, a multinomial logistic regression model was used to compare the outcomes among women who received a repeat prescription for a drug in the same class during the first trimester of pregnancy with those who did not. In recognition of the large number of categorisations in each analysis, 99% confidence intervals (CIs) were calculated for each measure of association, and exact (3dp) p-values were given.

5.4 Results

I identified 512,574 pregnancies among a cohort of 331,414 mothers. More than half of women were aged 25-34 years and 0.4% of their pregnancies ended in perinatal death (stillbirth or neonatal death), 12.6% in miscarriage and 14.7% in termination (Table 5-3). Compared with pregnancies ending in live births, pregnancies ending in terminations were more likely to be in younger women with a history of smoking and from socio-economically deprived groups whilst miscarriage was more common in older women. Pregnancies ending in perinatal death were also more likely to occur in women from deprived groups and in those who were overweight or obese compared with live-birth pregnancies.

Pregnancies ending in adverse outcomes were more common in all exposure groups compared with the referent group of women with no current or past depression or anxiety (Table 5-4). The prevalence of miscarriage and perinatal death was highest among women prescribed psychotropic drugs, especially those receiving benzodiazepines, the less common medications (Group 6) and those receiving multiple classes of medication. In women prescribed benzodiazepines only, 0.7% of pregnancies ended in perinatal death and 16.2% in miscarriage. The equivalent proportions for women with un-medicated depression or anxiety were 0.6% and 12.1%, and for those in the referent group were 0.4% and 12.1% respectively (Table 5-4). In addition, greater proportions of women terminated their pregnancies if they were exposed to psychotropic medication during early pregnancy.

Table 5-5 presents the relative risk ratios for each adverse outcome for each exposure category compared with the referent group. Compared with women from the referent group, women with a history of depression or anxiety and exposure to psychotropic medication during the first trimester of pregnancy had consistently increased risks of all non-live pregnancy outcomes. Effect estimates for exposures to

different drugs (especially to SSRIs, benzodiazepines and the less common drug classes, and to multiple classes) were greater than those for un-medicated current illness or for a historical depression or anxiety diagnosis. The greatest effects were found in women prescribed the less common medications (Group 6: unadjusted RRRs=4.2, 2.1 and 2.4, 99% CIs 2.1-8.5, 1.7-2.6 and 2.0-2.9 for the risks of perinatal death, miscarriage and termination, respectively) (Table 5-5).

Table 5-6 shows the results after adjusting for maternal age at the end of pregnancy, household socioeconomic status, smoking status before delivery and BMI before pregnancy. Compared with the unadjusted results, the adjusted RRRs reduced slightly for perinatal death and miscarriage, especially for drug associated risks. The pattern of risks remained the same. The RRRs for termination were almost unchanged.

Table 5-3 Maternal characteristic for all pregnancy outcomes

Basic characteristics	All		Live birth		Perinatal death[a]		Miscarriage		Termination	
	N=512,574		n=370,443		n=2,096		n=64,511		n=75,524	
	n	%	n	%	n	%	n	%	n	%
Maternal age at the end of pregnancy, years										
15-17	10,252	2.0	3,708	1.0	22	1.1	1,166	1.8	5,356	7.1
18-24	109,793	21.4	69,495	18.8	390	18.6	11,568	17.9	28,340	37.5
25-34	282,006	55.0	220,642	59.6	1,140	54.4	31,832	49.3	28,392	37.6
35-45	110,523	21.6	76,598	20.7	544	26.0	19,945	30.9	13,436	17.8
Townsend deprivation index										
1 (least deprived)	117,018	22.8	88,535	23.9	387	18.5	14,920	23.1	13,176	17.5
2	96,618	18.9	71,566	19.3	342	16.3	12,346	19.1	12,364	16.4
3	100,527	19.6	72,180	19.5	399	19.0	12,743	19.8	15,205	20.1
4	97,608	19.0	68,643	18.5	429	20.5	11,961	18.5	16,575	22.0
5 (most deprived)	74,482	14.5	51,287	13.8	425	20.3	9,030	14.0	13,740	18.2
Missing	26,321	5.1	18,232	4.9	114	5.4	3,511	5.4	4,464	5.9
Ever smoked before delivery	208,302	40.6	145,953	39.4	915	43.7	26,616	41.3	34,818	46.1
Maternal BMI before pregnancy (kg/m^2)										
Under-weight (<18.5)	17,485	3.4	12,223	3.3	66	3.2	2,195	3.4	3,001	4.0
Normal (18.5-24.9)	227,820	44.5	166,999	45.1	787	37.5	28,696	44.5	31,338	41.5
Over-weight(25-29.9)	87,909	17.2	65,033	17.6	435	20.8	11,797	18.3	10,644	14.1
Obese (30-39.9)	49,594	9.7	36,561	9.9	284	13.6	7,144	11.1	5,605	7.4
Missing	129,766	25.3	89,627	24.2	524	25.0	14,679	22.8	24,936	33.0

[a] Stillbirth or neonatal death within the first 28 days postpartum
BMI=body mass index

Table 5-4 Breakdown of live and non-live pregnancy outcomes by different antenatal diagnostic and drug exposures

Mental illness/drug exposures[a]			Live birth		Perinatal death		Miscarriage		Termination	
			N=370,443		N=2,096		N=64,510		N=75,524	
Referent category[b]	n	(%)	287,814	(73.7)	1,474	(0.4)	47,258	(12.1)	54,119	(13.9)
History of mental illness only	n	(%)	69,297	(69.0)	480	(0.5)	13,814	(14.0)	16,341	(16.5)
Un-medicated mental illness	n	(%)	2,640	(72.4)	20	(0.6)	442	(12.1)	545	(14.9)
TCAs	n	(%)	1,983	(65.7)	18	(0.6)	443	(14.7)	575	(19.1)
SSRIs	n	(%)	6,205	(60.2)	57	(0.6)	1,539	(14.9)	2,511	(24.4)
Benzodiazepines	n	(%)	1,416	(59.4)	16	(0.7)	386	(16.2)	566	(23.7)
Any other single class	n	(%)	645	(54.8)	14	(1.2)	223	(18.9)	296	(25.1)
Multiple classes	n	(%)	1,443	(59.2)	17	(0.7)	406	(16.7)	571	(23.4)

[a] Exposures were depression or anxiety with or without exposures to different classes of antidepressants or anti-anxiety drugs. All categories were mutually exclusive.
[b] Reference was no history of or current depression or anxiety
TCAs=tricyclic antidepressants
SSRIs=selective serotonin reuptake inhibitors

Table 5-5 Unadjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in each antenatal diagnostic and drug exposure category compared with no current/past depression or anxiety (512,574 pregnancies in 331,414 women)

Mental illness/drug exposures[a]	Perinatal death		Miscarriage		Termination	
	n=2,096		n=64,510		n=75,524	
	RRR (99% CI)	p	RRR (99% CI)	p	RRR (99% CI)	p
Referent category[b]	1.0		1.0		1.0	
History of mental illness only	1.4 (1.2-1.6)	<0.001	1.2 (1.2-1.3)	<0.001	1.3 (1.2-1.3)	<0.001
Un-medicated mental illness	1.5 (0.8-2.6)	0.084	1.0 (0.9-1.2)	0.706	1.1 (1.0-1.2)	0.049
TCAs	1.8 (1.0-3.3)	0.016	1.4 (1.2-1.6)	<0.001	1.5 (1.4-1.7)	<0.001
SSRIs	1.8 (1.2-2.6)	<0.001	1.5 (1.4-1.6)	<0.001	2.2 (2.0-2.3)	<0.001
Benzodiazepines	2.2 (1.1-4.2)	0.002	1.7 (1.4-1.9)	<0.001	2.1 (1.9-2.4)	<0.001
Any other single class	4.2 (2.1-8.5)	<0.001	2.1 (1.7-2.6)	<0.001	2.4 (2.0-2.9)	<0.001
Multiple classes	2.3 (1.2-4.3)	0.001	1.7 (1.5-2.0)	<0.001	2.1 (1.9-2.4)	<0.001

[a] Exposures were depression or anxiety with or without exposures to different classes of antidepressants or anti-anxiety drugs. All categories were mutually exclusive.
[b] Reference was no history of or current depression or anxiety
TCAs=tricyclic antidepressants
SSRIs=selective serotonin reuptake inhibitors
RRR=relative risk ratio
CI=confidence interval

Table 5-6 Adjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in each antenatal diagnostic and drug exposure category compared with no current/past depression or anxiety (512,574 pregnancies in 331,414 women)

Mental illness/drug exposures[a]	Perinatal death		Miscarriage		Termination	
	n=2,096		n=64,510		n=75,524	
	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p
Referent category[b]	1.0		1.0		1.0	
History of mental illness only	1.3 (1.1-1.5)	<0.001	1.2 (1.2-1.2)	<0.001	1.3 (1.3-1.4)	<0.001
Un-medicated mental illness	1.4 (0.8-2.5)	0.147	1.0 (0.9-1.2)	0.837	1.0 (0.9-1.2)	0.457
TCAs	1.6 (0.9-2.9)	0.056	1.3 (1.1-1.5)	<0.001	1.7 (1.5-1.9)	<0.001
SSRIs	1.6 (1.1-2.4)	0.001	1.5 (1.3-1.6)	<0.001	2.2 (2.1-2.4)	<0.001
Benzodiazepines	2.0 (1.0-3.8)	0.007	1.6 (1.4-1.9)	<0.001	2.2 (1.9-2.6)	<0.001
Any other single class	3.7 (1.9-7.5)	<0.001	2.0 (1.7-2.5)	<0.001	2.6 (2.1-3.1)	<0.001
Multiple classes	2.0 (1.0-3.7)	0.006	1.6 (1.4-1.9)	<0.001	2.2 (1.9-2.6)	<0.001

[a] Exposures were depression or anxiety with or without exposures to different classes of antidepressants or anti-anxiety drugs. All categories were mutually exclusive.
[b] Reference was no history of or current depression or anxiety
[c] Relative risk ratio after adjusted for maternal age at the end of pregnancy, household socioeconomic status, maternal smoking status before delivery and body mass index before pregnancy
TCAs=tricyclic antidepressants
SSRIs=selective serotonin reuptake inhibitors
CI=confidence interval

Results from sensitivity analyses of adjustment for pregnancy history

Table 5-7 shows relative risk ratios for all adverse pregnancy outcomes in the whole population of women (512,574 pregnancies in 331,414 women) after adding the variable of previous known live births (a proxy of parity) into the main multivariable model. The results were almost identical to the main estimates in Table 5-6. Table 5-8 shows the results from the same analysis but in the 146,887 pregnancies that occurred in women registered by age 20 (85,260 women, 26% of the total population). Although power was reduced, relative risk ratios were similar to the main results with almost all risk estimates remaining within the 99% confidence intervals of the estimates in Table 5-6. Risk estimates for termination did reduce modestly, yet all adverse outcomes still showed increased treatment-associated risks.

I found that current miscarriage or perinatal death was associated with a higher number of prior pregnancy losses ($p<0.001$) whereas termination was associated with fewer prior losses ($p<0.001$). The number of previous pregnancy losses was also associated with a higher likelihood of a recorded history of depression or anxiety before the current pregnancy ($p<0.001$). Associations of prior pregnancy losses with current un-medicated as well as treated depression or anxiety in early pregnancy were less marked and women with treated mental illness who had previous losses represented only a small proportion of the overall population (Table 5-9).

Table 5-10 shows the main analyses additionally adjusted for the number of prior pregnancy losses in the 146,887 pregnancies that occurred in women registered by age 20 (85,260 women, 26% of the total population). The result patterns were very similar to those from the analyses with adjustment for the number of previous known live births in women registered by age 20, such that relative risk ratios were similar to the main analyses with almost all risk estimates remaining within the 99% confidence intervals of the main risk estimates in Table 5-6. The risk estimates for termination

did reduce modestly, yet all adverse outcomes still showed increased treatment-associated risks. Table 5-11 and Table 5-12 show the results after excluding women with evidence of prior pregnancy losses from the total population (90% of the total population) and from women registered by age 20 (26% of the total population), respectively. Results again remained very similar to the main analyses in Table 5-6.

Table 5-7 Sensitivity analyses: Adjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in each antenatal diagnostic and drug exposure category compared with no current/past depression or anxiety

Mental illness/drug exposures[a]	Perinatal death		Miscarriage		Termination	
	n=2,096		n=64,510		n=75,524	
	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p
Referent category[b]	1.0		1.0		1.0	
History of mental illness only	1.1 (1.0-1.3)	0.025	1.2 (1.2-1.2)	<0.001	1.3 (1.3-1.4)	<0.001
Un-medicated mental illness	1.2 (0.7-2.3)	0.361	1.0 (0.9-1.2)	0.854	1.0 (0.9-1.2)	0.434
TCAs	1.6 (0.9-3.1)	0.051	1.3 (1.1-1.5)	<0.001	1.7 (1.5-1.9)	<0.001
SSRIs	1.4 (1.0-2.1)	0.015	1.5 (1.3-1.6)	<0.001	2.2 (2.1-2.4)	<0.001
Benzodiazepines	1.9 (1.0-3.8)	0.011	1.6 (1.4-1.9)	<0.001	2.2 (1.9-2.6)	<0.001
Any other single class	3.5 (1.6-7.3)	<0.001	2.0 (1.7-2.5)	<0.001	2.6 (2.1-3.1)	<0.001
Multiple classes	2.0 (1.1-3.8)	0.004	1.6 (1.4-1.9)	<0.001	2.2 (1.9-2.6)	<0.001

[a] Exposures were depression or anxiety with or without exposures to different classes of antidepressants or anti-anxiety drugs. All categories were mutually exclusive.
[b] Reference was no history of or current depression or anxiety
[c] Relative risk ratio adjusted for maternal age at the end of pregnancy, number of previous known live births, household socioeconomic status, maternal smoking status before delivery and body mass index before pregnancy
TCAs=tricyclic antidepressants
SSRIs=selective serotonin reuptake inhibitors
CI=confidence interval

Table 5-8 Sensitivity analyses: Adjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in each antenatal diagnostic and drug exposure category (women with computerised prospective data from age 20 only; 146,887 pregnancies in 85,260 women; 26% of total population)

Mental illness/drug exposures[a]	Perinatal death		Miscarriage		Termination	
	n=526		n=15,027		n=34,008	
	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p
Referent category[b]	1.0		1.0		1.0	
History of mental illness only	0.9 (0.7-1.2)	0.343	1.2 (1.1-1.3)	<0.001	1.1 (1.1-1.2)	<0.001
Un-medicated mental illness	1.0 (0.3-3.1)	0.994	1.0 (0.8-1.3)	0.996	0.8 (0.7-1.0)	0.014
TCAs	1.5 (0.4-5.4)	0.428	1.6 (1.2-2.1)	<0.001	1.2 (0.9-1.6)	0.073
SSRIs	1.1 (0.6-2.3)	0.626	1.5 (1.3-1.7)	<0.001	1.7 (1.5-1.9)	<0.001
Benzodiazepines	2.5 (0.7-8.7)	0.055	1.6 (1.2-2.2)	<0.001	1.7 (1.3-2.2)	<0.001
Any other single class	3.3 (0.8-13.0)	0.027	1.8 (1.2-2.7)	<0.001	1.4 (1.0-2.0)	0.024
Multiple classes	0.7 (0.1-5.1)	0.669	1.6 (1.2-2.2)	<0.001	1.6 (1.2-2.0)	<0.001

[a] Exposures were depression or anxiety with or without exposures to different classes of antidepressants or anti-anxiety drugs. All categories were mutually exclusive.
[b] Reference was no history of or current depression or anxiety
[c] Relative risk ratio adjusted for maternal age at the end of pregnancy, number of previous known live births, household socioeconomic status, maternal smoking status before delivery and body mass index before pregnancy
TCAs=tricyclic antidepressants
SSRIs=selective serotonin reuptake inhibitors
CI=confidence interval

Table 5-9 Sensitivity analyses: Diagnoses and medically treated mental illness in early pregnancy stratified by the number of previous pregnancy losses[a] (512,574 pregnancies in 331,414 women)

Mental illness/drug exposures[b]	Pregnancies by the number of previous pregnancy losses[a]									
	0		1		2		≥3		Total	
	N=460,122		N=45,030		N=6,061		N=1,361		N=512,574	
	n	%	n	%	n	%	n	%	n	%
No history of or current depression/anxiety	355,221	77.2	30,871	68.6	3,809	62.8	764	56.1	390,665	76.2
History of depression/anxiety only	84,785	18.4	11,729	26.0	1,916	31.6	502	36.9	98,932	19.3
Un-medicated antenatal depression/anxiety	3,099	0.7	469	1.0	65	1.1	14	1.0	3,647	0.7
Depression/anxiety treated with psychotropic drugs in early pregnancy	17,017	3.7	1,961	4.4	271	4.5	81	6.0	19,330	3.8

[a] Prior clinically recorded miscarriages or perinatal deaths
[b] Exposures were depression or anxiety with or without exposures to different classes of antidepressants or anti-anxiety drugs. All categories were mutually exclusive.

Table 5-10 Sensitivity analyses: Adjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in each antenatal diagnostic and drug exposure category (women registered by age 20 with computerised prospective data; 146,887 pregnancies in 85,260 women, 26% of total population)

Mental illness/drug exposures[a]	Perinatal death		Miscarriage		Termination	
	n=526		n=15,027		n=34,008	
	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p
Referent category[b]	1.0		1.0		1.0	
History of mental illness only	0.9 (0.7-1.3)	0.568	1.2 (1.1-1.2)	<0.001	1.1 (1.1-1.2)	<0.001
Un-medicated mental illness	1.1 (0.4-3.2)	0.819	1.0 (0.8-1.2)	0.764	0.8 (0.7-1.0)	0.032
TCAs	1.8 (0.5-5.7)	0.218	1.6 (1.2-2.0)	<0.001	1.2 (0.9-1.6)	0.055
SSRIs	1.3 (0.7-2.6)	0.284	1.5 (1.3-1.7)	<0.001	1.7 (1.5-1.9)	<0.001
Benzodiazepines	2.3 (0.7-7.6)	0.070	1.6 (1.1-2.1)	<0.001	1.7 (1.3-2.2)	<0.001
Any other single class	3.6 (1.1-12.5)	0.005	1.7 (1.2-2.6)	<0.001	1.4 (1.0-2.1)	0.016
Multiple classes	0.8 (0.1-5.2)	0.768	1.6 (1.2-2.1)	<0.001	1.6 (1.2-2.1)	<0.001

[a] Exposures were depression or anxiety with or without exposures to different classes of antidepressants or anti-anxiety drugs. All categories were mutually exclusive.
[b] Reference was no history of or current depression or anxiety
[c] Relative risk ratio adjusted for maternal age at the end of pregnancy, number of previous known pregnancy losses, household socioeconomic status, maternal smoking status before delivery and body mass index before pregnancy
TCAs=tricyclic antidepressants
SSRIs=selective serotonin reuptake inhibitors
CI=confidence interval

Table 5-11 Sensitivity analysis only in women with no previous clinically recorded miscarriages or perinatal deaths: adjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in each antenatal diagnostic and drug exposure category compared with no current/past depression or anxiety (460,112 pregnancies in 330,549 women, 90% of total pregnancies)

Mental illness/drug exposures[a]	Perinatal death		Miscarriage		Termination	
	n=1,529		n=54,957		n=71,615	
	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p
Referent category[b]	1.0		1.0		1.0	
History of mental illness only	1.1 (1.0-1.4)	0.047	1.2 (1.1-1.2)	<0.001	1.3 (1.3-1.4)	<0.001
Un-medicated mental illness	1.7 (0.9-3.2)	0.035	1.0 (0.9-1.2)	0.858	1.1 (0.9-1.2)	0.220
TCAs	1.9 (1.0-3.7)	0.009	1.2 (1.1-1.4)	<0.001	1.7 (1.5-1.9)	<0.001
SSRIs	1.4 (0.9-2.1)	0.076	1.5 (1.4-1.6)	<0.001	2.3 (2.1-2.4)	<0.001
Benzodiazepines	2.2 (1.1-4.6)	0.005	1.6 (1.3-1.8)	<0.001	2.2 (1.9-2.5)	<0.001
Any other single class	4.1 (1.9-9.1)	<0.001	2.1 (1.7-2.6)	<0.001	2.6 (2.1-3.2)	<0.001
Multiple classes	2.3 (1.1-4.6)	0.002	1.6 (1.4-1.9)	<0.001	2.2 (1.9-2.5)	<0.001

[a] Exposures were depression or anxiety with or without exposures to different classes of antidepressants or anti-anxiety drugs. All categories were mutually exclusive.
[b] Reference was no history of or current depression or anxiety
[c] Relative risk ratio adjusted for maternal age at the end of pregnancy, household socioeconomic status, maternal smoking status before delivery and body mass index before pregnancy
TCAs=tricyclic antidepressants
SSRIs=selective serotonin reuptake inhibitors
CI=confidence interval

Table 5-12 Sensitivity analysis only in women with no previous clinically recorded miscarriages or perinatal deaths: adjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in each antenatal diagnostic and drug exposure category (women registered by age 20 with computerised prospective data: 132,611 pregnancies in 85,157 women, 26% of total population)

Mental illness/drug exposures[a]	Perinatal death		Miscarriage		Termination	
	n=375		n=12,942		n=32,316	
	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p
Referent category[b]	1.0		1.0		1.0	
History of mental illness only	0.9 (0.6-1.2)	0.236	1.2 (1.1-1.2)	<0.001	1.1 (1.1-1.2)	0.002
Un-medicated mental illness	1.5 (0.5-4.8)	0.370	0.9 (0.7-1.2)	0.600	0.8 (0.7-1.0)	0.024
TCAs	2.6 (0.8-8.5)	0.036	1.6 (1.2-2.1)	<0.001	1.2 (0.9-1.6)	0.049
SSRIs	1.4 (0.6-3.2)	0.326	1.6 (1.4-1.8)	<0.001	1.7 (1.5-1.9)	<0.001
Benzodiazepines	2.7 (0.7-10.1)	0.048	1.5 (1.1-2.1)	0.002	1.6 (1.2-2.1)	<0.001
Any other single class	3.7 (0.8-16.9)	0.026	1.5 (0.9-2.4)	0.028	1.4 (1.0-2.1)	0.023
Multiple classes	1.2 (0.2-10.0)	0.757	1.6 (1.0-2.0)	0.004	1.5 (1.0-2.0)	<0.001

[a] Exposures were depression or anxiety with or without exposures to different classes of antidepressants or anti-anxiety drugs. All categories were mutually exclusive.
[b] Reference was no history of or current depression or anxiety
[c] Relative risk ratio adjusted for maternal age at the end of pregnancy, household socioeconomic status, maternal smoking status before delivery and body mass index before pregnancy
TCAs=tricyclic antidepressants
SSRIs=selective serotonin reuptake inhibitors
CI=confidence interval

Results from assessing risks of medication use in women with depression or anxiety or women continue their medication during pregnancy

Compared with pregnancies in women with un-medicated depression or anxiety, women prescribed psychotropic medication had increased risks of all non-live pregnancy outcomes, although most of the results for perinatal death were not statistically significant at the 1% level (Table 5-13). The greatest effects were again found among women in Group 6 (adjusted RRRs=2.7, 2.0 and 2.3, 99% CIs 1.1-6.6, 1.6-2.5 and 1.8-2.8 for the risks of perinatal death, miscarriage and termination, respectively).

Table 5-14 shows the adjusted RRRs of non-live pregnancy outcomes in pregnant women continuing with each psychotropic medication during the first trimester of pregnancy compared with those who discontinued the medication. There were no increased risks of non-live pregnancy outcomes in women continuing with TCAs during pregnancy compared with those discontinuing them. In contrast, women who continued with SSRIs and benzodiazepines had modest increased risks of miscarriage (RRRs=1.2 and 1.5, 99% CIs 1.0-1.3 and 1.0-2.1, respectively) as well as termination (RRRs=1.5 and 1.9, 99% CIs 1.3-1.6 and 1.4-2.6, respectively) compared with those who did not.

Table 5-13 Adjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in each antenatal drug exposure category compared with un-medicated antenatal depression or anxiety

Mental illness/drug exposures[a]	Perinatal death		Miscarriage		Termination	
	n=111		n=2,784		n=3,991	
	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p	RRR[c] (99% CI)	p
Referent category[b]	1.0		1.0		1.0	
TCAs	1.2 (0.5-2.7)	0.651	1.3 (1.1-1.5)	0.001	1.4 (1.2-1.7)	<0.001
SSRIs	1.2 (0.6-2.3)	0.558	1.4 (1.2-1.7)	<0.001	2.0 (1.8-2.3)	<0.001
Benzodiazepines	1.4 (0.6-3.4)	0.305	1.6 (1.3-1.9)	<0.001	1.9 (1.6-2.3)	<0.001
Any other single class	2.7 (1.1-6.6)	0.006	2.0 (1.6-2.5)	<0.001	2.3 (1.8-2.8)	<0.001
Multiple classes	1.4 (0.6-3.3)	0.308	1.6 (1.3-1.9)	<0.001	2.0 (1.6-2.3)	<0.001

[a] Exposures were depression or anxiety with or without exposures to different classes of antidepressants or anti-anxiety drugs. All categories were mutually exclusive.
[b] Reference was un-medicated depression or anxiety during the first trimester of pregnancy
[c] Relative risk ratio adjusted for maternal age at the end of pregnancy, household socioeconomic status, maternal smoking status before delivery and body mass index before pregnancy
TCAs=tricyclic antidepressants
SSRIs=selective serotonin reuptake inhibitors
CI=confidence interval

Table 5-14 Adjusted relative risk ratios of each adverse pregnancy outcome relative to live birth in pregnancies where women continued psychotropic medication use during the first trimester compared with those where women discontinued use

Drug exposures[a]	Perinatal death			Miscarriage			Termination		
	n	RRR[b] (99% CI)	p	n	RRR[b] (99% CI)	p	n	RRR[b] (99% CI)	p
TCAs only (N[c]=4,349)	**22**			**650**			**708**		
Discontinuing (n=2,708)	12	1.0		396	1.0		434	1.0	
Continuing (n=1,641)	10	1.5 (0.4-5.2)	0.406	254	1.0 (0.8-1.3)	0.861	274	1.1 (0.9-1.4)	0.387
SSRIs only (N[c]=14,191)	**69**			**2,069**			**3,090**		
Discontinuing (n=7,203)	30	1.0		1,005	1.0		1,411	1.0	
Continuing (n=6,988)	39	1.4 (0.7-2.6)	0.223	1,064	1.2 (1.0-1.3)	0.002	1,679	1.5 (1.3-1.6)	<0.001
Benzodiazepines only (N[c]=3,392)	**25**			**520**			**654**		
Discontinuing (n=2,717)	19	1.0		415	1.0		491	1.0	
Continuing (n=611)	6	1.7 (0.5-6.0)	0.293	105	1.5 (1.0-2.1)	0.004	163	1.9 (1.4-2.6)	<0.001

[a] Women with exposure to TCAs, SSRIs, or benzodiazepines during 90 days before conceptions continued or discontinued with the medication during the first trimester of pregnancy
[b] Relative risk ratio adjusted for maternal age at the end of pregnancy, household socioeconomic status, maternal smoking status before delivery and body mass index before pregnancy
[c] Total exposed pregnancies (ending in live and non-live outcomes)
TCAs=tricyclic antidepressants
SSRIs=selective serotonin reuptake inhibitors
CI=confidence interval

5.5 Discussion

5.5.1 Principal findings

I found that women with a history of depression or anxiety or exposure to psychotropic medication during the first trimester of pregnancy had increased risks of perinatal death and miscarriage compared with women in the general population. Among women with antenatal depression and anxiety, medicated illness was statistically significantly associated with greater risks of miscarriage than un-medicated illness for every class of psychotropic drugs. I also found that women prescribed SSRIs and benzodiazepines prior to pregnancy had greater risks of miscarriage if they continued to receive the medication than if they did not. The magnitude of the medication-associated risks was similar for perinatal death, although most results were not statistically significant. In addition, more women decided to terminate their pregnancy if they had medicated depression and/or anxiety during pregnancy than if they had not and the relative risks were similar to or higher than for miscarriage. The findings suggest that psychotropic drugs, especially SSRIs and benzodiazepines, during the first trimester of pregnancy were associated with an excess risk of non-live pregnancy outcomes, although the true effect is likely to be marginal.

5.5.2 Strengths and limitations

This study is the largest and most comprehensive so far to examine the association between maternal depression and anxiety, the use of pharmacological treatment for these illnesses during the first trimester of pregnancy and the risks of perinatal death, miscarriage and termination. This study is the first to investigate all of these outcomes whilst differentiating between past illness, current illness without medication use, and current medication use stratified by medication class and the number of

medication types prescribed. I have also examined the impact of drug discontinuation; to my best knowledge this analysis is novel.

The large sample size and assessments of significance at the 1% level mean that my findings are unlikely to be due to chance alone. Despite this, since perinatal deaths are comparatively rare in the UK population, negative results for these outcomes should be interpreted cautiously as power is somewhat limited and the possibility that I have failed to detect true risks cannot be excluded. However, given the rarity of these events, effects of the observed magnitude would in any case translate to fairly small excess risks in absolute terms.

The data used were obtained from a UK primary care database and prospectively recorded by GPs, excluding the possibility of recall bias. The study may have missed some non-live pregnancy outcomes, such as very early miscarriages and private terminations, however the observed prevalence of clinically-recognised adverse pregnancy outcomes is similar to UK national estimates.[180–182] In addition, I may have missed some women with depression and anxiety who do not report their symptoms to their GPs. Since all pregnant women must be registered with primary care physicians in the UK in order to benefit from antenatal checks and free medication, it is unlikely that a high proportion of women with depression and anxiety (and especially those with prescriptions for psychotropic medication) were not identified. Some women receiving drug prescription may not actually take the medication; this, however, would tend to bias the estimates to the null hypothesis (rather than produce spurious associations). Inevitably in these data my population of women with depression or anxiety represents those diagnosed and clinically treated and my identification of exposure is therefore pragmatic rather than exhaustive.

I have adjusted for the effects of maternal age, socio-economic deprivation, maternal smoking and maternal BMI. I do not have complete data on these factors, but the

absence of any evidence of confounding where data are available suggests that it is unlikely that there is substantial residual confounding where data are missing. I have also adjusted for women's prior pregnancy history (by using the number of known live births and prior pregnancy losses and adding them into the model separately) in the overall population and in a sub-set of women registered with a primary health care unit by age 20 years. Although there was some evidence of residual confounding as risk estimates did decrease slightly for prior mental illness before pregnancy and modestly for termination, drug-associated risks for perinatal death and miscarriage remained almost unchanged. The women in this sub-set population, however, represented the youngest group in the study population and were thus less likely both to have had a history of mental illness and to have had prior pregnancies. When I restricted to only women with no prior pregnancy losses clinically recorded, I again found antenatal treatment for depression or anxiety to be consistently associated with all adverse outcomes both in the overall population and in women registered by age 20. These analyses demonstrate that the patterns of increased risks did not change based on a woman's pregnancy history, particularly for the treatment-associated risks with miscarriage and perinatal death.

I acknowledge that other unmeasured factors might partly explain the results. One particularly important effect that I have not quantified is the severity of disease, whether in terms of symptoms or other measures. It is impossible to completely separate the effects of psychotropic drugs from the indications for treatment, and the receipt of medication might imply more severe illness. Pregnant women with more severe mental illness might be more likely to choose a subsequent termination. Since risk estimates were slightly higher for pregnancies ending in terminations than for perinatal death or miscarriage for almost every drug class, it is therefore possible that differing severity of underlying illness does partly explain my findings. However, in the analysis of drug continuation in pregnancy, the differing effect of continuing with

SSRIs or benzodiazepines from the effect of continuing with TCAs does suggest some medication-specific (and therefore pharmacological) contribution to the observed increases in risk, although the true effect could be marginal. In addition, I did not examine the effect of other maternal comorbidity (e.g. diabetes) on the observed risk estimates; however, such comorbidity is uncommon in the study population and is less likely to fully explain my findings.

5.5.3 Interpretation in context of previous studies

The findings of increased risks of miscarriage and perinatal death among women with a history of medicated depression or anxiety during early pregnancy found in this study were generally consistent with previous studies.[42,43,43–46,53,142,156–158] To some extent, however, the findings also differed from previous work.

A Swedish study found a 70% increased risk, though not statistically significant (adjusted risk ratio=1.7, 95% CI 0.6-3.6), of stillbirth in women exposed to newer antidepressants (venlafaxine, mirtazapine, miaserin and reboxetine) during the first trimester of pregnancy compared with those without such exposure after adjusting for maternal age, year of birth, parity, maternal smoking and maternal BMI, which is similar to my study.[160] However, there was no increased risk of stillbirth in women exposed to SSRIs (adjusted risk ratio=0.8, 95% CI 0.5-1.2). Women with a history of depression or anxiety but no medication during pregnancy were included in the referent group for comparison and fewer than 1% of women had received SSRIs (this is under half as many as in my UK population, suggesting differing clinical criteria for issuance of treatment), limiting statistical power, which may partly explain our different findings.

Four prospective cohort studies investigating women consulting the same teratology information service in Canada found on average a 1.5-2 fold increased risk of miscarriage in women taking TCAs, SSRIs and newer antidepressants such as

venlafaxine during the first trimester of pregnancy.[48,163,164,166] All four studies, however, had relatively small sample sizes (the largest being 534) and considerable uncertainty in the estimates. Chambers *et al.* conducted another cohort study in 408 women who contacted a teratology information service in the USA from 1989 to 1995 and did not find statistically significantly increased risks of miscarriages or stillbirths in pregnant women taking fluoxetine during the first trimester compared with those not taking fluoxetine.[49] However, by pooling the results from six studies (including the studies just mentioned),[48,49,163,164,166,168] Hemels and colleagues found a 45% (risk ratio=1.45, 95% CI 1.19-1.77) increased risk of miscarriage in mothers taking any antidepressants during early pregnancy.[174] Specifically, they found increased risks in women prescribed SSRIs and newer antidepressants, but not TCAs, compared with women who were not prescribed the respective class of drugs (risk ratios=1.23, 1.52 and 1.65, 95% CIs 0.84-1.78, 1.17-1.98 and 1.02-2.69 for TCAs, SSRIs, and new antidepressants, respectively). It is important to note, however, that study populations derived from teratology information services likely represent highly selected groups that exclude many exposed women in the general population.

A more recent case-control study including more than half a million pregnant women from Canada found a 68% (95% CI 1.38-2.06) increased risk of miscarriage in women prescribed antidepressants even after adjusting for depression, anxiety, history of medication use during one year before pregnancy and the severity of the illness (defined as the number of days antidepressants prescribed and the number of visits to a psychiatrist in the year before pregnancy).[47] Specifically, they observed a higher risk in women taking SSRIs, but not among those taking TCAs (odds ratios=1.61 and 1.27, 95% CIs 1.28-2.04 and 0.85-1.91, respectively). These findings suggest a potential pharmaceutical effect with SSRIs but not with TCAs, which is consistent with the observations in my study. The Canadian study also found a three-fold increased risk of miscarriage in women with multiple classes of antidepressants compared with

those with one class only (odds ratio=3.51, 95% CI 2.20-5.61 for at least 2 different classes of antidepressants). Again, the authors did not directly compare un-medicated cases with those prescribed medication, nor did they consider the effects of anxiolytics, such as benzodiazepines, which were also associated with greater risks of non-live pregnancy outcomes in my study.

My study also found increased risks of miscarriage and perinatal death in women prescribed benzodiazepines. To my best knowledge, only a few studies have examined the effect of anti-anxiety drugs on non-live pregnancy outcomes.[66,169,170,172] A large American study in the 1970s found a higher, though not statistically significant, risk of perinatal death in women prescribed meprobamate and chlordiazeproxide,[170] and a later case-control study in Sweden showed a 4-fold increased odds of perinatal death in women exposed to benzodiazepines during pregnancy (95% CI 2.0-7.9).[172] A prospective study in Israel examining women who contacted the teratogen information service during pregnancy found higher rates of miscarriage (8.7% vs. 5.2%) and termination (14.1% vs. 4.7%) in women exposed to benzodiazepines than those exposed to non-teratogenic drugs.[66] None of these studies considered however assessed the impact of women's underlying conditions or other maternal characteristics.

In addition, my finding that women with medicated anxiety or depression during pregnancy are more likely to terminate a pregnancy than those who do not receive medication is in line with prior research.[49,66,159] Unlike miscarriage and perinatal death (which typically occur due to trauma or via some biological mechanism) choosing to have a termination is usually voluntary, but occasionally due to in utero identification of a known chromosomal or congenital anomaly or of a potential risk to the foetus or mother if pregnancy continues to term (though such cases are likely uncommon in the UK population). Therefore, the majority of terminations identified in my study are more likely to be a matter of personal preference regarding the pregnancy.

Compared with the risks of miscarriage and perinatal death, the increases in risks of termination found in my study were much greater (e.g. RRRs=1.2, 1.4 and 2.0 for the risks of perinatal death, miscarriage and termination respectively in women prescribed benzodiazepines during pregnancy shown in Table 5-13), suggesting that women receiving medication for depression or anxiety during pregnancy may be those who suffer the most severe symptoms and consequently feel unable to cope with a child. The discovery of pregnancy when taking psychotropic medications could also contribute to such decisions since women may worry about the adverse impact on the health of their offspring subsequently.[159] There may also be a marginal degree of reverse causation insofar as the small number of mothers who discover that their foetus exhibits an abnormality may become depressed and commence treatment prior to having a termination. My findings concur with those of a recent study in Canada including 937 women taking antidepressants during early pregnancy, which found a 3-fold increased risks of termination in exposed women compared with those unexposed (OR=3.25, 95% CI 1.48-7.14), but only a 63% increased risk of miscarriage (OR=1.63, 95% CI 1.24-2.14).[159]

5.5.4 Conclusion and implications

This study has shown increased risks of miscarriage, perinatal death and decisions to terminate a pregnancy in women with anxiety or depression prior to pregnancy and with exposures to psychotropic drugs during the first trimester of pregnancy. I found even greater risks in women with medicated antenatal depression and anxiety compared with those who did not receive medication. Specifically, the risks were greatest among pregnant women prescribed SSRIs, benzodiazepines, and newer but less common drugs, and in those taking multiple drugs. While I cannot rule out confounding by severity of mental illness, the analysis of women who did and did not continue their medication when pregnant implies that longer exposure may be more harmful. Since the risk of developing a new depressive episode during pregnancy in

women discontinuing antidepressants remains unclear,[184,185] my findings suggest that clinicians and obstetricians should continue to take a cautious approach to drug treatment in pregnant women with mental illness.

6 The risks of congenital anomalies in live-born children exposed to psychotropic medication during the first trimester of pregnancy

This chapter describes a study examining the association of any major and system-specific congenital anomalies with maternal exposure to psychotropic drugs, mainly antidepressant or anti-anxiety drugs, during early pregnancy. A review of the current evidence in literature is firstly provided and followed by objectives, methods, results, discussion and final conclusions/implications.

6.1 Introduction

In recent years, a considerable number of studies have been carried out to investigate the potential toxic effects of various psychotropic drugs, mainly newly developed antidepressants such as paroxetine, fluoxetine, sertraline, and venlafaxine, on the human foetus in terms of the risk of congenital anomalies. Table 6-1 summarises all systematic reviews (including meta-analyses) of the association between antenatal exposure to psychotropic medication and congenital anomalies as published in English language journals from 1990 to June 2012.

Currently, most reviews have been focused on the safety of selective serotonin reuptake inhibitors (SSRIs), especially paroxetine, and suggested a small increased risk of congenital anomalies, particularly heart anomalies in children with first trimester exposure to paroxetine.[186] Less information is available for the safety of other antidepressant or anti-anxiety drugs. In addition, although lithium and mood stabilisers are generally considered to be teratogenic, such excess risk is likely to be modest (around 2 fold).[187–190] There has been very limited evidence available for the safety of antipsychotic drugs to draw valid conclusions.[38,187]

Table 6-1 Systematic reviews and/or meta-analyses on the association between psychotropic medication and congenital anomalies

Author(s), publication year	Study period	Outcome(s) assessed	Inclusion criteria			Studies initially identified	Studies finally included	Total pregnancies	Number of women exposed	Major findings
			Study design	Medication and period of exposure	Comparison group(s)					
Antidepressants										
Wurst et al., 2010[186]	Jan 1992 to Sep 2008	Cardiac and overall congenital anomalies (minor included)	Cohort and case-control studies	Paroxetine during the first trimester of pregnancy	Non- paroxetine	37	20	Not reported	Not reported	Cardiac: Prevalence OR=1.46 (1.17-1.82); Overall: Prevalence OR=1.24 (1.08-1.43)
O'Brien et al., 2008[191]	Jan 1985 and Nov 2007	Cardiovascular anomalies	Cohort and case-control studies	Paroxetine during pregnancy	Non- paroxetine	21	9	96,656	Not reported	Cohort: Risk difference=0.3% (-0.1-0.7%); Case-control: OR=1.18 (0.88-1.59)
Bar-Oz et al., 2007[192]	1985 to 2006	Major and cardiovascular anomalies	Case-control and cohort studies for pregnancies ending in live births only	Paroxetine during the first trimester (0-14 weeks of gestational age)	Other antidepressants or other non-teratogenic medication	Not reported	7	Not reported	Not reported	Major: OR=1.31 (1.03-1.67); Cardiac: OR=1.72 (1.22-2.42); Non-cardiac: OR=1.29 (0.86-1.92)
Bellantuono et al., 2007[193]	1966 to Oct 2006	Major congenital anomalies	Prospective cohort and retrospective designs	SRIs (SSRIs and SNRIs) during the first trimester of pregnancy	Various by studies	16	15	Not reported	Not reported	Fluoxetine, sertraline, citalopram and venlafaxine no increased risk; Paroxetine need caution; Other SRIs: the risk remains substantially undetermined

Author(s), publication year	Study period	Outcome(s) assessed	Inclusion criteria			Studies initially identified	Studies finally included	Total pregnancies	Number of women exposed	Major findings
			Study design	Medication and period of exposure	Comparison group(s)					
Rahimi et al., 2006[194]	1990 to Aug 2005	Major, cardiovascular, and minor anomalies	Not reported	SSRIs (of any therapeutic dosage) during pregnancy	Not reported	Not reported	9	1,782	Not reported	Major: OR=1.39 (0.91-2.15); Cardiac: OR=1.19 (0.53-2.68); Minor: OR=0.97 (0.14-6.93)
Einarson & Einarson, 2005[195]	1996 to 2005	Major anomalies	Prospective cohort studies	SSRIs, reboxetine, venlafaxine, nefazodone, trazodone, mirtazapine and bupropion during the first trimester	Non-exposed	22	7	1,774	Not reported	Overall: RR=1.01 (0.57-1.80); Fluoxetine: RR=1.19 (0.47-3.00)
Altshuler et al., 1996[196]	1966 to 1995	Congenital anomalies	Published studies written in English	TCAs in the first trimester	Non-exposed	14	13	over 300,000	414	Safe regarding the risk of congenital anomalies
Anxiolytics										
Enato et al., 2011[197]	1966 to June 2010	Major, cardiovascular anomalies and oral cleft	Cohort and case-control studies	Exposure to benzodiazepines during the first trimester of pregnancy	Not reported	Not reported	26	1,051,376	4,342	Major: OR=1.07 (0.91-1.25); Cardiac: OR=1.27 (0.69-2.32)
Dolovich et al., 1998[198]	1966 to present	Major anomalies and oral cleft	Cohort and case-control studies	Exposed to benzodiazepines at least during the first trimester of pregnancy	Non-exposed to benzodiazepines	Over 1,400 studies	23	Not reported	Not reported	Major (cohort): OR=0.90 (0.61-1.35); Major (case-control): OR=3.01 (1.32-6.84); Oral cleft (cohort): OR=1.19 (0.34-4.15); Oral cleft (case-control): OR=1.79 (1.13-2.82)

Author(s), publication year	Study period	Outcome(s) assessed	Inclusion criteria			Studies initially identified	Studies finally included	Total pregnancies	Number of women exposed	Major findings
			Study design	Medication and period of exposure	Comparison group(s)					
Altshuler et al., 1996[196]	1966-1995	Congenital anomalies and oral cleft	Published studies written in English	Benzodiazepines in the first trimester	Non-exposed	14 (4 for oral cleft)	14 (3 for oral cleft)	Range from 473 to over 100,000	Range from 4 to 1,354	Oral cleft: OR=2.4 (1.40-4.03)
Lithium, mood stabilizers/anti-epileptic drugs, and antipsychotic drugs										
Galbally et al., 2010[187]	1950-Jun 2009	Congenital anomalies	Original research in English-language journals	Lithium, valproate, lamotrigine, and carbamazepine	Non-exposed	Not reported	28	Not reported	Not reported	Lithium: limited evidence to draw any valid conclusion; all mood stabilizers were associated with a risk of congenital anomalies
Einarson and Boskovic, 2009[38]	1966-2008	Congenital anomalies	Original research published in English	Antipsychotic drugs	Non-exposed	Not reported	Not reported	Not reported	Not clearly reported (range from 45 to 1,309)	No association was found but no good quality data and limited information
Nguyen et al., 2009[188]	1966-2008	Major congenital anomalies	Original research published in English-language journals	Valproate, lamotrigine, carbamazepine, lithium and antipsychotic drugs	Not reported	Not reported	19	Not reported	Not reported	Incidence in: valproates: 6.2-20.3%; lamotrigine: 1.0-5.6%; carbama: 2.2-7.9%; lithium: 4.0-12.0; Antipsychotics: no good data
Meador et al., 2008[189]	1966-May 2007	Congenital anomalies	Prospective cohort studies	Pregnant women with epilepsy	Healthy women	1,003	59	Nearly 1,900,000	65,533	Incidence in epilepsy: 7.08% (5.62, 8.54); Carbamazepine alone: 4.62%(3.48-5.76); Valproate alone: 10.73% (8.16-13.29); Healthy women: 2.28% (1.46, 3.10);

Author(s), publication year	Study period	Outcome(s) assessed	Inclusion criteria			Studies initially identified	Studies finally included	Total pregnancies	Number of women exposed	Major findings
			Study design	Medication and period of exposure	Comparison group(s)					
Altshuler et al., 1996[196]	1966-1995	Congenital anomalies	Published studies written in English	Lithium, mood stabilizers and antipsychotics	Non-exposed	Not reported	Not reported	74,337 for phenothiazine	2,591	Phenothiazine: OR=1.21; Lithium with a10-20 times increased risk of Ebstein's anomaly; Mood stabilizer associated with increased risks of spina bifida
Cohen et al., 1994[190]	Not reported	All congenital anomalies and Ebstein's anomaly	All published studies	Lithium in the first trimester	Non-exposed	Not reported	Not reported	Not reported	Not reported	slightly increased risks of heart congenital anomalies, though not statistically significant

SSRIs=selective serotonin reuptake inhibitors, including citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
TCAs=tricyclic antidepressants

6.1.1 Maternal use of antidepressant and anti-anxiety drugs accounting for impact of underlying illness

There is concern over the use of some selective serotonin reuptake inhibitors (SSRIs), particularly paroxetine, during early pregnancy in terms of the risk of major congenital anomalies in the offspring. The company GlaxoSmithKline,[199] the manufacturer of PAXIL® (paroxetine hydrochloride tablets), revised their paroxetine label in 2005 and added a warning that there may be a small increased risk of congenital anomalies, particularly congenital heart anomalies, in children whose mother took paroxetine in the first trimester of pregnancy but no other psychotropic drugs have had warnings released by their manufactures. Table 6-2 (for cohort studies) and Table 6-3 (for case-control studies) summarise all studies published in English language journals (identified through searching the website of PubMed) on the association of congenital anomalies with antidepressant or anti-anxiety drugs by cohort and case-control study designs separately, showing that most studies have few drug-exposed cases of congenital anomalies.

Previous studies on the teratogenic impact of antidepressant and anti-anxiety drugs in early pregnancy have been conducted based on data from different resources and have also focused on various combinations of specific drugs and categories of congenital anomalies. Some earlier studies have used detailed information of maternal drug use in a small number of patients recruited from teratology information centres in various countries. Others have used retrospective case–control designs, with the potential for substantial recall bias and often relatively large nonresponse rates. More recent studies have identified antenatal drug exposure from medical registers for a large number of patients, such as studies from Sweden, Denmark, and Finland. Although there are potential problems of misclassification in the exposure as a woman who buy a drug might not take it during the organogenetic period, they provide a large representative study population. Variations in different study

populations by prevalence of congenital anomalies and antenatal drug use may also have some effects on the teratogenic risk estimates. In addition, whilst the effects of SSRIs have been increasingly examined in the literature, very few studies have considered the potential effects of other drugs and/or comorbid conditions in women during pregnancy.

Table 6-2 Cohort studies for antenatal exposure to psychotropic medication with congenital anomalies in offspring

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (%) of mothers exposed	Outcome(s)	Other co-variables considered and/or adjusted	Major findings
Antidepressants										
Colvin et al., 2011[200]	Australia	2002-05	Population-based health datasets and a national pharmaceutical claims dataset	97,262	Dispensed an SSRI during the first trimester of pregnancy compared with exposed to all non-SSRIs	Y	2,701 (2.8)	Major congenital anomalies	Y (maternal age only)	Overall: OR=1.05 (0.87-1.27); Cardiac: OR=1.60 (1.10-2.31) but not found in individual drugs; Respiratory: sertraline (<3); Gastrointestinal: fluoxetine
Malm et al., 2011[53]	Finland	1996-2006	Birth registry data	635,583	SSRIs during the first trimester	Y	6,976 (1.1)	Major congenital anomalies	Y	SSRIs overall: OR=1.08 (0.96-1.22); Fluoxetine with isolated ventricular septal defects; Paroxetine with right ventricular outflow tract defects; Citalopram with neural tube defects
Kornum et al., 2010[201]	Denmark	1991-2007	Prescription database and National Registry of Patients	216,042	At least one SSRI (incl. individual drugs) prescription in the first trimester of pregnancy	Y	2,062 (1.0)	Congenital anomalies	Y	SSRIs with any anomaly: OR=1.3 (1.1-1.6); Sertraline: Cardiac: OR=3.0 (1.4-6.4) and Sepal heart defects: OR=3.3 (1.5-7.5)

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (%) of mothers exposed	Outcome(s)	Other co-variables considered and/or adjusted	Major findings
Reis and Källén, 2010[58]	Sweden	1 July 1995 to 2007	Medical birth registry data	1,077,002	Antidepressants in pregnancy (SSRIs and TCAs and specific SSRI drugs)	Y	14,821 (1.4)	Congenital anomalies	Y	TCAs: higher risk of severe anomalies and cardiac defects (VAS and/or ASD) Cardiac: paroxetine: OR=1.66 (1.09-2.53); fluoxetine: OR=1.31 (0.85-2.02)
Einarson et al., 2009[202]	Canada	Not reported	Teratogenic information service	928+928	Antidepressants during the first trimester of pregnancy	Y	928	Major congenital anomalies	Y (matched)	OR=0.9 (0.5-1.61)
Merlob et al., 2009[203]	Israel	2000-07	Maternal ward in a local tertiary health care centre	1,318	SSRI use during the first trimester of pregnancy	Y	235 (17.8)	Nonsyndromic congenital heart anomalies	N	RR=2.17 (1.07-4.39)
Pedersen et al., 2009[56]	Denmark	1996-2003	Several nationwide registries	496,881	Two or more redemptions for SSRIs from 28 days before to 112 days after the beginning of gestation	Y	1,370 (0.3)	Congenital anomalies (minor, major and 12 specific categories)	Y	Only found increased risk for septal heart defects: OR=1.99 (1.13-3.53) (esp in citalopram, sertraline and more than one type of SSRIs)
Wichman et al., 2009[204]	USA	Jan 1993 to 15 Jul 2005	Medical records from Mayo Clinic	25,214	Treated with SSRIs during pregnancy	Y	808 (3.2)	Congenital heart disease	N	No association (0.4% vs. o.8%, p=0.23)

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (%) of mothers exposed	Outcome(s)	Other co-variables considered and/or adjusted	Major findings
Wisner et al., 2009[205]	USA	Jan 2000 - Apr 2001 / Apr 2003 - Jul 2007	Recruitment of pregnant women from Cleveland and Pittsburgh	238	Depression and/or SSRI during pregnancy	Y	107 (4.5)	Congenital malformations	Y	No associations
Diav-Citrin et al., 2008[45]	Israel, Italy and Germany	1994-2002 and 2002-05	Teratology information service	2,191	Paroxetine and fluoxetine during the first trimester of pregnancy	Y	410 (paroxetine) and 314 (fluoxetine)	Major and cardiac anomalies	Y	Higher prevalence of major anomalies in exposed groups (mainly due to cardiac anomalies); Fluoxetine with increased risk of cardiac defects: adjusted OR=4.47 (1.31-15.27); Paroxetine not: adjusted OR=2.66 (0.80-8.90)
Einarson et al., 2008[57]	Canada & Worldwide	Not reported	Teratology information services and published studies	Not reported	Paroxetine during the first trimester of pregnancy	Y	1,174+2,205	Cardiovascular anomalies	N	OR=1.1 (0.36-2.78)
Oberlander et al., 2008*[206]	Canada (British Columbia)	April 1997 to March 2002	Data from several registry datasets	119,547	SSRI mono-therapy and SSRI+ benzodiazepines in combination during the first trimester	Y	7,883 (depression alone), 2,625 (SSRIs alone), 968 (benzos only) and 359 (both drugs)	Major anomalies and congenital heart disease	Y	Combination therapy associated with increased risk of cardiac defects: risk difference=1.18 (0.18-2.18)

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (%) of mothers exposed	Outcome(s)	Other co-variables considered and/or adjusted	Major findings
Cole et al., 2007[207]	USA	Jan 1995 to Sep 2004	UnitedHealthcare (an insurer)	5,791	Paroxetine and compared with all other antidepressants during the first trimester	Y	998 and 797 mono-therapy only	congenital malformations (and by organ system category)	Y	All CAs (mono-therapy): OR=1.89 (1.20-2.98); All CAs (mono- or poly-therapy): OR=1.76 (1.18-2.64); Not for cardiac anomalies
Davis et al., 2007[59]	USA	1996-2000	5 health centres	50,931	TCAs or SSRIs during pregnancy	Y	1,047 (SSRIs) and 221 (TCAs)	Congenital anomalies	N	SSRIs: no association; TCAs: an increased risk of limb abnormalities and spina bifida
Källén and Otterblad Olausson, 2007[55]	Sweden	1995-2004	Medical birth register	960,215	SSRIs during early pregnancy	Y	6,481 (0.7)	Congenital anomalies	Y	No association (overall and for each class)
Lennestål and Källén, 2007[160]	Sweden	Up to 2004	Medical birth register	860,215	SSRIs and newly introduced antidepressants	Y	6,481 and 732	Congenital anomalies	N	No association
Djulus et al., 2006[161]	Canada & Worldwide (incl. UK)	June 2002 to August 2005	5 teratogen information services	312	Mirtazapine during pregnancy	Y	104	Major anomalies	N	No association
Källén and Otterblad Olausson, 2006[208]	Sweden	July 1995-2003	Birth registry data	Not reported	Antidepressants in early pregnancy	Y	6,896	Congenital anomalies and cardiac anomalies	Y	Clomipramine (cardiac): OR=2.22 (1.29-3.82); Paroxetine (cardiac): OR=2.29 (1.28-4.09)

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (%) of mothers exposed	Outcome(s)	Other co-variables considered and/or adjusted	Major findings
Wen et al., 2006[46]	Canada	1990-2000	Database	972+3,878	SSRIs in the year before delivery	Y	972	Structural anomalies	Y (matched)	No association
Wogelius et al., 2006[209]	Denmark	1991-2003	Several national databases	151,831	SSRIs from 30 days before conception until the end of the first trimester	Y	1,051 (0.7)	Congenital anomalies	Y	Within the second or third month after conception : OR=1.84 (1.25-2.71)
Chun-Fai-Chan et al., 2005[210]	Canada and UK	Not reported	Teratogenic information service	136+133	Bupropion during the first trimester of pregnancy	Y	136	Major congenital anomalies	Y (matched)	No association
Malm et al., 2005[211]	Finland	1996-2001	Several national databases	1,782+ 1,782	>=1 purchase of SSRIs during the period 1 month before and during pregnancy	Y	1,782	Major congenital anomalies	Y (matched)	No association (neither for individual drugs)
Sivojelezova et al., 2005[162]	Canada	1999-2002	Teratogenic information service	396 (matched)	Citalopram during the first trimester of pregnancy	Y	132	Major congenital anomalies	Y	No association
Williams and Wooltorton, 2005[212]	USA	Not reported	Insurance databases	3,581	SSRIs during the first trimester of pregnancy	Y	527 for paroxetine exclusively	Major congenital anomalies	Y	Paroxetine: OR=2.20 (1.34-3.63)
Einarson et al., 2003[163]	Canada	Not reported	Teratogenic information service	147+147+ 147 (matched)	Trazodone or nefazodone during the first trimester of pregnancy	Y	147	Major congenital anomalies	Y	RR=1.67 (0.85-3.28)

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (%) of mothers exposed	Outcome(s)	Other co-variables considered and/or adjusted	Major findings
Hendrick et al., 2003[213]	USA	June 1997 and May 2002	Not reported	138 (no comparison group)	SSRIs during pregnancy	Y	138	Congenital anomalies	N	No association
Simon et al., 2002[214]	USA	1986-98	Insurance data	788	Antidepressants during the 270 days before delivery	Y	209 (TCAs)+185 (SSRIs)	Congenital anomalies	Y (matched)	No association
Einarson et al., 2001[164]	Canada	Not reported	Teratogenic information service	450	Venlafaxine during 4th to 14th week gestation	Y	150	Major congenital anomalies	Y (matched)	No association
Ericson et al., 1999[215]	Sweden	1995-97	Birth registry data	969 (no comparison group)	Antidepressants during pregnancy	Y	533 (SSRIs)	Congenital anomalies	N	No association
Kulin et al., 1998[166]	North America	Not reported	Teratogenic information service	267+267 (matched)	SSRIs during the first trimester of pregnancy	Y	267	Major congenital anomalies	Y	No association
Goldstein et al., 1997[216]	Worldwide	Not reported	Drug company data	796 (no comparison)	Fluoxetine during the first trimester of pregnancy	Y	796	Congenital anomalies	N	No association
Chamber et al., 1996[49]	USA	1989-95	Teratogenic information service	228+254	Fluoxetine during pregnancy	Y	228	Congenital anomalies	N	No difference in major structural anomalies but in three or more minor anomalies (p=0.03)

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (%) of mothers exposed	Outcome(s)	Other co-variables considered and/or adjusted	Major findings
Pastuszak et al., 1993[48]	Canada	Not reported	Teratogenic information service	128+128 (matched)	Fluoxetine during the first trimester of pregnancy	Y	128	Major congenital anomalies	Y	No association
Anxiolytics										
Gidai et al., 2010[217]	Hungary	1960-93	Toxicological inpatients clinics	43+29 sib controls	Large dose of nitrazepam alone or combination with other drugs	Y	43	Structural congenital anomalies	Y	OR=3.8 (1.0-14.6)
Leppée et al., 2010[218]	Yugoslavia	May 2004	4 hospitals in Zagreb	893 (no comparison)	Benzodiazepines in pregnancy	Y	893	Congenital anomalies	N	Not clear
Gidai et al., 2008[63]	Hungary	1960-93	Toxicological inpatients clinics	224	Diazepam in pregnancy	Y	112	Congenital anomalies	Y (matched sibs)	OR=2.0 (0.8-5.0)
Gidai et al., 2008[219]	Hungary	1960-93	Toxicological inpatients clinics	35+22 (sibs)	Chlordiazepoxide	Y	35	Congenital anomalies	Y	No association
Wikner et al., 2007[220]	Sweden	1st July 1995 to 2004	Birth register data	875,858	Benzodiazepines in early pregnancy	Y	1,979 (0.2)	Congenital anomalies	Not clear	Major congenital anomalies: OR=1.24 (1.00-1.55)
Ornoy et al., 1998[66]	Israel	1988-Jul 1996	Teratogenic information service	460+424	Benzodiazepines prior to or in pregnancy	Y	460	Congenital anomalies	N	No association (3.1% vs. 2.6%)
Bergman, 1992[221]	USA	1980-83	Public health insurance system (Medicaid)	104,339	10 or more prescriptions of benzodiazepines in pregnancy	Y	80	Congenital anomalies	Y	13 vs. 7% (no statistical analysis carried out)

Author(s), year	Country	Study period	Source of study population	Number of pregnancies	Exposure(s)	Exposure information collected prior to outcome occurrence	Number (%) of mothers exposed	Outcome(s)	Other co-variables considered and/or adjusted	Major findings
St Clair and Schirmer, 1992[222]	USA	June 1982-1990	From health professionals or self-referred	411	Alprazolam during the first trimester of pregnancy	Y	411	Congenital anomalies	N	Not clear
Hartz et al., 1975[223]	USA	1958-1966	Hospital records	5,282	Meprobamate/ chlordiazeproxide in the first 16 weeks of pregnancy	Y	356+257	Congenital anomalies	Y	No association
Milkovich, 1974[170]	USA	1959-1966	Health registry data	19,044	Meprobamate/ chlordiazeproxide in the first 6 weeks of pregnancy	Y	395+172	Severe congenital anomalies	N	Higher prevalence in exposed groups

* Examined both antidepressants and anxiolytics.
CAs=congenital anomalies
SSRIs=selective serotonin reuptake inhibitors
TCAs=tricyclic antidepressants
USA=United States of America
UK=United Kingdom

Table 6-3 Case-control studies for antenatal exposure to psychotropic medication with congenital anomalies

Author(s), year	Country	Study period	Source of study population	Total number of cases/controls	Outcome(s)	Number (%) of cases with exposures	Exposure	Other co-variables considered and/or adjusted	Major findings
Antidepressants									
Bakker et al., 2010[54]	Netherlands	1997-2007	Birth registry data	178/4077	Infantile hypertrophic pyloric stenosis	3 (1.7)	Fluoxetine in the first trimester of pregnancy	Y	OR=8.7 (2.3-33.2) compared with other congenital anomalies
Bakker et al., 2010[224]	Netherlands	1997-2006	Birth registry data	678/615	Isolated heart anomalies	1.5%	Paroxetine during the first trimester of pregnancy	Y	OR=1.5 (0.5-4.0); for atrial septal defects: OR=5.7 (1.4-23.7)
Ramos et al., 2008*[225]	Canada	Jan 1998 to Dec 2002	Data from medication and pregnancy registry by linking three databases	189/2,140	Major congenital anomalies	Not reported	Antidepressant during the first trimester of pregnancy	N	No association
Bérard et al., 2007*[226]	Canada	1997 to Jun 2003	Data from Medication and Pregnancy registry	101/1,302	Major and cardiac anomalies	43 (42.6)	Paroxetine during the first trimester of pregnancy	Y	>25 mg/day of paroxetine during the first trimester: Major anomalies: OR=2.23 (1.19, 4.17); Major cardiac: OR=3.07 (1.00, 9.42)
Alwan et al., 2007[227]	USA	Oct 1997 to Dec 2002	National birth-defects surveillance systems; Hospital records or state birth-certificate records	9,622/4,092	Major birth defects and subcategories	230 (2.4)	SSRIs from 1 month before to 3 months after conception	Y	No association for heart defects; but anencephaly, craniosynostosis, and omphalocoele

Author(s), year	Country	Study period	Source of study population	Total number of cases/controls	Outcome(s)	Number (%) of cases with exposures	Exposure	Other co-variables considered and/or adjusted	Major findings
Louik et al., 2007[228]	USA	1993-2004	5 study centres	9,849/5,860	7 subgroups of birth defects re development	100 (2.7) in offspring with cardiac anomalies	Any SSRI from 28 days before through 112 days after the last menstrual period	Y	Sertraline associated with omphalocoele and septal defects; Paroxetine and right ventricular outflow tract obstruction defects
Källén and Robert-Gnansia, 2005[229]	Sweden and France	1995-2002	Health registers	323/674,491	Craniostenosis	Not reported	Antidepressant during the first trimester of pregnancy	Y	No association
Källén and Otterblad Olausson, 2003**[230]	Sweden	Jul 1995 to Dec 2001	Birth registry data	5,015/577,730	Cardiovascular anomalies	1,408	Any drug use in early pregnancy	Y	Tricyclic: OR=1.77 (1.07-2.91); Clomipramine: OR=2.03 (1.22-3.40); No association with SSRIs or benzodiazepines
Greenberg et al., 1977**[231]	UK	1969-1974	Voluntary reporting to health authority	836/836	Major defects	26	Any drug use during the first trimester of pregnancy	Y (matched)	No associations for both antidepressants and benzodiazepines
Anxiolytics									
Czeizel et al., 2004[232]	Hungary	1980-1996	Health registry data	22,865/38,151	Congenital anomalies	201 (0.9)	Oral chlordiazepoxide during early pregnancy	Y (matched)	Cardiac anomalies: OR=2.5 (1.0-6.0)
Eros et al., 2002[64]	Hungary	1980-1996	Health registry data	22,865/38,151	Congenital anomalies	57 (0.25)	Benzodiazepines in pregnancy	Y (matched)	No association

Author(s), year	Country	Study period	Source of study population	Total number of cases/controls	Outcome(s)	Number (%) of cases with exposures	Exposure	Other co-variables considered and/or adjusted	Major findings
Bonnot et al., 2001[65]	France	1976-1998	Linked health registry data	13,703 (self-controlled: other categories of congenital anomalies)	Congenital anomalies (specific categories)	262 (7.3)	Benzodiazepines during the first trimester of pregnancy	Y	No association overall; Lorazepam with anal atresia: OR=6.19 (2.44-15.71); Bromazepam with other digestive anomalies: OR=6.15 (1.88-1.20); Oxazepam with genetic anomalies: OR=0.43 (0.23-0.81); Prazepam with neural tube defects: OR=6.80 (1.80-25.73)
Laegreid et al., 1990[60]	Sweden	1985-1986	Hospital records	18/60	Congenital anomalies	8 (44)	Maternal plasma: benzodiazepines during pregnancy	N	44% vs. 3.3%
Czeizel, 1987[67]	Hungary	1980-1984	Health registry data	630/630	Facial clefts	63 (10.0)	Benzodiazepines during pregnancy	Y (matched)	No association
Rosenberg et al., 1983[68]	USA	Mar 1976 to April 1982	Birth defects surveillance data	611/ 2,498	Facial clefts	Not reported	Diazepam during the first trimester of pregnancy	N	No association
Safra and Oakley, 1975[62]	USA	1968-1974	Birth registry data	278/709	Congenital anomalies	Not reported	Diazepam in the first trimester of pregnancy	N	Increased risk of facial clefts

Author(s), year	Country	Study period	Source of study population	Total number of cases/controls	Outcome(s)	Number (%) of cases with exposures	Exposure	Other co-variables considered and/or adjusted	Major findings
Saxén, 1975[233]	Finland	1967-1971	Register of congenital malformations	599/599	Oral clefts and cleft palate	44.4%	Diazepam in the first trimester of pregnancy	Y (matched)	Yes, p<0.001

*nested case-control study
** Examined both antidepressants and anxiolytic drugs
SSRIs=selective serotonin reuptake inhibitors
TCAs=tricyclic antidepressants
UK=United Kingdom
USA=United States of America

Antidepressants

Selective serotonin reuptake inhibitors

Recent large, population-based studies are increasingly focused on the safety of SSRIs overall and individual SSRI drugs, such as paroxetine, sertraline and fluoxetine. For example, a large population-based cohort study carried out by Malm *et al.* in Finland in 2011 using national birth registry data from 1996 to 2006 examined the risks of major congenital anomalies in children of women exposed to SSRIs during the first trimester of pregnancy compared with those not exposed to SSRIs.[53] After adjusting for maternal age at the end of pregnancy, parity, year of pregnancy ending, marital status, smoking during pregnancy, other reimbursed psychiatric drug purchases, and pre-pregnancy diabetes, this study found an association, though not statistically significant, between major congenital anomalies and maternal exposure to SSRIs (OR=1.08, 95% CI 0.96-1.22). Malm *et al.* also examined the teratogenic effects of individual SSRI drugs and found associations between maternal use of paroxetine and right ventricular outflow tract defects, fluoxetine with isolated ventricular septal defects, and citalopram with neural tube defects (OR=2.46, 95% CI 1.20-5.07), suggesting that psychotropic drugs from the same class may work differently in the foetus development, unless the results were chance findings.

In addition, a population-based Australian study included 97,265 pregnancies from national medical and pharmaceutical datasets in 2002-2005 and found increased risks of cardiovascular anomalies in children exposed to SSRIs in the first trimester of pregnancy compared with children unexposed (OR=1.60, 95% CI 1.10-2.31),[200] similar to the findings from an Israeli study (relative risk=2.17, 95% CI 1.07-4.39 for any SSRIs).[203] The Australian study also found similar excess risks for specific SSRI drugs (i.e. citalopram, sertraline, fluoxetine, and paroxetine), though the results were not statistically significant, which could be due to limited study power available for

individual drugs. In addition to the excess risks of congenital heart anomalies, the Australian study found associations of respiratory system anomalies with first trimester exposure to sertraline (OR=3.73, 95% CI 1.18-11.82) and gastrointestinal anomalies with fluoxetine (OR=3.08, 95% CI 1.27-7.48).

Pedersen *et al.* conducted a population-based cohort study using registry data in Denmark from 1996 to 2004 and selected women with two and more SSRI redemptions as exposed (1,370, 0.3% of the study population).[56] The Danish study however only found a higher risk of septal heart defects in children exposed to SSRIs (OR=1.99, 95% CI 1.13-3.53), particularly in children with first trimester exposure to citalopram, sertraline and more than one type of SSRI.

In addition, by pooling data from teratology information service centres of several high-income countries, a prospective, multicentre, observational study found children of women prescribed paroxetine and fluoxetine have higher prevalence of major anomalies than of those prescribed drugs deemed to be non-teratogenic (such as penicillin, cephalosporin).[45] Specifically, this study also demonstrated increased risks of cardiac defects in offspring exposed to these drugs (OR=4.81 and 3.47, 95% CIs 1.56-14.71 and 1.13-10.58 for fluoxetine and paroxetine, respectively) compared to those exposed to non-teratogenic agents. However, after adjustment for concomitant psychotropic medications and other maternal factors (such as maternal smoking), the odds ratio remained significant only for fluoxetine (OR=4.47, 95% CI 1.31-15.27) but not paroxetine (OR=2.66, 95% CI 0.80-8.90). Despite this, the results for fluoxetine are inconsistent and three early studies found no association between fluoxetine during early pregnancy and major malformations in offspring,[48,49,167] except a slightly increased risk in three or more minor anomalies.[49] These early studies however had very small sample sizes (796 maximum) thus may not be able to detect small differences.

Although paroxetine has been increasingly investigated in observational studies, very few have examined the effect of dosage. A previous case-control study in Canada[226] used information from medication and pregnancy registry in 1997-2003 and found that maternal use of paroxetine at more than 25mg per day during the first trimester of pregnancy was associated with increased risks of major congenital anomalies (OR=2.2, 95% CI 1.2-4.2) and mainly congenital anomalies in heart (OR=3.1, 95% CI 1.0-9.4). This Canadian study however had a relatively small number of children with congenital anomalies (101 cases) and nearly half of the cases were exposed.[226] In addition, some other studies on the effects of paroxetine during early pregnancy found no increased risks of congenital heart congenital anomalies in offspring of women prescribed paroxetine.[57,207]

A large US case-control study (9,622 cases obtained through eight national birth-defects surveillance systems and 4,092 controls obtained from hospital or state birth-certificate records) published in 2007 found no association between use of SSRIs and the risks of heart defects but found increased risks in neural tube defects, craniosynostosis and omphalocoele.[227] Another similar US study examined each individual SSRI drug and found use of sertraline was associated with omphalocoele and septal heart defects and paroxetine associated with right ventricular outflow tract obstruction defects.[228] These studies however did not fully assess the effects of the underlying condition and/or other maternal factors which could potentially affect the association of congenital anomalies with maternal exposure to SSRIs.

Tricyclic and other antidepressants

Very few studies have examined the effects of different classes of antidepressant drugs in a single population. Overall, there have been fewer studies specifically focusing on the safety of old antidepressants such as tricyclic antidepressants (TCAs). For example, a population-based study in Sweden that examined maternal drug use

in early pregnancy and infant cardiovascular anomalies found that among many other drugs women were prescribed, maternal exposure to TCAs during early pregnancy was associated with an 80% increased risk of cardiovascular anomalies in offspring (OR=1.77, 95% CI 1.07-2.91) after adjusting for year of birth, maternal age, parity, smoking habits in early pregnancy and years of involuntary childlessness.[230] This study did not find any association with SSRIs and benzodiazepines, although it did not examine the impact for each specific drug class exclusively or concurrently. In addition, a previous large study carried out in British Columbia, Canada found that it was SSRIs combined with benzodiazepines but not SSRIs alone were associated with an increased risk of congenital heart defects.[206]

Anti-anxiety drugs

Although anti-anxiety drugs are commonly prescribed to women of childbearing age, little information is available for the safety of these drugs in women during early pregnancy. A large prospective population-based study using birth register data in Sweden found a borderline increased risk of major malformations in children of women prescribed benzodiazepines during early pregnancy (OR=1.24, 95% CI 1.00-1.55),[220] though other studies in different countries did not find an association.[63–66]

No studies have examined the effects of anti-anxiety drugs with consideration of women's underlying health conditions and concurrent exposures of other medications. Two case-control studies from the 1970s found that women prescribed diazepam (the most commonly prescribed benzodiazepine) in the first trimester of pregnancy had increased risks of facial clefts (oral clefts and clefts palate) in their offspring.[62,233] These two studies had however fairly small sample sizes and did not control for any other maternal underlying health conditions and lifestyle factors. Two more recent and larger case-control studies using similar methods did not find any association

between use of benzodiazepines during early pregnancy and the risk of facial cleft[67,68] and therefore it is unclear that whether such an association really exists.

6.1.2 Lithium, mood stabilisers and antipsychotic drugs

There have been very few studies of the association between serious mental illness and the risk of congenital anomalies and such studies generally have had small numbers, likely due to the fact that both serious mental illness and congenital anomalies are uncommon health conditions in the general population. Far fewer studies were conducted on the safety of antipsychotic drugs and no clear evidence about these exists so far. Although no definitive association has been found between maternal exposure to antipsychotic drugs during pregnancy and an increased risk of congenital anomalies, there is a lack of large, population-based prospective studies.[38] This is similar for the research on the safety of lithium in pregnant women.[187] Recent systematic reviews on the safety of mood stabilisers (including valproate, lamotrigine, and carbamazepine) in women during pregnancy found a higher incidence of major congenital anomalies, especially neural tube defects, in children of women exposed to valproate during pregnancy compared with women exposed to other or no mood stabilisers.[188,189] Since women with these medications are more likely to suffer from severe mental illness and other chronic comorbidity, the reported drug associated risks cannot have excluded the potential impact of underlying mental health conditions.

6.2 Rationale and objectives

Although the potential association of congenital anomalies with psychotropic drugs, especially newly developed antidepressants (such as paroxetine), have been frequently examined in various populations, the results are very inconsistent and there remain no UK-based studies. In addition, there is little information available on the safety of TCAs and benzodiazepines in pregnant women despite their continued use in this population and few studies have examined the contribution of women's underlying mental health condition as well as their non-mental health related comorbidity.

The objectives of this UK population-based cohort study therefore were to estimate the risk prevalence of major and system-specific major congenital anomalies in live-born children with or without maternal depression or anxiety during the first trimester of pregnancy, and to investigate whether children exposed to SSRIs, TCAs or benzodiazepines during early pregnancy had greater risks compared with those unexposed, with consideration of women's depression and/or anxiety and other underlying chronic medical comorbidity.

6.3 Methods

6.3.1 Study population

The study population comprised all singleton live-born children born to linked women aged 15-45 years between 1990 and 2009 from THIN (Population 5 in Figure 2-1). Since there were very few children born to women with serious mental illness (6,124 children of whom 198 had major congenital anomalies; absolute risk=323 per 10,000), I excluded children whose mothers had bipolar disorder, schizophrenia, other serious psychotic disorders or prescriptions for anti-manic and antipsychotic drugs, comprising less than 0.5% of the study population.

6.3.2 Extracting and defining major congenital anomalies

All diagnoses of major congenital anomalies were identified in the children's medical records using Read codes that were classified into 16 system-specific groups according to the European Surveillance of Congenital Malformations (EUROCAT) subgroups,[234] which is based on ICD-10 codes (mainly in Q-chapter). Children with recordings of genetic anomalies and known teratogenic anomalies (such as Read codes for anomalies due to maternal infections and foetal alcohol syndrome) were excluded, comprising less than 0.01% of the original population.

In addition to the system level, I assessed individual specific anomalies for the three most prevalent groups, namely major heart, limb and genital congenital anomalies. In order to directly compare my results with previous research,[53] I grouped major heart congenital anomalies as follows: septal defects (including atrial sepatal defects, ventricular septal defects and atrioventricular septal defects), right ventricular outflow tract defects, left ventricular outflow tract defects and others (including transposition off great vessels, total anomalous pulmonary venous connection, coarctation of the aorta, Ebstein's anomaly, tricuspid atresia and stenosis, patent ductus arterosis, single ventricle, tetralogy of Fallot, and truncus arteriosus). I grouped congenital limb

anomalies into hip dislocation and/or dysplasia, club foot and others (including limb reduction, complete absence of a limb, polydactyly, syndactyly and arthrogryposis multiplex congenital). Congenital anomalies of the genital system were divided into hypospadias and others (including indeterminate sex and other unspecific congenital anomalies).

6.3.3 Definition of antenatal exposures

Maternal exposure to depression and/or anxiety was defined as diagnoses of depression or anxiety during the year before conception and the first trimester. Antenatal exposure to major psychotropic drugs (SSRIs, TCAs, and benzodiazepines) during the first trimester of pregnancy was defined according to the presence or absence of relevant drug prescription in the women's primary care electronic health records from four weeks before the estimated conception dates up to 12 weeks after. The period of four weeks before conception was included to enable inclusion of drug prescriptions received immediately before pregnancy and potentially used during early pregnancy as used just before conception.[53,56,227,228] I therefore grouped children into six mutually exclusive categories according to their mothers' diagnostic and treatment status as follows:

Group 0: No maternal depression or anxiety (non-exposed group).

Group 1: Maternal depression and/or anxiety in the year before conception and the first trimester but with no antidepressant or anti-anxiety drugs during the first trimester of pregnancy.

Group 2: Antenatal exposed to SSRIs (alone – i.e. no TCAs or benzodiazepines) in the first trimester.

Group 3: Antenatal exposed to TCAs (alone) in the first trimester.

Group 4: Antenatal exposed to benzodiazepines (alone) in the first trimester.

Group 5: Antenatal exposed to multiple classes of drugs (i.e. prescriptions of two or three classes of SSRIs, TCAs, and benzodiazepines) in the first trimester.

6.3.4 Maternal socio-demographic characteristics and comorbidity

I identified potential confounders, by extracting data on the following maternal characteristic: maternal age at the end of pregnancy, whether women had ever been a smoker before or during pregnancy, maternal body mass index (BMI, kg/m^2) before pregnancy and socioeconomic deprivation measured using the Townsend Index of Deprivation, in quintiles. Since depression and/or anxiety is often comorbid with other chronic medical conditions that could be associated with increased risks of congenital anomalies in the offspring, I extracted diagnoses of prior asthma, epilepsy, diabetes and hypertension from women's records. Detailed definitions of these co-variables are given in Section 4.3.3.

6.3.5 Statistical analyses

To estimate the disease burden of all major and individual system-specific congenital anomaly groups, we calculated absolute risks (per 10,000 live births) for the total population and children with different antenatal exposures. Since SSRIs were the most commonly prescribed psychotropic drugs in the study population, absolute risks were estimated for children born to women exclusively prescribed each individual SSRI drug, namely fluoxetine, citalopram, paroxetine, sertraline, and escitalopram, during the first trimester of pregnancy, apart from fluvoxamine as this was only prescribed exclusively to 27 women. In addition, I did not include children born to women prescribed more than one type of SSRIs as there were only 523 children and 345 of them were exposed to fluoxetine. Besides absolute risks, I also calculated the number of children exposed to SSRIs when only one would have congenital anomalies that would not have otherwise (number needed to harm), using 1 divided by the absolute risk differences between antenatal exposures to individual SSRI

drugs and not exposed to depression and/or anxiety,[235] in groups showing higher risks with maternal drug use.

Logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for any major and each system-specific group of major congenital anomalies in offspring and maternal depression or anxiety with or without psychotropic medication or with different individual SSRIs during the first trimester of pregnancy, with adjustment for all co-variables. The generalised estimating equation approach with exchangeable correlation structure[236] was applied to control for potential clustering effects for children born to the same women by using women's unique identification number. I repeated the main analysis after restricting the overall population to children born to women who never smoked before childbirth and had no chronic medical comorbidities, with adjustment for the remaining co-variables, namely maternal age, year of childbirth, household socioeconomic status and maternal BMI.

6.3.6 Sample size calculations

I expected that 2.5% of children with at least one major congenital anomaly.[175,237] In addition, based on the results in the previous chapter (Section 5.4), approximately 3% children had maternal exposure to SSRIs during the first trimester of pregnancy and 1% with maternal antenatal exposure to TCAs and benzodiazepines. For each antenatal exposure and system-specific congenital anomaly group pair, I used the absolute numbers in the study population to calculate the desirable sample size to detect a 2.0-fold increased risk of major congenital anomalies in children with different antenatal exposures with over 80% power and a 5% significant level by using GPower 3.1.[238] Based on the series of calculations, I estimated ORs only for exposed groups with large enough numbers of children. For example, I need only 43,663 children to detect a 2-fold increased risk of congenital heart anomalies in exposure to SSRIs with over 80% power and 5% statistical significance, but need at least 318,404 children for digestive system anomalies, in which case OR was not calculated.

6.4 Results

6.4.1 Study population

From Population 5 in Figure 2-1, I identified 349,211 live-born singletons, of which 2.7% had at least one major congenital anomaly. Table 6-4 shows the maternal characteristics of children with and without major congenital anomalies. The median maternal age at the end of pregnancy was 30 years (IQR 26-34). Women whose children had and had not had major congenital anomalies had similar distributions of maternal age, socioeconomic status, maternal smoking before childbirth and maternal BMI before conception. Women whose children had major congenital anomalies were more likely to have chronic medical comorbidities, particularly pre-gestational diabetes (1.8% vs. 1.0%) and epilepsy (0.8% vs. 0.4%), than those whose children had no major congenital anomalies (Table 6-4).

Table 6-5 shows the maternal characteristics in children with different antenatal exposures. Women with depression, anxiety or antenatal psychotropic medications were more likely from socioeconomically deprived groups and to have ever smoked and abnormal BMI than women with no depression or anxiety. These women were also more likely to have other chronic illnesses, including prior diabetes, hypertension, asthma and epilepsy (Table 6-5). Other than SSRIs were prescribed much more in later calendar time compared with TCAs, there was no considerable difference in the women's baseline characteristics by antenatal exposure to different classes of psychotropic drugs (Table 6-5).

Table 6-4 Maternal characteristics of all singleton live-born children and children with and without major congenital anomalies

	All children		Children without CAs		Children with CAs	
	N=349,211		n=339,812		n=9,399	
	n	%	n	%	n	%
Maternal age at the end of pregnancy, years (Median, IQR)	30	26-34	30	26-34	30	26-34
Year of childbirth						
1990-1994	51,448	14.7	49,895	14.7	1,553	16.5
1995-1999	86,611	24.8	84,133	24.8	2,478	26.4
2000-2004	103,256	29.6	100,363	29.5	2,893	30.8
2005-2009	107,896	30.9	105,421	31.0	2,475	26.3
Townsend deprivation index						
1 (Least deprived)	85,164	24.4	82,854	24.4	2,310	24.6
2	67,980	19.5	66,205	19.5	1,775	18.9
3	68,244	19.5	66,389	19.5	1,855	19.7
4	63,293	18.1	61,604	18.1	1,689	18.0
5 (Most deprived)	47,216	13.5	45,875	13.5	1,341	14.3
Missing	17,314	5.0	16,885	5.0	429	4.6
Ever smoked before delivery	132,994	38.1	129,473	38.1	3,521	37.5
BMI before pregnancy (kg/m^2)						
Under-weight (<18.5)	11,351	3.3	11,039	3.2	312	3.3
Normal (18.5-24.9)	154,148	44.1	150,136	44.2	4,012	42.7
Over-weight(25-29.9)	59,016	16.9	57,427	16.9	1,589	16.9
Obese (30-39.9)	32,158	9.2	31,181	9.2	977	10.4
Missing	92,538	26.5	90,029	26.5	2,509	26.7
Diabetes	3,624	1.0	3,454	1.0	170	1.8
Hypertension	10,958	3.1	10,637	3.1	321	3.4
Asthma	23,054	6.6	22,396	6.6	658	7.0
Epilepsy	1,348	0.4	1,274	0.4	74	0.8

CAs=congenital anomalies
IQR=interquartile range
BMI=body mass index

Table 6-5 Numbers and proportions of different maternal characteristics in children with different maternal exposures

Congenital anomalies	No depression or anxiety		Depression or anxiety[a]		SSRIs alone		TCAs alone		Benzodiazepines alone		Multiple classes of drugs[b]	
	n=306,902		n=23,888		n=10,568		n=3,225		n=2,699		n=1,929	
	n	%	n	%	n	%	n	%	n	%	n	%
Maternal age at the end of pregnancy, years (Median, IQR)	30	26-34	29	25-33	29	24-33	29	25-33	30	26-34	29	24-33
Year of childbirth												
1990-1994	47,872	15.6	2,210	9.3	401	3.8	534	16.6	303	11.2	128	6.6
1995-1999	78,111	25.5	4,785	20.0	1,816	17.2	936	29.0	561	20.8	402	20.8
2000-2004	89,145	29.0	7,631	31.9	3,937	37.3	981	30.4	856	31.7	706	36.6
2005-2009	91,774	29.9	9,262	38.8	4,414	41.8	774	24.0	979	36.3	693	35.9
Townsend deprivation index												
1 (Least deprived)	77,551	25.3	4,533	19.0	1,748	16.5	570	17.7	485	18.0	277	14.4
2	60,980	19.9	4,118	17.2	1,615	15.3	552	17.1	453	16.8	262	13.6
3	59,970	19.5	4,659	19.5	2,153	20.4	557	17.3	533	19.7	372	19.3
4	54,043	17.6	5,097	21.3	2,363	22.4	717	22.2	603	22.3	470	24.4
5 (Most deprived)	39,150	12.8	4,354	18.2	2,104	19.9	687	21.3	483	17.9	438	22.7
Missing	15,208	5.0	1,127	4.7	585	5.5	142	4.4	142	5.3	110	5.7
Ever smoked before delivery	110,331	35.9	12,556	52.6	5,938	56.2	1,596	49.5	1,398	51.8	1,175	60.9
BMI before pregnancy (kg/m^2)												
Under-weight (<18.5)	9,589	3.1	1,020	4.3	411	3.9	115	3.6	121	4.5	95	4.9
Normal (18.5-24.9)	135,967	44.3	10,468	43.8	4,435	42.0	1,405	43.6	1,132	41.9	741	38.4
Over-weight(25-29.9)	51,069	16.6	4,528	19.0	1,968	18.6	597	18.5	511	18.9	343	17.8
Obese (30-39.9)	26,630	8.7	2,979	12.5	1,521	14.4	420	13.0	317	11.7	291	15.1
Missing	83,647	27.3	4,893	20.5	2,233	21.1	688	21.3	618	22.9	459	23.8
Diabetes	3,032	1.0	305	1.3	173	1.6	49	1.5	36	1.3	29	1.5
Hypertension	9,332	3.0	851	3.6	462	4.4	123	3.8	118	4.4	72	3.7
Asthma	18,391	6.0	2,440	10.2	1,217	11.5	405	12.6	320	11.9	281	14.6
Epilepsy	1,099	0.4	127	0.5	46	0.4	18	0.6	33	1.2	25	1.3

[a] diagnosed in the year before conception up to the end of the first trimester but with no psychotropic drug prescriptions;
[b] prescribed drugs in at least two different classes during the first trimester; BMI=body mass index ; SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic antidepressants

6.4.2 Absolute risks of major and system-specific congenital anomalies

Table 6-6 shows the numbers and absolute risks of any major and system-specific major congenital anomalies in the total population and also in children with different maternal antenatal exposures. Children born to women with depression and/or anxiety had higher risks of major congenital anomalies than those born to women with no depression or anxiety. This was more marked in children exposed to psychotropic medication (SSRIs and TCAs but not benzodiazepines) during the first trimester of pregnancy. For specific congenital anomalies, heart congenital anomalies were the most common group (76 per 10,000 live births). Compared with children born to women with no depression or anxiety, those children born to women with depression and/or anxiety had higher risks of major heart congenital anomalies, particularly in those with maternal exposure to psychotropic medications during the first trimester.

Table 6-6 Absolute risks (per 10,000 live births) of major congenital anomalies according to antenatal first trimester exposure to maternal depression, anxiety, antidepressant and anxiolytic medications in UK primary care between 1990 and 2009

	All children		No depression or anxiety		Depression and/or anxiety[a]		SSRIs alone		TCAs alone		Benzodiazepines alone		Multiple classes of drugs[b]	
	N=349,211		n=306,902		n=23,888		n=10,568		n=3,225		n=2,699		n=1,929	
	n	n/10,000	n	n/10,000	n	n/10,000	n	n/10,000	n	n/10,000	n	n/10,000	n	n/10,000
All major CAs combined	9,399	269	8,210	268	665	278	307	290	92	285	68	252	57	295
Heart	2,648	76	2,276	74	197	82	99	94	29	90	25	93	22	114
Limb	1,869	54	1,654	54	127	53	50	47	18	56	16	59	4	21
Genital system	1,392	40	1,223	40	106	44	38	36	12	37	4	15	9	47
Urinary system	886	25	756	25	72	30	34	32	10	31	7	26	7	36
Chromosomal	593	17	518	17	49	21	15	14	7	22	3	11	1	5
Oro-facial cleft	471	13	418	14	33	14	14	13	4	12	1	4	1	5
Nervous system	513	15	434	14	40	17	21	20	4	12	5	19	9	47
Musculoskeletal system	468	13	414	13	29	12	15	14	5	16	3	11	2	10
Digestive system	338	10	294	10	20	8	13	12	4	12	4	15	3	16
Eye	331	9	298	10	13	5	13	12	2	6	3	11	2	10
Other malformations[c]	328	9	286	9	23	10	11	10	7	22	1	4	0	0
Respiratory system	222	6	191	6	15	6	10	9	4	12	1	4	1	5
Ear, face and neck	90	3	77	3	13	5	0	0	0	0	0	0	0	0
Abdominal wall	74	2	66	2	2	1	5	5	0	0	1	4	0	0

[a] diagnosed in the mother in the year before conception up to the end of the first trimester but with no psychotropic drug prescriptions
[b] prescribed drugs in at least two different classes during the first trimester
[c] e.g. asplenia, conjoined twins, situs inversus and skin disorders
SSRIs=selective serotonin reuptake inhibitors
TCAs=tricyclic antidepressants
CAs=congenital anomalies

6.4.3 Relative risks of major and system-specific congenital anomalies

The results from statistical analyses are shown in Table 6-7, where missing indicates not enough cases available for the analyses, based on my sample size calculation (Section 6.3.6). There was an increased, though not statistically significant, risk of major congenital anomalies in children exposed to SSRIs during the first trimester, compared with those born to women with no depression or anxiety, after adjusting for all maternal characteristics (OR=1.11, 95% CI 0.99-1.25). Although there were very few children with first trimester exposure to multiple drug classes, 86.8% of them were exposed to SSRIs and the excess risk was fairly similar to children exposed to SSRIs exclusively (adjusted OR=1.10, 95% CI 0.85-1.42). There were no increased risks of major congenital anomalies in children exposed to TCAs (adjusted OR=1.03, 95% CI 0.83-1.27) or benzodiazepines (adjusted OR=0.93, 95% CI 0.73-1.19). For specific congenital anomalies, most 95% CIs of ORs included unity. However, there was an increased risk of major heart congenital anomalies in children exposed to SSRIs during the first trimester (adjusted OR=1.25, 95% CI 1.02-1.53) (Table 6-7). After restricting to children born to women who never smoked before childbirth and had no pre-gestational diabetes, pre-gestational hypertension, asthma or epilepsy, the observed effects decreased for antenatal exposure to psychotropic medication, especially to TCAs and benzodiazepines, but slightly increased for un-medicated illness (Table 6-8).

Table 6-7 Adjusted odds ratios for major congenital anomalies in children with antenatal first trimester exposure to maternal depression, anxiety, antidepressant and anxiolytic medications compared with children born to women with no depression or anxiety

	Depression and/or anxiety[a]	SSRIs alone	TCAs alone	Benzodiazepines alone	Multiple classes of drugs[b]
	n=23,888	n=10,568	n=3,225	n=2,699	n=1,929
	AOR[c] (95% CI)	AOR[c] (95% CI)	AOR[c] (95% CI)	AOR[c] (95% CI)	AOR[c] (95% CI)
All major CAs combined	**1.05 (0.97-1.14)**	**1.11 (0.99-1.25)**	**1.03 (0.83-1.27)**	**0.93 (0.73-1.19)**	**1.10 (0.85-1.42)**
Heart	1.10 (0.95-1.27)	1.25 (1.02-1.53)	1.16 (0.80-1.70)	1.21 (0.80-1.82)	1.48 (0.98-2.26)
Limb	1.03 (0.86-1.24)	0.94 (0.71-1.25)	1.01 (0.63-1.60)	1.11 (0.66-1.87)	0.40 (0.15-1.06)
Genital system	1.11 (0.91-1.35)	0.88 (0.63-1.23)	0.91 (0.52-1.61)	0.36 (0.14-0.97)	1.10 (0.57-2.13)
Urinary system	1.23 (0.96-1.57)	1.33 (0.94-1.88)			
Chromosomal	1.28 (0.94-1.72)	0.92 (0.55-1.55)			
Oro-facial cleft	0.99 (0.69-1.42)	0.95 (0.56-1.62)			
Nervous system	1.19 (0.85-1.64)	1.39 (0.89-2.16)			
Musculoskeletal system	0.92 (0.63-1.35)	1.11 (0.61-2.02)			
Digestive system	0.86 (0.55-1.36)				
Eye	0.56 (0.32-0.99)				
Other malformations[d]	1.14 (0.73-1.78)				
Respiratory system	0.97 (0.57-1.66)				
Ear, face and neck					
Abdominal wall					

[a] diagnosed in the mother in the year before conception up to the end of the first trimester but with no psychotropic drug prescriptions
[b] prescribed drugs in at least two different classes during the first trimester
[c] adjusted for maternal age at the end of pregnancy, year of childbirth, Townsend deprivation index, maternal smoking history, maternal body mass index before pregnancy, maternal pre-existing diabetes, pre-existing hypertension, asthma and epilepsy
[d] e.g. asplenia, conjoined twins, situs inversus and skin disorders
AOR=adjusted odds ratio
SSRIs=selective serotonin reuptake inhibitors
TCAs=tricyclic antidepressant
CI=confidence interval
CAs=congenital anomalies

Table 6-8 Subgroup analyses in children born to women never smoked before childbirth and with no pre-gestational diabetes, pre-gestational hypertension, asthma or epilepsy: Absolute risks (per 10,000 live births) and adjusted odds ratios for major congenital anomalies in children with antenatal first trimester exposure to maternal depression, anxiety, antidepressant and anxiolytic medications compared with children born to women with no depression or anxiety (N=196,745)

	Unexposed	Depression and/or anxiety[a]		SSRIs alone		TCAs alone		Benzodiazepines alone		Multiple classes of drugs[b]	
	n=179,795	n=9,878		n=3,945		n=1,390		n=1,118		n=619	
	n/10,000	n/10,000	AOR[c] (95% CI)	n/10,000	AOR[c] (95% CI)	n/10,000	AOR[c] (95% CI)	n/10,000	AOR[c] (95% CI)	n/10,000	AOR[c] (95% CI)
All major CAs combined	**266**	**288**	**1.10 (0.97-1.24)**	**286**	**1.11 (0.92-1.34)**	**273**	**1.00 (0.71-1.40)**	**179**	**0.67 (0.43-1.04)**	**323**	**1.21 (0.79-1.87)**
Heart	72	89	1.23 (0.99-1.53)	86	1.20 (0.85-1.68)	58	0.79 (0.39-1.59)	45	0.62 (0.26-1.49)	81	1.12 (0.46-2.69)
Limb	58	52	0.98 (0.74-1.31)	53	1.05 (0.68-1.63)	58	1.01 (0.51-2.04)	54	1.00 (0.45-2.22)	32	0.62 (0.16-2.49)
Genital system	38	48	1.25 (0.93-1.68)	28	0.72 (0.39-1.31)	43	1.12 (0.50-2.52)	0		65	1.55 (0.59-4.09)
Urinary system	25	30	1.22 (0.84-1.76)	35	1.43 (0.84-2.45)	29		27		81	
Chromosomal	19	24	1.29 (0.84-1.97)	15	0.83 (0.37-1.86)	14		0		0	
Oro-facial cleft	13	14	1.10 (0.64-1.89)	13	0.98 (0.40-2.38)	14		9		0	
Nervous system	14	22	1.60 (1.03-2.47)	18	1.23 (0.58-2.63)	29		27		32	
Musculoskeletal system	14	9	0.71 (0.36-1.39)	10	0.81 (0.30-2.19)	22		9		16	
Digestive system	9	10	1.08 (0.57-2.03)	15		14		9		0	
Eye	10	7	0.76 (0.36-1.61)	15		7		0		0	
Other malformations[d]	10	13	1.48 (0.83-2.62)	13		0		0		0	
Respiratory system	6	6	0.96 (0.42-2.19)	3		0		9		16	
Ear, face and neck	2	3		0		0		0		0	
Abdominal wall	1	1		5		0		9		0	

[a] diagnosed in the mother in the year before conception up to the end of the first trimester but with no psychotropic drug prescriptions
[b] prescribed drugs in at least two different classes during the first trimester
[c] adjusted for maternal age at the end of pregnancy, year of childbirth, Townsend deprivation index, maternal body mass index before pregnancy
[d] e.g. asplenia, conjoined twins, situs inversus and skin disorders
AOR=adjusted odds ratio
SSRIs=selective serotonin reuptake inhibitors
TCAs=tricyclic antidepressant
CI=confidence interval
CAs=congenital anomalies

6.4.4 Risks of congenital anomalies for individual SSRI drugs

The most commonly prescribed SSRI drugs to the women in the study population during the first trimester of pregnancy were fluoxetine (1.3%), followed by citalopram (0.7%) and paroxetine (0.4%). Table 6-9 shows that the increased risks of heart congenital anomalies were mainly found in children with antenatal exposure to paroxetine (OR=1.89, 95% CI 1.24-2.88) but not in those exposed to fluoxetine (OR=1.02, 95% CI 0.72-1.45) nor citalopram (OR=1.12, 95% CI 0.74-1.71), after adjusted for all maternal characteristics. Also, children exposed to sertraline and escitalopram had increased risks of heart congenital anomalies, although these excess risks were no statistically significant (adjusted ORs=1.53 and 1.83, 95% CIs 0.87-2.69 and 0.82-4.13, respectively).

Nevertheless, the absolute risks of congenital anomalies in children exposed to SSRIs were small. Table 6-10 shows that if only 455 children had antenatal exposure to SSRIs, one would develop major congenital anomalies which otherwise would not have. The number need to harm was much lower for paroxetine and sertraline, particularly for congenital heart anomalies (145 for exposure to paroxetine and 233 for sertraline).

Table 6-9 Absolute risks (per 10,000 live births) and adjusted odds ratios for major congenital anomalies in children born to women exclusively prescribed specific SSRI drugs during the first trimester of pregnancy compared with children born to women with no depression or anxiety

	SSRIs during the first trimester of pregnancy[a]									
	Fluoxetine		**Citalopram**		**Paroxetine**		**Sertraline**		**Escitalopram**	
	n=4,401		**n=2,615**		**n=1,540**		**n=1,028**		**n=434**	
	n/10,000	**AOR[b] (95% CI)**	**n/10,000**	**AOR[b] (95% CI)**	**n/10,000**	**AOR[b] (95% CI)**	**n/10,000**	**AOR[b] (95% CI)**	**n/10,000**	**AOR[b] (95% CI)**
All major CAs combined	**273**	**1.03 (0.86-1.25)**	**298**	**1.17 (0.93-1.48)**	**325**	**1.19 (0.90-1.58)**	**331**	**1.25 (0.88-1.79)**	**276**	**1.11 (0.62-1.96)**
Heart	77	1.02 (0.72-1.45)	84	1.12 (0.74-1.71)	143	1.89 (1.24-2.88)	117	1.53 (0.87-2.69)	138	1.83 (0.82-4.13)
Limb	48	0.94 (0.61-1.45)	50	1.05 (0.61-1.81)	58	1.08 (0.56-2.08)	39	0.77 (0.29-2.06)	23	0.50 (0.07-3.57)
Genital system	27	0.66 (0.38-1.18)	34	0.85 (0.44-1.64)	45	1.10 (0.52-2.32)	39	0.95 (0.29-3.13)	46	1.20 (0.30-4.84)
Urinary system	30		46		26		19		23	
Chromosomal	9		4		26		39		0	
Oro-facial cleft	14		27		0		10		0	
Nervous system	25		19		6		29		23	
Musculoskeletal system	9		19		19		19		0	
Digestive system	18		11		0		19		0	
Eye	16		8		6		10		46	
Other malformations[c]	11		15		0		10		0	
Respiratory system	11		4		6		29		0	
Ear, face and neck	0		0		0		0		0	
Abdominal wall	5		4		0		0		0	

[a] Children born to women treated with each specific SSRI drug exclusively during the first trimester; excluding children born to women treated with fluvoxamine (27 children), multiple SSRI drug classes (523 children) or co-prescribed with other antidepressant or anxiolytic drug classes
[b] adjusted for maternal age at the end of pregnancy, year of childbirth, Townsend deprivation index, maternal smoking history, maternal body mass index before pregnancy, maternal pre-existing diabetes, pre-existing hypertension, asthma and epilepsy
[c] e.g. asplenia, conjoined twins, situs inversus and skin disorders
AOR=adjusted odds ratio
CAs=congenital anomalies
CI=confidence interval
OR=odds ratio
SSRI=selective serotonin reuptake inhibitors

Table 6-10 The number of children exposed to specific SSRI drugs alone during early pregnancy when one would develop major congenital anomalies that would not have otherwise

	SSRIs during the first trimester of pregnancy					
	Any SSRI[a]	**Fluoxetine**	**Citalopram**	**Paroxetine**	**Sertraline**	**Escitalopram**
	n=10,568	**n=4,401**	**n=2,615**	**n=1,540**	**n=1,028**	**n=434**
All major CAs combined	455	2,000	333	175	159	1,250
Heart	500	3,333	1,000	145	233	156
Limb	---	---	---	2,500	---	---
Genital system	---	---	---	2,000	---	1,667
Urinary system	1,429	2,000	476	10,000	---	---
Chromosomal	---	---	---	1,111	455	---
Oro-facial cleft	---	---	769	---	---	---
Nervous system	1,667	909	2,000	---	667	1,111
Musculoskeletal system	10,000	---	1,667	1,667	1,667	---
Digestive system	5,000	1,250	10,000	---	1,111	---
Eye	5,000	1,667	---	---	---	278
Other malformations[b]	10,000	5,000	1,667	---	10,000	---
Respiratory system	3,333	2,000	---	---	435	---
Ear, face and neck	---	---	---	---	---	---
Abdominal wall	3,333	3,333	5,000	---	---	---

[a] Children born to women treated with each specific SSRI drug exclusively during the first trimester; excluding children born to women co-prescribed with other antidepressant or anxiolytic drug classes
[b] e.g. asplenia, conjoined twins, situs inversus and skin disorders
CAs=congenital anomalies
SSRIs=selective serotonin reuptake inhibitors

6.4.5 Risks of specific heart, limb and genital anomalies

Table 6-11 shows the risks of specific congenital anomalies in heart, limb and genital system. Although the 95% CI included unity, there was a 2-fold increased risk of right ventricular outflow tract anomalies in children with maternal antenatal exposure to SSRIs (OR=2.04, 95% CI 0.96-4.35). Similar increased risks of right ventricular outflow tract anomalies were also found in children exposed to TCAs, benzodiazepines and multiple drug classes, although such observed excess risks had less power and certainty. No clear risk pattern was found in specific limb and genital congenital anomalies (Table 6-11). When assessing the risks of specific heart, limb and genital congenital anomalies in children born to women exclusively prescribed specific SSRI drugs during the first trimester of pregnancy (Table 6-12), there were more children with septal defects if they were exposed to paroxetine, sertraline and escitalopram compared with fluoxetine and citalopram.

Table 6-11 Absolute risks (per 10,000 live births) and adjusted odds ratios for specific heart, limb and genital congenital anomalies according to antenatal first trimester exposure to maternal depression, anxiety, antidepressant and anxiolytic medications

Major CAs	No depression or anxiety	Depression and/or anxiety[a]		SSRIs alone		TCAs alone		Benzodiazepines alone		Multiple classes of drugs[b]	
	n=306,902	n=23,888		n=10,568		n=3,225		n=2,699		n=1,929	
	n/10,000	n/10,000	AOR[c] (95% CI)	n/10,000	AOR[c] (95% CI)	n/10,000	AOR[c] (95% CI)	n/10,000	AOR[c] (95% CI)	n/10,000	AOR[c] (95% CI)
Heart											
Septal defect[d]	47	49	1.03 (0.85-1.25)	48	1.04 (0.78-1.38)	65	1.33 (0.87-2.05)	56	1.15 (0.67-1.97)	57	1.19 (0.66-2.16)
ASD	10	11	1.11 (0.74-1.65)	16	1.59 (0.97-2.60)	22	2.03 (0.97-4.25)	15	1.37 (0.41-4.57)	16	1.45 (0.46-4.57)
VSD	33	31	0.94 (0.74-1.19)	27	0.84 (0.58-1.22)	37	1.07 (0.60-1.88)	41	1.20 (0.66-2.17)	41	1.23 (0.61-2.48)
RVOTD	3	5	1.75 (0.98-3.10)	7	2.04 (0.96-4.35)	6	1.93 (0.48-7.77)	7	2.36 (0.58-9.62)	10	3.25 (0.78-13.46)
LVOTD	1	2	1.90 (0.66-5.53)	2	2.15 (0.50-9.26)	3	3.50 (0.47-25.79)	0	---	0	---
Other[e]	32	39	1.16 (0.94-1.45)	50	1.50 (1.14-1.99)	31	0.91 (0.46-1.81)	44	1.33 (0.75-2.36)	47	1.38 (0.72-2.64)
Limb											
Hip dislocation and/or dysplasia	22	16	0.83 (0.60-1.17)	17	0.98 (0.61-1.58)	19	0.85 (0.38-1.89)	15	0.74 (0.28-1.98)	5	0.29 (0.04-2.05)
Club foot	14	18	1.29 (0.95-1.76)	16	1.11 (0.68-1.80)	16	1.05 (0.43-2.54)	19	1.27 (0.52-3.05)	5	0.34 (0.05-2.45)
Other[f]	19	19	1.01 (0.74-1.37)	15	0.81 (0.49-1.33)	22	1.13 (0.53-2.38)	30	1.55 (0.77-3.11)	10	0.54 (0.13-2.15)
Genital system											
Hypospadias	34	41	1.17 (0.95-1.44)	32	0.90 (0.63-1.28)	31	0.89 (0.48-1.65)	15	0.42 (0.16-1.12)	36	0.98 (0.47-2.07)
Other[g]	6	4	0.78 (0.41-1.48)	4	0.73 (0.27-1.97)	6	1.02 (0.25-4.17)	0	---	10	1.87 (0.46-7.55)

[a] diagnosed in the mother in the year before conception up to the end of the first trimester but with no psychotropic drug prescriptions
[b] prescribed drugs in at least two different classes during the first trimester
[c] adjusted for maternal age at the end of pregnancy, year of childbirth, Townsend deprivation index, maternal smoking history, maternal body mass index before pregnancy, maternal pre-existing diabetes, pre-existing hypertension, asthma and epilepsy
[d] atrial, ventricular or combined septal defects
[e] transposition off great vessels, total anomalous pulmonary venous connection, coarctation of the aorta, Ebstein's anomaly, tricuspid atresia and stenosis, patent ductus arterosis, single ventricle, tetralogy of Fallot, truncus arteriosus
[f] limb reduction or complete absence, polydactyly, syndactyly and arthrogryposis multiplex congenital
[g] Including indeterminate sex; AOR=adjusted odds ratio; CAs=congenital anomalies; CI=confidence interval
ASD=atrial septal defects; VSD=ventricular septal defects; RVOTD=right ventricular outflow tract defects; LVOTD=left ventricular outflow tract defects

Table 6-12 Absolute risks of specific heart, limb and genital congenital anomalies in children born to women exclusively prescribed specific SSRI drugs during the first trimester of pregnancy

Major CAs	No depression or anxiety		SSRIs during the first trimester of pregnancy[a]									
			Fluoxetine		Citalopram		Paroxetine		Sertraline		Escitalopram	
	n=306,902		n=4,401		n=2,615		n=1,540		n=1,028		n=434	
	n	n/10,000	n	n/10,000	n	n/10,000	n	n/10,000	n	n/10,000	n	n/10,000
Heart	**2,276**	**74**	**34**	**77**	**22**	**84**	**22**	**143**	**12**	**117**	**6**	**138**
Septal defects	1,436	47	17	39	10	38	12	78	7	68	3	69
ASD	308	10	5	11	5	19	4	26	1	10	0	0
VSD	1,027	33	9	20	4	15	7	45	6	58	3	69
RVOTD	98	3	2	5	3	11	1	6	1	10	0	0
LVOTD	28	1	1	2	1	4	0	0	0	0	0	0
Others	997	32	16	36	14	54	12	78	4	39	5	115
Limb	**1,654**	**54**	**21**	**48**	**13**	**50**	**9**	**58**	**4**	**39**	**1**	**23**
Hip dislocation and/or dysplasia	678	22	8	18	3	11	2	13	3	29	1	23
Club foot	419	14	5	11	8	31	3	19	0	0	0	0
Others	573	19	8	18	3	11	4	26	1	10	0	0
Genital system	**1,223**	**40**	**12**	**27**	**9**	**34**	**7**	**45**	**4**	**39**	**2**	**46**
Hypospadias	1,050	34	10	23	7	27	7	45	4	39	2	46
Others	177	6	2	5	2	8	0	0	0	0	0	0

[a] Children born to women treated with each specific SSRI drug exclusively during the first trimester; excluding children born to women treated with fluvoxamine (27 children), multiple SSRI drug classes (523 children) or co-prescribed with other antidepressant or anxiolytic drug classes

ASD=atrial septal defects; VSD=ventricular septal defects; RVOTD=right ventricular outflow tract defects; LVOTD=left ventricular outflow tract defects; CAs=congenital anomalies

6.5 Discussion

6.5.1 Principal findings

My study shows that there was an 11% increased risk of major congenital anomalies in children born to women prescribed SSRIs during the first trimester of pregnancy compared with those born to women with no depression or anxiety, although the absolute risk was small. This excess risk appeared to be mostly related to an increased risk of heart congenital anomalies. Specifically, there was an increased risk of septal heart defects in children with first trimester exposure to paroxetine, but not to fluoxetine or citalopram, although children exposed to sertraline and escitalopram also showed similar increased risks. For benzodiazepines or TCAs, there were no increased risks of overall major congenital anomalies in children exposed to these drugs. However, the risks of right ventricular outflow tract anomalies were notably higher for all drug classes.

6.5.2 Strengths and limitations

This study is the only UK study that has estimated the risks of major and system-specific major congenital anomalies in children born to women with depression and/or anxiety with and without psychotropic drug treatment during the first trimester of pregnancy. I have also examined the risks of some more specific congenital anomalies (e.g. atrial septal defects) and the safety of individual SSRI drugs. Major congenital anomalies are uncommon conditions, especially when divided into system-specific groups. Power therefore is an important issue to consider before performing any statistical analyses. I conducted sample calculations and estimated ORs only when enough cases were available.

The data were from UK general practices and prospectively recorded by GPs, thus excluding the possibly of recall bias. Since all pregnant women in the UK are required to be registered with a GP in order to benefit from antenatal check and free

medication, it is unlikely that a high proportion of women with depression and/or anxiety, especially those with prescriptions of psychotropic drugs, were not identified through antenatal care. There was potential misclassification in the exposure as a woman receiving a drug prescription may not actually take the medication or take it during the organogenetic period, which could bias my estimates to the null hypothesis.

I have examined the risks of all major and system-specific congenital anomalies in a study population representative of the UK population. In terms of the completeness and specificity of congenital anomalies in these data, THIN prevalence figures are very comparable to UK data from the European congenital anomaly registers (EUROCAT), which are considered the gold standard of population level congential anomaly data (Appendix IV). The prevalence of congenital anomalies diagnosed in the first year of life are very similar to EUROCAT, although as I included major congenital anomalies diagnosed in children any age, and the median follow-up from birth is about 5 years, THIN data overall show a higher prevalence of anomalies than in EUROCAT, particularly for certain systems. Therefore, I believe that this makes THIN data very robust for assessing these congenital anomaly risks.

I have adjusted for the effects of a substantial number of potential confounders, including maternal age, year of childbirth, socio-economic deprivation, maternal smoking history, maternal BMI, and other maternal comorbidities, including pre-gestational diabetes, pre-gestational hypertension, asthma, and epilepsy. Following this the adjusted results remained almost identical to the unadjusted ones. In addition, I have repeated the main analyses after restricting to children born to women who never smoked before childbirth and had none of the mentioned chronic medical conditions I was interested in (please see Table 6-8). The results from the sub-group analyses showed that the increase in the risks of major heart congenital anomalies exposed to medications observed in the main analyses decreased, particularly for TCAs and benzodiazepines, but the relative risk for un-medicated illness increased

slightly compared with non-depression or anxiety. This may suggest that women's underlying mental health problems could also contribute to the observed increased risks.

Although it is impossible to completely separate the effects of psychotropic drugs from more severe illness itself, I have tried to assess the effects of underlying maternal mental health problems (depression or anxiety) on the risks of major congenital anomalies in offspring and I acknowledge that I have not been able to directly quantify the disease severity. It is possible that GPs may prescribe certain SSRIs to pregnant women who have more severe symptoms. However there were not considerably marked differences in women's baseline characteristics based on the different SSRI drugs they were prescribed during pregnancy, except that women were more likely from socioeconomically deprived groups if they were prescribed sertraline and escitalopram compared to women prescribed other SSRI drugs. This may indicate that sertraline and escitalopram could be used to treat women with more severe depressed symptoms and previous research has showed these two drugs significantly more efficacious than fluoxetine and paroxetine.[239]

6.5.3 Interpretation in context of previous studies

In line with the results observed in this study, recent large population-based studies have raised concerns about increased risks of major heart congenital anomalies in children with first trimester exposure to SSRIs,[200,201,209] particularly to paroxetine.[58,207,208,226] However, the results on the risks of specific congenital anomalies with specific drugs have been inconsistent.[45,53,56] In addition, far fewer studies have been conducted to examine the safety of TCAs and benzodiazepines exclusively regarding the risk of major congenital anomalies and majority of such studies have very small sample size.[196] The results from my large population-based study show no increased risks of major congenital anomalies in children with maternal antenatal exposure to TCAs or benzodiazepines, which is consistent to most previous

studies.[64–66,214,240] There are however some other studies showing increased risks.[58,206,230]

Colvin *et al.* conducted a population-based study containing nearly 4,000 births with major congenital anomalies in Western Australia from 2002 to 2005.[200] They found that the risk of congenital heart anomalies was higher in children born to women prescribed an SSRI during the first trimester of pregnancy than in those unexposed (unadjusted OR=1.60, 95%CI 1.10-2.31), but the risk was not increased for overall major congenital anomalies (unadjusted OR=1.05, 95%CI 0.87-1.27).[200] This Australian study also found excess risks of congenital heart anomalies, though not statistically significant, in children with first trimester exposure to specific individual drugs namely sertraline (OR=1.74, 95% CI 0.96-3.17), citalopram (OR=1.48, 95% CI 0.74-2.99), paroxetine (OR=1.76, 95% CI 0.83-3.72) and fluoxetine (OR=1.98, 95% CI 0.74-5.33), compared to those not exposed to SSRI drugs. However, this Australian adjusted their results for maternal age only and did not consider women's underlying mental and physical health problems.

In contrast, a Finish study containing approximately 7,000 children exposed to SSRIs during the first trimester of pregnancy found an increased risk of cardiovascular congenital anomalies in children exposed to fluoxetine (adjusted OR=1.40, 95%CI 1.01-1.95), but not to paroxetine (adjusted OR=1.09, 95%CI 0.66-1.79), after adjustment for maternal age, parity, year of pregnancy ending, marital status, smoking, other psychiatric drug purchases, and prescription reimbursement for pre-pregnancy diabetes.[53]

Very few studies have been conducted to examine the risks of different classes of psychotropic drugs in a single population. A previous study in Sweden[58] including 15,000 children with maternal antenatal exposure to SSRIs from 1995 to 2007 found an increased risk of cardiovascular congenital anomalies in children exposed to

paroxetine (OR=1.66, 95%CI 1.09-2.53), but not to fluoxetine (OR=1.31, 95%CI 0.85-2.02), after adjustment for maternal age, year of childbirth, parity, maternal smoking history and BMI. To some extent, my study is fairly similar to this Swedish study in terms of sample size and results. However, unlike my study finding no excess risks in TCAs, this Swedish study[58] found an increased risk of major congenital anomalies in children with maternal antenatal exposure to TCAs (OR=1.36, 95%CI 1.07-1.72), particularly clomipramine, which was consistently reported in earlier studies of the same dataset.[208,230]

In addition, a previous case-control study in US included 9,622 children with congenital anomalies and 4,092 without congenital anomalies and found children with first trimester exposure to SSRIs overall had no increased risks of congenital heart anomalies or most other specific congenital anomalies.[227] This study however found an increased risks, though not statistically significant, of congenital heart anomalies in children with first trimester exposure to paroxetine (OR=1.7, 95% CI 0.9-3.1), after adjusting for maternal ethnicity, obesity, smoking status and family income. This study also reported increased risks of anecephaly, craniosynostosis and omphalocele in children exposed to SSRIs, specifically to paroxetine (OR=4.2, 95% CI 2.1-8.5) and citalopram (OR=4.0, 1.3-11.9). In contrast, another slightly bigger case-control studies in US[228] (9,849 cases and 5,860 controls) did not find increased risks of craniosynostosis and omphalocele in children exposed to SSRIs overall, but did find statistically significant associations between first trimester exposure to sertraline and excess risks of omphalocele (OR=5.7, 95% CI 14.6-20.7) and septal defects (OR=2.0, 95% CI 1.2-4.0) and between first trimester exposure to paroxetine and right ventricular outflow tract defects (OR=3.3. 95% CI 1.3-8.8).

Pedersen *et al.* conducted a study using data from Danish national registries and identified 1,370 children exposed to SSRIs during the first trimester of pregnancy.[56] After adjustment for maternal age, calendar year, income, marital status, and smoking,

the Danish study reported a significant increased risk of septal heart defects (OR=1.99, 95%CI 1.13-3.53), but not all major cardiovascular anomalies (OR=1.44, 95% CI 0.86-2.40), in children with SSRI exposure compared to unexposed. In addition, the Danish study found excess risks of septal heart defects in children exposed to citalopram (OR=2.5, 95% CI 1.0-6.1), sertraline (OR=3.3, 95% CI 1.2-8.8), and more than one type of SSRIs (OR=4.7, 95% CI 1.7-12.7), but not to fluoxetine and paroxetine. Another recent Danish study published in 2010 also found increased risks of septal heart defects in children exposed to sertraline (OR=3.3, 95% CI 1.5-7.5) and escitalopram (OR=4.2, 95% CI 1.0-17.1), but not to citalopram.[201] These studies however contained very small numbers of exposed cases (e.g. in children with septal heart defects, 5 exposed to citalopram and 4 to sertraline and more than one type of SSRIs[56]), and did not consider women's underlying physical and mental health problems.

6.5.4 Conclusion and implications

The findings of this study indicate an increased risk of major congenital heart anomalies in children born to women prescribed SSRIs, especially paroxetine, during the first trimester of pregnancy. Children with first trimester exposure to sertraline and escitalopram also have similar increased risks of congenital heart anomalies, though the excess risks are not statistically significant. Maternal use of TCAs and benzodiazepines could also be associated with increased risks of specific congenital heart anomalies. Despite this, the overall absolute risk of congenital heart anomalies in the general population and the possible excess risks associated with these psychotropic drugs are still relatively small. GPs, obstetricians and other health professionals are advised to discuss the potential risks and benefits of treated and untreated mental health problems with pregnant women. The findings in this first UK study provide vital information for this purpose and can be used to help communicate

magnitude of risk of major congenital anomalies to women with use of different psychotropic drugs in context of the baseline risk in the general population.

7 Conclusion and implications of the work

7.1 Summary of main findings

7.1.1 Clinical burden of maternal mental illness

The work in this thesis has shown that a substantial burden of maternal mental illness, particularly depression and anxiety, presents to and is managed in UK general practice. Furthermore, GP prescribing of psychotropic drugs, especially antidepressants, has increased considerably in the last two decades in women of childbearing age. Although the number of women with a diagnosis of depression and anxiety has also increased, the increases have been more modest compared with drug prescribing.

Compared with the antenatal period, more women have their first episode or repeated episodes of depression, anxiety or other serious mental illnesses identified and/or treated in general practice in the 9 months after pregnancy. There is also considerable variation in the absolute risks of experiencing maternal mental illness according to different maternal characteristics, such as higher risks in mothers from more socioeconomically deprived areas compared with those from less deprived areas, which persist with increasing maternal age. Women with mental illnesses are also more likely to have ever smoked and to have other comorbidity prior to pregnancy. When women's initial clinical presentation of mental illness is during or after pregnancy, the impact of socioeconomic deprivation is modestly attenuated, indicating that this is only partially due to a history of mental illness commonly recurring in the perinatal period.

7.1.2 Impact of treated and untreated perinatal mental illness

Besides the considerable burden of maternal depression and anxiety in UK primary care, these women are also more likely to have adverse pregnancy outcomes.

Although it is impossible to completely separate the effects of psychotropic drugs from more severe illness itself and other residual confounding, it is likely that women treated with antidepressant or anxiolytic drugs, particularly SSRIs, during pregnancy have small increased risks of unfavourable pregnancy outcomes, such as miscarriage, perinatal death and major congenital anomalies. I found that women with medicated depression and anxiety during pregnancy had 1.5-2 fold increased risks of miscarriage compared to women with no depression or anxiety. In addition, women prescribed SSRIs and benzodiazepines prior to pregnancy had greater risks of miscarriage if they continued to receive these medications than if they did not. The magnitude of the medication-associated risks was similar for perinatal death. I also found that a woman was more likely to have a medical termination of her pregnancy if she had medicated depression or anxiety than if not. The risks associated with termination are often higher than those associated with miscarriage or perinatal death, which indicates the effects were partially but not fully explained by severity of mental illness.

I have carried out the first UK study to assess the absolute and relative risks of major congenital anomalies in children with first trimester exposure to SSRIs, TCAs and benzodiazepines in a single population. The findings show that whilst there was no important increase in the risk of congenital anomalies overall for any drug classes, children with in utero exposure to SSRIs during the first trimester of pregnancy have a small increased risk of congenital heart anomalies. In line with some previous observational studies from other countries, such increased risks are found in children with first trimester exposure to paroxetine (and, with less power, to sertraline and escitalopram), but not to fluoxetine or citalopram, which may suggest a biological mechanism in the association. Despite this, the absolute risk of congenital heart anomalies is relatively small in the general population (7.6 per 1000 children) and the excess risk in children exposed to paroxetine is 6.7 per 1000 children. Further

analyses of specific heart anomalies suggest that the excess risks found in children exposed to paroxetine, sertraline and escitalopram appear to be mostly related to increased risks of septal heart defects, which can be self-limited and mostly spontaneously close in the first year of a child's life.[241–244] For TCAs and benzodiazepines, although no increased risks of overall congenital anomalies were found, my findings support remaining concerns for a potential association with right ventricular outflow tract anomalies.

7.2 Clinical and policy implications from this thesis

This thesis provides evidence that there is a high prevalence of antepartum and postpartum mental illness, mainly depression, presenting to and being treated in UK primary care. Women in more socioeconomically deprived circumstances are at particularly high risk of these illnesses. This reinforces the need for greater recognition at policy level to target detection and effective interventions to high risk women in order to promote general population health.

With regard to the potential teratogenic effects of psychotropic drugs, especially paroxetine, sertraline and escitalopram, clinicians and obstetricians should continue to take a cautious approach to drug treatment in women of childbearing age. When prescribing psychotropic drugs to these women prior to pregnancy, clinicians should be aware of a woman's fertility plan during the treatment period. The findings in this thesis reinforce current guidelines of managing maternal mental illness. Adequate health care should be provided to women with mental illness based on whether they are prior to, in early, in late or after pregnancy, and also in consideration of their mental health history.

GPs and other clinicians should conduct an appropriate psychiatric assessment to evaluate whether a woman need psychotropic drug treatment to control her symptoms, via the initial case identification proposed by NICE guidelines (Appendix V). Considering that current evidence raises uncertainty over the effectiveness of psychotropic medication over non-pharmacological treatment, such as cognitive behaviour therapy particularly in less severe depression, health care professionals should communicate that pharmacological treatment may pose small excess risks of non-live pregnancy outcomes and major congenital anomalies. Although I did not completely exclude the potential effect of disease severity, discontinuing medication when pregnant showed no more harm in the risks of adverse pregnancy outcomes.

The information provided in the thesis could be used to help communicate the magnitude of these risks for women using different psychotropic drugs in context of the baseline risk for all pregnancies in the general population. Finally, the adverse pregnancy effects of mental illness itself when untreated had continued and increased recognition by clinicians and policy makers as a priority for maternal and child health in the UK.

7.3 Suggestions for further research

The work in this thesis, alongside other research using general practice data, has hopefully demonstrated the potential and usefulness of large routinely collected primary care databases for future epidemiological research in maternal mental health. The suggestions in this section are therefore mainly related to database research.

Risks of recurrent mental illness episodes following pregnancy losses

Although there have been several studies on the association between therapeutic abortion and the increased risks of subsequent mental illness, these studies have inadequately controlled for previous mental health problems. Although I have found an increased risk of termination in women with depression or anxiety even after considering their prior pregnancy losses, it would be useful to examine the association between therapeutic termination and subsequent occurrence of mental health problems, and how this in turn impacts upon the outcome of any subsequent pregnancy. One possible way to do this would be to examine two or more consecutive pregnancies in the same woman and assess the changes in risk of termination in women with or without mental illness after the first pregnancy. The fact that the excess risks observed for termination were similar to or higher than those risks for miscarriage and perinatal death also needs to be examined in further research using data with an internal comparison. The potential explanations for observed increased risks of termination and other pregnancy losses related to maternal mental health need further exploration.

Non-pharmacological treatment

In this thesis, due to the limitations of the data, I was unable to evaluate the effectiveness of non-pharmacological treatment compared with drug treatment for women during the perinatal period. One possible way to study this would be to conduct interviews with women with mental illness, preferably linked to primary care

data. Although the potential financial cost of carrying out such research in a great number of women could be substantial, there are few current studies in this area.

Cost-effectiveness of antenatal interventions

Some researchers have suggested foetal echocardiography screening for women taking SSRIs or specifically paroxetine during pregnancy.[245] The cost-effectiveness of such performance needs to be fully assessed in future research.

Serious mental illness and assessment of disease severity

Statistical power is a very important concern for uncommon mental health conditions (e.g. schizophrenia). Even larger studies are needed to assess the potential effects of serious mental illness on the risk of adverse pregnancy outcomes, especially for rare outcomes, such as perinatal death and congenital heart anomalies. Since women with more severe symptoms of mental illness are also more likely to be treated in psychiatric hospitals and outpatient units, especially when they get pregnant, further research links with prospective data collected from hospitals, such as hospital episode statistics, and outpatient units could provide more comprehensive information on the severity of perinatal mental illness.

The effect of psychotropic medication in late pregnancy

Previous research has suggested that maternal use of antidepressants during the third trimester of pregnancy has an adverse impact on early neonatal health, such as respiratory distress syndrome.[59] Less information however is available in UK population. The linked mother-child dataset used in this thesis provides a great opportunity to examine this association in a large representative UK population.

Long-term mental and physical health outcomes in children

Less information is available for the long-term mental and physical health of children born to women with mental illness. The UK primary care data used in this thesis

contain a large cohort of children who are prospectively followed over time. The median time of child follow-up in the linked mother-and-child dataset in THIN is 4.5 years (IQR 1.8-9.0), so this is an ideal dataset to assess the longer-term health outcomes in children exposed to different maternal risk factors during pregnancy. One example is to investigate the impact of pre-existing, antenatal or episodic mental illness in mothers during their children's early life on the risk of developing chronic conditions, such as autism, or acute health outcomes, such as childhood injuries, in offspring over time.

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9 Appendices

9.1 Appendix I Read codes for mental illnesses

A. Read codes for depression

1B17.00	Depressed
1B17.11	C/O - feeling depressed
1B1U.00	Symptoms of depression
1B1U.11	Depressive symptoms
1BT..00	Depressed mood
1BT..11	Low mood
2257.00	O/E - depressed
62T1.00	Puerperal depression
6G00.00	Postnatal depression counselling
E11..12	Depressive psychoses
E112.00	Single major depressive episode
E112.11	Agitated depression
E112.12	Endogenous depression first episode
E112.13	Endogenous depression first episode
E112.14	Endogenous depression
E112000	Single major depressive episode, unspecified
E112100	Single major depressive episode, mild
E112200	Single major depressive episode, moderate
E112300	Single major depressive episode, severe, without psychosis
E112400	Single major depressive episode, severe, with psychosis
E112z00	Single major depressive episode NOS
E113.00	Recurrent major depressive episode
E113.11	Endogenous depression - recurrent
E113000	Recurrent major depressive episodes, unspecified
E113100	Recurrent major depressive episodes, mild
E113200	Recurrent major depressive episodes, moderate
E113300	Recurrent major depressive episodes, severe, no psychosis
E113400	Recurrent major depressive episodes, severe, with psychosis
E113700	Recurrent depression
E113z00	Recurrent major depressive episode NOS
E118.00	Seasonal affective disorder
E11y200	Atypical depressive disorder
E11z200	Masked depression
E130.00	Reactive depressive psychosis
E130.11	Psychotic reactive depression
E135.00	Agitated depression
E200300	Anxiety with depression
E204.00	Neurotic depression reactive type
E204.11	Postnatal depression
E290.00	Brief depressive reaction
E290z00	Brief depressive reaction NOS
E291.00	Prolonged depressive reaction
E2B..00	Depressive disorder NEC
E2B0.00	Postviral depression
E2B1.00	Chronic depression
Eu32.00	[X]Depressive episode
Eu32.11	[X]Single episode of depressive reaction

Eu32.12	[X]Single episode of psychogenic depression
Eu32.13	[X]Single episode of reactive depression
Eu32000	[X]Mild depressive episode
Eu32100	[X]Moderate depressive episode
Eu32200	[X]Severe depressive episode without psychotic symptoms
Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms
Eu32212	[X]Single episode major depression w'out psychotic symptoms
Eu32300	[X]Severe depressive episode with psychotic symptoms
Eu32311	[X]Single episode of major depression and psychotic symptoms
Eu32312	[X]Single episode of psychogenic depressive psychosis
Eu32313	[X]Single episode of psychotic depression
Eu32314	[X]Single episode of reactive depressive psychosis
Eu32400	[X]Mild depression
Eu32y00	[X]Other depressive episodes
Eu32y11	[X]Atypical depression
Eu32z00	[X]Depressive episode, unspecified
Eu32z11	[X]Depression NOS
Eu32z12	[X]Depressive disorder NOS
Eu32z13	[X]Prolonged single episode of reactive depression
Eu32z14	[X] Reactive depression NOS
Eu33.00	[X]Recurrent depressive disorder
Eu33.11	[X]Recurrent episodes of depressive reaction
Eu33.12	[X]Recurrent episodes of psychogenic depression
Eu33.13	[X]Recurrent episodes of reactive depression
Eu33.14	[X]Seasonal depressive disorder
Eu33.15	[X]SAD - Seasonal affective disorder
Eu33000	[X]Recurrent depressive disorder, current episode mild
Eu33100	[X]Recurrent depressive disorder, current episode moderate
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt
Eu33211	[X]Endogenous depression without psychotic symptoms
Eu33212	[X]Major depression, recurrent without psychotic symptoms
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu33311	[X]Endogenous depression with psychotic symptoms
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33315	[X]Recurrent severe episodes of psychotic depression
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Eu33y00	[X]Other recurrent depressive disorders
Eu33z00	[X]Recurrent depressive disorder, unspecified
Eu33z11	[X]Monopolar depression NOS
Eu34100	[X]Dysthymia
Eu34111	[X]Depressive neurosis
Eu34113	[X]Neurotic depression
Eu34114	[X]Persistant anxiety depression
Eu3y111	[X]Recurrent brief depressive episodes
Eu41200	[X]Mixed anxiety and depressive disorder
Eu41211	[X]Mild anxiety depression
Eu53011	[X]Postnatal depression NOS
Eu53012	[X]Postpartum depression NOS
R007z13	[D]Postoperative depression

NOS=not otherwise specified; C/O=complain of; O/E=on examination of

B. Read codes for anxiety

1B13.00	Anxiousness
1B13.11	Anxiousness - symptom
1B1L.00	Stress related problem
1B1T.00	Feeling stressed
1B1V.00	C/O - panic attack
1Ba0.00	Obsessional thoughts
2258.00	O/E - anxious
E200.00	Anxiety states
E200000	Anxiety state unspecified
E200100	Panic disorder
E200111	Panic attack
E200200	Generalised anxiety disorder
E200300	Anxiety with depression
E200400	Chronic anxiety
E200500	Recurrent anxiety
E200z00	Anxiety state NOS
E203.00	Obsessive-compulsive disorders
E203000	Compulsive neurosis
E203100	Obsessional neurosis
E203z00	Obsessive-compulsive disorder NOS
E292y00	Adjustment reaction with mixed disturbance of emotion
E292z00	Adjustment reaction with disturbance of other emotion NOS
E293.00	Adjustment reaction with predominant disturbance of conduct
E293000	Adjustment reaction with aggression
E293100	Adjustment reaction with antisocial behaviour
E293200	Adjustment reaction with destructiveness
E293z00	Adjustment reaction with predominant disturbance conduct NOS
E294.00	Adjustment reaction with disturbance emotion and conduct
E29y.00	Other adjustment reactions
E29y100	Other post-traumatic stress disorder
E29y200	Adjustment reaction with physical symptoms
E29y300	Elective mutism due to an adjustment reaction
E29y400	Adjustment reaction due to hospitalisation
E29y500	Other adjustment reaction with withdrawal
E29yz00	Other adjustment reactions NOS
E29z.00	Adjustment reaction NOS
Eu34114	[X]Persistant anxiety depression
Eu40012	[X]Panic disorder with agoraphobia
Eu41.00	[X]Other anxiety disorders
Eu41000	[X]Panic disorder [episodic paroxysmal anxiety]
Eu41011	[X]Panic attack
Eu41012	[X]Panic state
Eu41100	[X]Generalized anxiety disorder
Eu41111	[X]Anxiety neurosis
Eu41112	[X]Anxiety reaction
Eu41113	[X]Anxiety state
Eu41200	[X]Mixed anxiety and depressive disorder
Eu41211	[X]Mild anxiety depression
Eu41300	[X]Other mixed anxiety disorders
Eu41z00	[X]Anxiety disorder, unspecified
Eu41z11	[X]Anxiety NOS
Eu42.00	[X]Obsessive - compulsive disorder
Eu42.12	[X]Obsessive-compulsive neurosis

Eu42000	[X]Predominantly obsessional thoughts or ruminations
Eu42100	[X]Predominantly compulsive acts [obsessional rituals]
Eu42200	[X]Mixed obsessional thoughts and acts
Eu42z00	[X]Obsessive-compulsive disorder, unspecified
Eu43.00	[X]Reaction to severe stress, and adjustment disorders
Eu43000	[X]Acute stress reaction
Eu43011	[X]Acute crisis reaction
Eu43012	[X]Acute reaction to stress
Eu43014	[X]Crisis state
Eu43100	[X]Post - traumatic stress disorder
Eu43111	[X]Traumatic neurosis
Eu43200	[X]Adjustment disorders
Eu43y00	[X]Other reactions to severe stress
Eu43z00	[X]Reaction to severe stress, unspecified
Eu51511	[X]Dream anxiety disorder
Z4L1.00	Anxiety counselling

C/O=complain of; O/E=on examination of

C. Read codes for bipolar disorder

1BY..00	Elevated mood
225C.00	O/E - elated
E11..11	Bipolar psychoses
E11..13	Manic psychoses
E110.00	Manic disorder, single episode
E110.11	Hypomanic psychoses
E110000	Single manic episode, unspecified
E110100	Single manic episode, mild
E110200	Single manic episode, moderate
E110300	Single manic episode, severe without mention of psychosis
E110400	Single manic episode, severe, with psychosis
E110z00	Manic disorder, single episode NOS
E111.00	Recurrent manic episodes
E111000	Recurrent manic episodes, unspecified
E111100	Recurrent manic episodes, mild
E111200	Recurrent manic episodes, moderate
E111300	Recurrent manic episodes, severe without mention psychosis
E111400	Recurrent manic episodes, severe, with psychosis
E111z00	Recurrent manic episode NOS
E114.00	Bipolar affective disorder, currently manic
E114.11	Manic-depressive - now manic
E114000	Bipolar affective disorder, currently manic, unspecified
E114100	Bipolar affective disorder, currently manic, mild
E114200	Bipolar affective disorder, currently manic, moderate
E114300	Bipolar affect disord, currently manic, severe, no psychosis
E114400	Bipolar affect disord, currently manic,severe with psychosis
E115.00	Bipolar affective disorder, currently depressed
E115.11	Manic-depressive - now depressed
E115000	Bipolar affective disorder, currently depressed, unspecified
E115100	Bipolar affective disorder, currently depressed, mild
E115200	Bipolar affective disorder, currently depressed, moderate
E115300	Bipolar affect disord, now depressed, severe, no psychosis
E115400	Bipolar affect disord, now depressed, severe with psychosis
E116.00	Mixed bipolar affective disorder
E116000	Mixed bipolar affective disorder, unspecified
E116200	Mixed bipolar affective disorder, moderate
E116300	Mixed bipolar affective disorder, severe, without psychosis
E116400	Mixed bipolar affective disorder, severe, with psychosis
E116z00	Mixed bipolar affective disorder, NOS
E117.00	Unspecified bipolar affective disorder
E117000	Unspecified bipolar affective disorder, unspecified
E117100	Unspecified bipolar affective disorder, mild
E117200	Unspecified bipolar affective disorder, moderate
E117300	Unspecified bipolar affective disorder, severe, no psychosis
E117400	Unspecified bipolar affective disorder,severe with psychosis
E117z00	Unspecified bipolar affective disorder, NOS
E11y.00	Other and unspecified manic-depressive psychoses
E11y000	Unspecified manic-depressive psychoses
E11y100	Atypical manic disorder
E11y300	Other mixed manic-depressive psychoses
E11yz00	Other and unspecified manic-depressive psychoses NOS
Eu30.00	[X]Manic episode
Eu30.11	[X]Bipolar disorder, single manic episode

Eu30000	[X]Hypomania
Eu30100	[X]Mania without psychotic symptoms
Eu30200	[X]Mania with psychotic symptoms
Eu30212	[X]Mania with mood-incongruent psychotic symptoms
Eu30y00	[X]Other manic episodes
Eu30z11	[X]Mania NOS
Eu31.00	[X]Bipolar affective disorder
Eu31.11	[X]Manic-depressive illness
Eu31.12	[X]Manic-depressive psychosis
Eu31.13	[X]Manic-depressive reaction
Eu31000	[X]Bipolar affective disorder, current episode hypomanic
Eu31100	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Eu31200	[X]Bipolar affect disorder cur epi manic with psychotic symp
Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn
Eu31400	[X]Bipol aff disord, curr epis sev depress, no psychot symp
Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp
Eu31600	[X]Bipolar affective disorder, current episode mixed
Eu31y00	[X]Other bipolar affective disorders
Eu31z00	[X]Bipolar affective disorder, unspecified
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu34000	[X]Cyclothymia
Eu3y011	[X]Mixed affective episode

O/E=on examination of

D. Read codes for schizophrenia and other related psychoses

1B1E.00	Hallucinations
1BH..00	Delusions
1BH..11	Delusion
E1...00	Non-organic psychoses
E10..00	Schizophrenic disorders
E100.00	Simple schizophrenia
E100000	Unspecified schizophrenia
E100100	Subchronic schizophrenia
E100200	Chronic schizophrenic
E100300	Acute exacerbation of subchronic schizophrenia
E100400	Acute exacerbation of chronic schizophrenia
E100z00	Simple schizophrenia NOS
E101.00	Hebephrenic schizophrenia
E101000	Unspecified hebephrenic schizophrenia
E101100	Subchronic hebephrenic schizophrenia
E101200	Chronic hebephrenic schizophrenia
E101300	Acute exacerbation of subchronic hebephrenic schizophrenia
E101400	Acute exacerbation of chronic hebephrenic schizophrenia
E101z00	Hebephrenic schizophrenia NOS
E102.00	Catatonic schizophrenia
E102000	Unspecified catatonic schizophrenia
E102100	Subchronic catatonic schizophrenia
E102200	Chronic catatonic schizophrenia
E102300	Acute exacerbation of subchronic catatonic schizophrenia
E102400	Acute exacerbation of chronic catatonic schizophrenia
E102z00	Catatonic schizophrenia NOS
E103.00	Paranoid schizophrenia
E103000	Unspecified paranoid schizophrenia
E103100	Subchronic paranoid schizophrenia
E103200	Chronic paranoid schizophrenia
E103300	Acute exacerbation of subchronic paranoid schizophrenia
E103400	Acute exacerbation of chronic paranoid schizophrenia
E103z00	Paranoid schizophrenia NOS
E104.00	Acute schizophrenic episode
E104.11	Oneirophrenia
E105.00	Latent schizophrenia
E105000	Unspecified latent schizophrenia
E105100	Subchronic latent schizophrenia
E105200	Chronic latent schizophrenia
E105300	Acute exacerbation of subchronic latent schizophrenia
E105400	Acute exacerbation of chronic latent schizophrenia
E105z00	Latent schizophrenia NOS
E106.00	Residual schizophrenia
E106.11	Restzustand - schizophrenia
E107.00	Schizo-affective schizophrenia
E107.11	Cyclic schizophrenia
E107000	Unspecified schizo-affective schizophrenia
E107100	Subchronic schizo-affective schizophrenia
E107200	Chronic schizo-affective schizophrenia
E107300	Acute exacerbation subchronic schizo-affective schizophrenia
E107400	Acute exacerbation of chronic schizo-affective schizophrenia
E107z00	Schizo-affective schizophrenia NOS
E10y.00	Other schizophrenia

E10y.11	Cenesthopathic schizophrenia
E10y000	Atypical schizophrenia
E10y100	Coenesthopathic schizophrenia
E10yz00	Other schizophrenia NOS
E10z.00	Schizophrenia NOS
E11..00	Affective psychoses
E11..11	Bipolar psychoses
E11..12	Depressive psychoses
E11..13	Manic psychoses
E110.11	Hypomanic psychoses
E110400	Single manic episode, severe, with psychosis
E111400	Recurrent manic episodes, severe, with psychosis
E112400	Single major depressive episode, severe, with psychosis
E113400	Recurrent major depressive episodes, severe, with psychosis
E114400	Bipolar affect disord, currently manic,severe with psychosis
E115400	Bipolar affect disord, now depressed, severe with psychosis
E116400	Mixed bipolar affective disorder, severe, with psychosis
E117400	Unspecified bipolar affective disorder,severe with psychosis
E11y.00	Other and unspecified manic-depressive psychoses
E11y000	Unspecified manic-depressive psychoses
E11y300	Other mixed manic-depressive psychoses
E11yz00	Other and unspecified manic-depressive psychoses NOS
E11z.00	Other and unspecified affective psychoses
E11z000	Unspecified affective psychoses NOS
E11zz00	Other affective psychosis NOS
E12..00	Paranoid states
E120.00	Simple paranoid state
E121.00	Chronic paranoid psychosis
E122.00	Paraphrenia
E123.11	Folie a deux
E12y.00	Other paranoid states
E12yz00	Other paranoid states NOS
E12z.00	Paranoid psychosis NOS
E13..00	Other nonorganic psychoses
E13..11	Reactive psychoses
E130.00	Reactive depressive psychosis
E130.11	Psychotic reactive depression
E131.00	Acute hysterical psychosis
E132.00	Reactive confusion
E133.00	Acute paranoid reaction
E134.00	Psychogenic paranoid psychosis
E13y.00	Other reactive psychoses
E13y000	Psychogenic stupor
E13y100	Brief reactive psychosis
E13yz00	Other reactive psychoses NOS
E13z.00	Nonorganic psychosis NOS
E13z.11	Psychotic episode NOS
E1y..00	Other specified non-organic psychoses
E1z..00	Non-organic psychosis NOS
E212200	Schizotypal personality
Eu2..00	[X]Schizophrenia, schizotypal and delusional disorders
Eu20.00	[X]Schizophrenia
Eu20000	[X]Paranoid schizophrenia
Eu20011	[X]Paraphrenic schizophrenia

Eu20100	[X]Hebephrenic schizophrenia
Eu20111	[X]Disorganised schizophrenia
Eu20200	[X]Catatonic schizophrenia
Eu20211	[X]Catatonic stupor
Eu20212	[X]Schizophrenic catalepsy
Eu20213	[X]Schizophrenic catatonia
Eu20214	[X]Schizophrenic flexibilatis cerea
Eu20300	[X]Undifferentiated schizophrenia
Eu20311	[X]Atypical schizophrenia
Eu20400	[X]Post-schizophrenic depression
Eu20500	[X]Residual schizophrenia
Eu20511	[X]Chronic undifferentiated schizophrenia
Eu20512	[X]Restzustand schizophrenic
Eu20600	[X]Simple schizophrenia
Eu20y00	[X]Other schizophrenia
Eu20y11	[X]Cenesthopathic schizophrenia
Eu20y12	[X]Schizophreniform disord NOS
Eu20y13	[X]Schizophrenifrm psychos NOS
Eu20z00	[X]Schizophrenia, unspecified
Eu21.00	[X]Schizotypal disorder
Eu21.11	[X]Latent schizophrenic reaction
Eu21.12	[X]Borderline schizophrenia
Eu21.13	[X]Latent schizophrenia
Eu21.14	[X]Prepsychotic schizophrenia
Eu21.15	[X]Prodromal schizophrenia
Eu21.16	[X]Pseudoneurotic schizophrenia
Eu21.17	[X]Pseudopsychopathic schizophrenia
Eu21.18	[X]Schizotypal personality disorder
Eu22.00	[X]Persistent delusional disorders
Eu22000	[X]Delusional disorder
Eu22011	[X]Paranoid psychosis
Eu22012	[X]Paranoid state
Eu22013	[X]Paraphrenia - late
Eu22014	[X]Sensitiver Beziehungswahn
Eu22015	[X]Paranoia
Eu22100	[X]Delusional misidentification syndrome
Eu22111	[X]Capgras syndrome
Eu22200	[X]Cotard syndrome
Eu22y00	[X]Other persistent delusional disorders
Eu22y11	[X]Delusional dysmorphophobia
Eu22y12	[X]Involutional paranoid state
Eu22y13	[X]Paranoia querulans
Eu22z00	[X]Persistent delusional disorder, unspecified
Eu23.00	[X]Acute and transient psychotic disorders
Eu23000	[X]Acute polymorphic psychot disord without symp of schizoph
Eu23011	[X]Bouffee delirante
Eu23012	[X]Cycloid psychosis
Eu23100	[X]Acute polymorphic psychot disord with symp of schizophren
Eu23111	[X]Bouffee delirante with symptoms of schizophrenia
Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia
Eu23200	[X]Acute schizophrenia-like psychotic disorder
Eu23211	[X]Brief schizophreniform disorder
Eu23212	[X]Brief schizophrenifrm psych

Eu23213	[X]Oneirophrenia
Eu23214	[X]Schizophrenic reaction
Eu23300	[X]Other acute predominantly delusional psychotic disorders
Eu23312	[X]Psychogenic paranoid psychosis
Eu23y00	[X]Other acute and transient psychotic disorders
Eu23z00	[X]Acute and transient psychotic disorder, unspecified
Eu23z11	[X]Brief reactive psychosis NOS
Eu23z12	[X]Reactive psychosis
Eu24.00	[X]Induced delusional disorder
Eu24.11	[X]Folie a deux
Eu24.12	[X]Induced paranoid disorder
Eu24.13	[X]Induced psychotic disorder
Eu25.00	[X]Schizoaffective disorders
Eu25000	[X]Schizoaffective disorder, manic type
Eu25011	[X]Schizoaffective psychosis, manic type
Eu25012	[X]Schizophreniform psychosis, manic type
Eu25100	[X]Schizoaffective disorder, depressive type
Eu25111	[X]Schizoaffective psychosis, depressive type
Eu25112	[X]Schizophreniform psychosis, depressive type
Eu25200	[X]Schizoaffective disorder, mixed type
Eu25211	[X]Cyclic schizophrenia
Eu25212	[X]Mixed schizophrenic and affective psychosis
Eu25y00	[X]Other schizoaffective disorders
Eu25z00	[X]Schizoaffective disorder, unspecified
Eu25z11	[X]Schizoaffective psychosis NOS
Eu2y.00	[X]Other nonorganic psychotic disorders
Eu2y.11	[X]Chronic hallucinatory psychosis
Eu2z.00	[X]Unspecified nonorganic psychosis
Eu2z.11	[X]Psychosis NOS
Eu32300	[X]Severe depressive episode with psychotic symptoms
Eu32311	[X]Single episode of major depression and psychotic symptoms
Eu32312	[X]Single episode of psychogenic depressive psychosis
Eu32313	[X]Single episode of psychotic depression
Eu32314	[X]Single episode of reactive depressive psychosis
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu33311	[X]Endogenous depression with psychotic symptoms
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33315	[X]Recurrent severe episodes of psychotic depression
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Eu53111	[X]Puerperal psychosis NOS
R001.00	[D]Hallucinations
R001000	[D]Hallucinations, auditory
R001100	[D]Hallucinations, gustatory
R001200	[D]Hallucinations, olfactory
R001300	[D]Hallucinations, tactile
R001400	[D]Visual hallucinations
R001z00	[D]Hallucinations NOS

9.2 Appendix II BNF codes for psychotropic drugs

A. BNF codes for list of antidepressants

BNF code	04.03.01.00	04.03.02.00	04.03.03.00	04.03.04.00
List of drugs	Amitriptyline Hydrochloride	Iproniazid	Citalopram	Duloxetine
	Amoxapine	Isocarboxazid	Escitalopram	Flupentixol
	Butriptyline	Moclobemide	Fluoxetine	L-tryptophan
	Clomipramine	Phenelzine	Fluvoxamine	Mirtazapine
	Desipramine	Tranylcypromine	Paroxetine	Nefazodone
	Dibenzepin Hydrochloride	Trifluoperazine	Sertraline	Reboxetine
	Dosulepin			Tryptophan
	Dothiepin Hydrochloride			Venlafaxine
	Doxepin			
	Imipramine			
	Iprindole			
	Lofepramine			
	Maprotiline			
	Mianserin			
	Nomifensine Hydrogen Maleate			
	Nortriptyline			
	Opipramol Hydrochloride			
	Protriptyline			
	Trazodone			
	Trimipramine Maleate			
	Viloxazine			
	Zimeldine Hydrochloride			

B. BNF codes for list of hypnotics and anxiolytics

BNF code	04.01.01.00	04.01.02.00
List of drugs	Chloral Hydrate	Alprazolam
	Clomethiazole	Bromazepam
	Dipenhydramine	Buspirone Hydrochloride
	Flunitrazepam	Chlordiazepoxide Hydrochloride
	Flurazepam	Chlormezanone
	Loprazolam	Diazepam
	Lormetazepam	Ketazolam
	Melatonin	Lorazepam
	Methyprylone	Medazepam
	Nitrazepam	Meprobamate
	Nitrados	Oxazepam
	Promethazine	Prazepam
	Temazepam	Sardiazepam
	Triazolam	
	Zaleplon	
	Zolpidem Tartrate	
	Zopiclone	

C. BNF codes for list of lithium and mood stabilisers

BNF code	04.02.03.00	04.08.01.00
List of drug(s)	Lithium	Carbamazepine Sodium Valproate Valproic acid

D. BNF codes for list of antipsychotics

BNF code	04.02.01.00	04.02.02.00
List of drugs	Amisulpride	Flupentixol Decanoate
	Aripiprazole	Fluphenazine Decanoate
	Benperidol	Fluspirilene
	Chlorpromazine	Haloperidol
	Clozapine	Pipotiazine Palmitate
	Cyamemazine	Zuclopenthixol Decanoate
	Droperidol	
	Flupentixol	
	Fluphenazine	
	Haloperidol	
	Levomepromazine	
	Loxapine	
	Olanzapine	
	Oxypertine	
	Paliperidone	
	Pericyazine	
	Perphenazine	
	Pimozide	
	Promazine	
	Quetiapine	
	Remoxipride	
	Risperidone	
	Sertindole	
	Sulpiride	
	Thiopropazate Hydrochloride	
	Trifluoperazine	
	Zotepine	
	Zuclopenthixol Dihydrochloride	
	Ziprasidone	

9.3 Appendix III Edinburgh Postnatal Depression Scale (EPDS)

Edinburgh Postnatal Depression Scale[1] (EPDS)

Name: _____ Address: _____

Your Date of Birth: _____ _____

Baby's Date of Birth: _____ Phone: _____

As you are pregnant or have recently had a baby, we would like to know how you are feeling. Please check the answer that comes closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today.

Here is an example, already completed.

I have felt happy:
- ☐ Yes, all the time
- ☒ Yes, most of the time — This would mean: "I have felt happy most of the time" during the past week.
- ☐ No, not very often — Please complete the other questions in the same way.
- ☐ No, not at all

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - ☐ As much as I always could
   - ☐ Not quite so much now
   - ☐ Definitely not so much now
   - ☐ Not at all

2. I have looked forward with enjoyment to things
   - ☐ As much as I ever did
   - ☐ Rather less than I used to
   - ☐ Definitely less than I used to
   - ☐ Hardly at all

*3. I have blamed myself unnecessarily when things went wrong
   - ☐ Yes, most of the time
   - ☐ Yes, some of the time
   - ☐ Not very often
   - ☐ No, never

4. I have been anxious or worried for no good reason
   - ☐ No, not at all
   - ☐ Hardly ever
   - ☐ Yes, sometimes
   - ☐ Yes, very often

*5 I have felt scared or panicky for no very good reason
   - ☐ Yes, quite a lot
   - ☐ Yes, sometimes
   - ☐ No, not much
   - ☐ No, not at all

*6. Things have been getting on top of me
   - ☐ Yes, most of the time I haven't been able to cope at all
   - ☐ Yes, sometimes I haven't been coping as well as usual
   - ☐ No, most of the time I have coped quite well
   - ☐ No, I have been coping as well as ever

*7 I have been so unhappy that I have had difficulty sleeping
   - ☐ Yes, most of the time
   - ☐ Yes, sometimes
   - ☐ Not very often
   - ☐ No, not at all

*8 I have felt sad or miserable
   - ☐ Yes, most of the time
   - ☐ Yes, quite often
   - ☐ Not very often
   - ☐ No, not at all

*9 I have been so unhappy that I have been crying
   - ☐ Yes, most of the time
   - ☐ Yes, quite often
   - ☐ Only occasionally
   - ☐ No, never

*10 The thought of harming myself has occurred to me
   - ☐ Yes, quite often
   - ☐ Sometimes
   - ☐ Hardly ever
   - ☐ Never

Administered/Reviewed by _____ Date _____

[1] Source: Cox, J.L, Holden, J.M., and Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786.

9.4 Appendix IV Risk estimates of major and system-specfic congenital anomalies identified in THIN and in EUROCAT

	THIN population				EUROCAT population[a]	
	N=349,211				N=3,254,489	
	Diagnosed at any age		Diagnosed before age 1			
	n	n/10,000	n	n/10,000	n	n/10,000
All major CAs combined	**9,399**	**269**	**6,880**	**197**	**54,499**	**168**
Heart	2,648	76	2,096	60	14,996	46
Limb	1,869	54	1,461	42	9,195	28
Genital system	1,392	40	994	28	4,862	15
Urinary system	886	25	653	19	7,297	22
Chromosomal	593	17	461	13	5,896	18
Oro-facial cleft	471	13	405	12	4,582	14
Nervous system	513	15	318	9	2,943	9
Musculoskeletal system	468	13	289	8	1,861	6
Digestive system	338	10	290	8	4,755	15
Eye	331	9	201	6	1,188	4
Other malformations[b]	328	9	151	4	1,420	4
Respiratory system	222	6	189	5	1,592	5
Ear, face and neck	90	3	51	1	429	1
Abdominal wall	74	2	72	2	1,605	5

[a] Data were extracted from EUROCAT website (http://www.eurocat-network.eu/) by Rachel Sokal; [b] e.g. asplenia, conjoined twins, situs inversus and skin disorders

9.5 Appendix V NICE clinical guideline on identification and recognition of depression in UK general practice

Case identification and recognition[1]

Be alert to possible depression (particularly in people with a past history of depression or a chronic physical health problem with associated functional impairment) and consider asking people who may have depression two questions, specifically:

- During the last month, have you often been bothered by feeling down, depressed or hopeless?
- During the last month, have you often been bothered by having little interest or pleasure in doing things?

If a person answers 'yes' to either of the depression identification questions (see 1.3.1.1) but the practitioner is not competent to perform a mental health assessment, they should refer the person to an appropriate professional. If this professional is not the person's GP, inform the GP of the referral.

If a person answers 'yes' to either of the depression identification questions (see 1.3.1.1), a practitioner who is competent to perform a mental health assessment should review the person's mental state and associated functional, interpersonal and social difficulties.

[1] National institute for Health and Clinical Excellence. Depression: The treatment and management of depression in adults. 2009. Available at: http://www.nice.org.uk/guidance/index.jsp?action=byID&o=12329.