Early comorbid parental depression and its effects on child outcomes

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Declaration

I, Linda Petronella Martina Maria Wijlaars confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Background: Although depression can affect anyone at any time, the first year after the birth of a child appears to be a time when both parents are more likely to experience depression. Research has mainly focussed on maternal perinatal or early depression which has an estimated incidence of 10-15%. Less is known about early paternal depression or early comorbid depression, where both parents experience depression.

Methods: I conduct a systematic review on the prevalence of early comorbid parental depression and associated childhood outcomes. Next, I explore adolescent depression recording in UK primary care, and trends over time. Finally, I use structural equation modelling to provide a quantitative analysis of the association between early comorbid parental depression and adolescent outcomes, focussing on the effects of recurrent parental depression and internalizing behaviours in childhood. I examine depression and its intergenerational transmission using data from a large UK primary care database, The Health Improvement Network (THIN).

Results: Prevalence of early comorbid depression in parents ranged from 0 to 20%. However, it was not feasible to perform a meta-analysis due to measurement variation and study quality. I identified only two studies assessing child outcomes. Diagnoses of adolescent depression and antidepressant prescribing have increased in recent years despite a temporary drop in 2002-2005. Symptom recording increased steadily between 1995-2009. I did not find evidence for an association between early comorbid parental depression and adolescent depression (OR: 2.02, 95% CI: 0.42-9.67). Early maternal depression does increase the risk of adolescent depression. The effect is mainly indirect, mediated by recurrent parental depression (OR: 1.54, 95% CI: 1.26-1.87), as opposed to direct (OR: 1.06, 95% CI: 0.69-1.63). Childhood internalizing behaviour might be an early indicator of depression risk.

Conclusion: Early parental depression increases the risk of adolescent depression, but the effect is strongly mediated by recurrent parental depression.

Samenvatting van de thesis

Summary in Dutch

Achtergrond: Hoewel depressie een aandoening is die iedereen op elk moment kan treffen, lijkt het eerste jaar na de geboorte van een kind een tijd te zijn waarin beide ouders een verhoogd risico op depressie hebben. Tot dusver heeft onderzoek zich vooral gericht op depressie in moeders rond de geboorte (perinatale of vroege depressie), een stoornis die in 10-15% van nieuwe moeders voorkomt. We weten minder over vroege depressie in vaders en comorbide depressie, waarbij beide ouders een depressive episode ervaren.

Methoden: In mijn thesis presenteer ik een literatuurstudie naar het vrkomen (prevalentie) van comorbide vroege depressie in ouders en gezondheidsgerelateerde gevolgen in hun kinderen. Daarnaast onderzoek ik de registratie van depressie in kinderen in de elektronische patintendossiers van huisarten in het Verenigd Koninkrijk, en kijk of en hoe dit is veranderd tussen 1995 en 2009. Tenslotte gebruik ik Structural Equation Modelling (SEM) voor een kwantitatieve analyse van de associatie tussen vroege comorbide depressie in ouders en depressie in hun kinderen. Hierbij richt ik mij vooral op de effecten van chronische depressie in ouders en symptomen die kunnen wijzen op internaliserend gedrag (gedrag waarbij men in zichzelf keert en een schadelijke uitwerking heeft waarbij een person zichzelf i.p.v. anderen schade kan berokkenen) in kinderen. Ik onderzoek depressie en de overdracht deze stoornis van de ene op de andere generatie met behulp van The Health Improvement Network (THIN) database, een grote Britse database van elektronische patintendossiers van huisarten.

Resultaten: Schattingen van het aantal ouders dat beide vroege depressie ervaart variren van 0 tot 20%. Het was niet mogelijk om middels een meta-analyse een puntschatting te maken doordat de geïncludeerde studies sterk verschilden in hoe en wanneer depressie gemeten werd, en in studie kwaliteit. Ik kon slechts twee studies identificeren

die gevolgen voor de gezondheid van kinderen hadden gemeten. Diagnoses en recepten voor antidepressiva voor adolescenten zijn de afgelopen jaar sterk toegenomen, ondanks een tijdelijke dip tussen 2002 en 2005. Registratie van symptomen van depressie steeg gestaag tussen 1995 en 2009. Ik heb geen bewijs gevonden voor een associatie tussen vroege comorbide depressie in ouders en depressie in adolescenten (OR: 2.02, 95% BI: 0.42-9.67). Vroege depressie in moeders verhoogt het risico of depressie in adolescenten. Dit effect is voornamelijk indirect en wordt gemedieerd door recidiverende depressie (OR: 1.54, 95% BI: 1.26-1.87). Het directe effect van vroege depressie op depressie in adolescenten is verwaarloosbaar (OR: 1.06, 95% BI: 0.69-1.63). Internalisatie symptomen in kinderen lijken een belangrijke vroege indicator te zijn van een verhoogd risico op depressie als adolescent.

Conclusie: Vroege depressie in ouders verhoogt het risico op depressie in adolescenten. Echter, dit effect speelt slechts voor kinderen van ouders met recidiverende depressie.

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Contents

5-HTT	Serotonin Transporter
5-HTTLPR	Serotonin Transporter-Linked Polymorphic Region
ACU	Acceptable Computer Usage
AD	Antidepressant
ADHD	Attention Deficit Hyperactivity Syndrome
ALSPAC	Avon Longitudinal Study of Parents and Children
AMR	Acceptable Mortality Reporting
APC	Annual Percentage Change
ASD	Autism Spectrum Disorders
BAP	British Association for Psychopharmacology
BCS70	1970 British Cohort Study
BDI	Beck Depression Inventory
BGA	Bundesgesundheitsamt
BIC	Bayesian information criteria
BNF	British National Formulary
BSI	Brief Symptom Inventory
CAMHMS	Child and Adolescent Mental Health Services
CBP	Cognitive Behavioural Prevention
CDC	Centers for Disease Control and Prevention
CDRS	Children's Depression Rating Scale, Revised
CES-D	Center for Epidemiological Studies Depression Scale
CFA	Confirmatory Factor Analysis
CHMP	Committee on Human Medicinal Products
CI	Confidence Interval
CIDI	World Health Organisation Composite International Diagnostic Interview
CNS	Central Nervous System
CPRD	Clinical Practice Research Datalink
CSD	Cedegim Strategic Data
CSM	Committee for Safety of Medicines
DAG	Directed Acyclic Graph
DIS	Diagnostic Interview Schedule
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSSI	Delusions-Symptoms-States Inventory
EFA	Exploratory Factor Analysis
EMEA	European Medicines Evaluation Agency
EPD	Early Parental Depression

EPDS	Edinburgh Postnatal Depression Scale
ESEM	Exploratory Structural Equation Modelling
FDA	Food and Drug Administration
FDB	First Databank
FDC	Full Data Collection
GHQ	General Health Questionnaire
GP	General Practitioner
GPRD	General Practice Research Database
GSK	GlaxoSmithKline
HAM-D	Hamilton Rating Scale for Depression
HBQ	Health and Behavior Questionnaire
HES	Hospital Episodes Statistics
HPA	Hypothalamic-Pituitary-Adrenal
HR	Hazard Ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
INPS	In Practice Systems
IPW	Inverse Probability Weighting
IRR	Incidence Rate Ratio
MAOI	Mono-Amine Oxidase Inhibitor
MCS	Millennium Cohort Study
MDD	Major Depressive Disorder
MHRA	Medicines and Healthcare products Regulatory Agency
MSM	Marginal Structural Model
NCDS	National Child Development Study
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIMH	National Institute of Mental Health
NSHD	National Survey of Health & Development
ONS	Office of National Statistics
OR	Odds Ratio
OTC	Over the Counter
PCT	Primary Care Trust
PYAR	Person-Years at Risk
RCT	Randomised Controlled Trial
R_x	Prescription

SADS	Self-Assessing Depression Scale
SCCS	Self-Controlled Case Series
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SEM	Structural Equation Modelling
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SRC	Scientific Review Committee
TCA	Tricyclic Antidepressant
THIN	The Health Improvement Network
UK	United Kingdom
US	United States
VAMP	Value Added Information Medical Products
VRD	Vamp Research Databank

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Part I

Background

In this thesis, I provide a quantitative analysis of the association between parental depression in the first postpartum year and depression in adolescent offspring, with internalizing behaviour in children as a mediator. I examine depression and its intergenerational transmission in a large UK primary care database, The Health Improvement Network (THIN), using one of the largest birth cohorts currently available worldwide.

Depressive disorders are common, serious, and treatable [Regier et al., 1988]. In the World Health Organization's Global Burden of Disease Study, unipolar major depression was predicted to be the second most common cause of disability worldwide by 2020, and the leading cause for developing countries [Murray and Lopez, 1997]. Although depression can affect anyone at any time, the first year after the birth of a child appears to be a time when both men and women are at an increased risk of depression [Davé et al., 2010].

Research has mainly focussed on maternal perinatal depression. The incidence of depression onset in the first five weeks after delivery was threefold higher in postnatal women compared to control women [Cox et al., 1993]. The incidence of maternal postnatal depression has been estimated at 10% in the early weeks postpartum, with episodes typically lasting two to six months [Cooper and Murray, 1998].

Although early parental depression (EPD) is generally associated with mothers, depression rates are also increased for fathers in the first year after the birth of a child [Davé et al., 2010]. Several studies have found that maternal and paternal depression in the first year postpartum are highly correlated [Paulson and Bazemore, 2010]. Leading on from this, the incidence of comorbid early parental depression (where both the mother and the father are depressed simultaneously) might be increased during the first year postpartum as well.

Comorbid parental depression could have detrimental effects on childhood outcomes. Research focussing on maternal postnatal depression has found that children (especially daughters) of mothers who were depressed after childbirth were more likely than children of non-depressed mothers to develop depression themselves in adolescence. A similar effect, though less pronounced, has been found for children of depressed fathers.

Research on the effect of comorbid parental depression is sparse. The current hypo-

thesis is that in the case of single parental depression, the non-depressed parent can form a buffer to the effects of depression on the child. However, as this shielding opportunity is not present in families with comorbid parental depression, the effects on children are hypothesised to be much more severe.

The time span between early parental depression and adolescent depression is very long, and although previous studies have found the two to be correlated, many children of parents with early depression will not develop depression themselves. Therefore, an intermediate variable or mediator measured during childhood could provide more information on risk of depression and identify high risk groups as a target for prevention. Studies have assessed a variety of internalizing behaviours in children aged from a few months old to adolescence to examine effects of postnatal depression on child outcomes in studies with short follow-up times. In this thesis, I propose a model in which early parental depression is associated with adolescent depression, mediated by childhood internalizing behaviour.

The main research question I try to answer is whether children of parents who both had depression in the first year after childbirth (early comorbid parental depression) are more likely to develop depression in adolescence compared to children of non-depressed parents or families in whom only one parent was depressed.

I aim to answer this question by exploring the following sub-questions:

1. What is the prevalence of early comorbid parental depression?
2. How has adolescent depression been recorded in UK primary care over time?
3. What is the association between early comorbid parental depression and adolescent depression?

In the first part of my thesis, I will provide background information. In Chapter 1, I will present a literature review on depression: how it is defined and measured, what is known on parental depression, how it could be transmitted across generations, and what childhood outcomes are linked to parental depression. In Chapter 2 I will introduce The Health Improvement Network (THIN) database, which I will use for the analysis in my thesis.

In part II, I will explore the first two subquestions, exploring the main exposure (early comorbid parental depression) and outcome (adolescent depression) of my thesis.

Chapter 3 will present a systematic review on the prevalence of early comorbid parental depression and associated child outcomes. Chapter 4 will detail trends in the recording of adolescent depression in UK primary care.

In part III I will present my main analysis. First, in Chapter 5, I will introduce the family cohort by explaining how families were linked together in THIN and describe the characteristics in the cohort. Next, I will explore the association between sleep disorders and depression in Chapter 6. I have included this chapter as I will investigate internalizing behaviours in childhood as a potential mediator in the association between parental and adolescent depression and will test whether this is possible by using sleep disorders as an example. Finally, I will present my main analysis in Chapter 7.

The final part of my thesis, Chapter 8, will provide a summary of my thesis, list implications on conclusions resulting from the work presented in earlier chapters.

Chapter 1

Introduction and literature review

1.1 Objectives of the chapter

In this chapter I aim to provide an introduction by discussing background literature on early parental depression, which will be the exposure in my main analysis. I will provide various definitions for depression, discuss the literature on parental postnatal depression, explore mechanisms for intergenerational transmission of depression and child outcomes associated with parental depression.

1.2 Definition of depression

As early as 1621, Robert Burton attempted to describe what we now call depression in his magnum opus 'The Anatomy of Melancholia' [Burton and Jackson, 1827]:

> "Melancholy, the subject of our present discourse, is either in disposition or in habit. In disposition, is that transitory melancholy which goes and comes upon every small occasion of sorrow, need, sickness, trouble, fear, grief, passion, or perturbation of the mind, any manner of care, discontent, or thought, which causes anguish, dulness, heaviness and vexation of spirit, any ways opposite to pleasure, mirth, joy, delight, causing frowardness in us, or a dislike. In which equivocal and improper sense, we call him melancholy, that is dull, sad, sour, lumpish, ill-disposed, solitary, any way moved, or displeased. And from these melancholy dispositions no man living is free,

> no stoic, none so wise, none so happy, none so patient, so generous, so godly, so divine, that can vindicate himself; so well composed, but more or less, some time or other, he feels the smart of it. Melancholy in this sense is the character of mortality.

Although Robert Burton was not the first person to try and define what we now call depression[1] , his early description of melancholy through a list of symptoms bears a striking resemblance to the present day method of classifying mental health disorders.

Today, depression is often diagnosed using criteria set by the Diagnostic and Statistical Manual of Mental Disorders (DSM). The DSM uses lists of symptoms to identify a range of mental disorders. Although the fifth version of the DSM was published in May 2013, I will use the 4th revised version (IV-TR, published in 1994 [American Psychiatric Association, 2000]) to define depression in this thesis as the period during which clinical diagnoses of depression were made by GPs relates to a period before 2013.

The diagnosis of Major Depressive Disorder according to DSM requires the presence of one or more Major Depressive Episodes (see Table 1.1). Also, the episode should not be better accounted for by other diagnoses such as schizoaffective disorder and should not be superimposed by other mental disorders. Finally, persons who have ever experienced a (hypo)manic episode, are classified as suffering from bipolar disorder rather than depressive disorder. In this thesis, I will focus on major depressive disorder; related disorders such as bipolar disorder and seasonal affective disorder are not included.

Another commonly used set of diagnostic criteria is the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [World Health Organisation, 2007]. ICD-10 differs slightly from the DSM-IV-TR in its definition of depression. Whereas DSM-IV-TR has one entry for 'Major Depressive Disorder', with specifiers for a single episode or a recurrent disorder, ICD-10 has separated them in an entry 'Depressive episode' for a single episode and 'Recurrent depressive disorder' for repeated episodes. A second difference appears in the main symptoms used to define

[1] The Greek founder of medicine, Hippocrates (460-377 BCE), described melancholia in his Aphorisms as a distinct disease. The word is derived from the ancient Greek words $\mu\epsilon\lambda\alpha\sigma$ (melas - black) and $\chi\ o\lambda\eta$ (chole - bile), indicating the humours Hippocrates thought to be imbalanced in melancholia.

depression. While the DSM-IV-TR requires both a depressed mood and anhedonia to be present, ICD-10 requires two of three possible main symptoms (depressed mood, anhedonia, and reduced energy) to be present for the diagnosis of a depressive disorder.

Table 1.1: DSM-IV-TR diagnosis for a Major Depressive Episode

Present during the same 2-week period and represent a change from previous functioning;

At least one of the symptoms:

- Depressed mood

Note: In children and adolescents, can be irritable mood

- Loss of interest or pleasure

Note: In children, consider failure to make expected weigth gain

Plus four or more of the following symptoms:

- Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
- Insomnia or hypersomnia nearly every day
- Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

It is important to distinguish depression from low mood, which is part of the normal spectrum of mood, and is thought to be useful in certain situations such as after a bereavement when it can indicate a need for caring [Nesse, 2000]. However, when low mood is excessive, prolonged, or expressed in the wrong situation it becomes pathological depression. Lifetime prevalence of major depressive disorder has been estimated at 16.6% [Kessler RC, 2005].

1.2.1 Measuring depression

The gold standard for measuring depression is through a structured clinical interview with a trained professional. However, due to time and financial constraints, depression is often measured using questionnaires in research.

One of the most commonly used clinical interviews is the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [Spitzer RL, 1992]. It is a semi-structured interview, originally based on DSM-III but updated for DSM-IV. The SCID is designed to both measure current (in the past month) and lifetime occurrence of any of the DSM axis I disorders (clinical disorders and other conditions that may be a focus of clinical attention). A full SCID-I assessment can take between 1-2 hours and is designed to be administered by a clinician. However, many epidemiological studies have used the World Health Organisation Composite International Diagnostic Interview (CIDI) [Robins LN, 1988], designed to be administered by a lay person, instead. The CIDI was used most notably in the US National Comorbidity Survey [Kessler RC, 1994], which used the questionnaire to provide estimates of the prevalence of mental disorders in the US general public.

There is a multitude of validated questionnaires that are designed to measure depressive symptoms without the need of an interviewer. One of the most commonly used rating scales, especially in clinical trials, is the Hamilton Rating Scale for Depression (HAM-D) [Hamilton, 1960]. The score on this scale can range from 0 to 52, and it is commonly used to classify severity of depression. The HAM-D was developed over 50 years ago, in 1960, based on a study of major depressive disorder in patients confined to asylums. As few trial participants now suffer from that level of illness, some experts wonder if what pharmaceutical companies now refer to as depression is the same disease

that the HAM-D was designed to diagnose [Kriston and von Wolff, 2011].

Another criticism of the HAM-D is its focus on somatic symptoms such as insomnia, rather than suicidal behaviour and thinking. Because of this emphasis it is possible for patients to show improvement on the HAM-D while suicidal behaviour and thinking has increased [Bagby et al., 2004]. Moreover, there are several standards for interpreting the score (Figure 1.1) [Kriston and von Wolff, 2011]. The differences between HAM-D interpretations can have effects on inclusion of patients into clinical trials and interpretation of trial outcomes, as well as the ability to compare studies in meta-analyses.

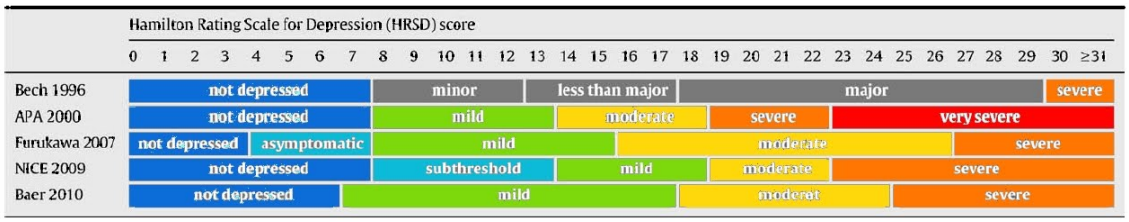

Figure 1.1: Levels of depression in relation to the HAM-D according to different recommendations, figure adapted from Kriston et al [Kriston and von Wolff, 2011, Neuroskeptic, 2010]

Observational studies tend to use shorter questionnaires to assess depression. Commonly used questionnaires are the Beck Depression Inventory (BDI) [Beck et al., 1961], consisting of 21 items, and the Center for Epidemiological Studies Depression Scale (CES-D) [Radloff, 1977], consisting of 20 items. Both questionnaires have been validated and are estimated to take only five to ten minutes to complete [Sharp and Lipsky, 2002]. However, similar to the HAM-D, studies employing the BDI or CES-D have used different cut-offs to define depression and depression severity. Moreover, updated versions of these questionnaires have become available over the years (e.g. the BDI-II [Beck et al., 1996], updated to correspond to DSM-IV), as well as shortened versions to use in specialised settings such as primary care (e.g. the BDI for Primary Care or BDI-PC [Beck et al., 1997]), making it more difficult to compare estimates for depression from studies using different questionnaires, or different versions of the same questionnaire.

Furthermore, specialised questionnaires have been developed for some populations, such as perinatal women and children and adolescents, as these groups might express

symptoms of depression differently. One of these questionnaires, the Edinburgh Postnatal Depression Scale (EPDS), was developed in the 1980s specifically for women in the postpartum period as these women were known to be at an increased risk of developing depression [Cox and Holden, 2003, Cox et al., 1987]. The available questionnaires at the time gave a high number of false-positives as parts of these questionnaires focussed on somatic symptoms (e.g. sleep difficulty) which are considered normal for postpartum women. The EPDS has since also been validated for detecting depression in antenatal women [Murray and Cox, 1990], non-postnatal women with older children [Cox et al., 1996], and men [Matthey et al., 2000].

Few other questionnaires have also been used that measure psychiatric disorder or symptoms, rather than depression specifically. The General Health Questionnaire (GHQ) is an example of such a general questionnaire. It was developed in the 1970s to detect psychiatric disorder in the general population and within community or non-psychiatric clinical settings such as primary care [Goldberg and Williams, 2006, Goldberg and Hillier, 1979]. The GHQ focusses on both physical and psychiatric symptoms.

1.2.2 Depression in primary care

Questionnaires are often used to assess patients newly diagnosed with depression. According to NICE guidelines [National Institute for Health and Clinical Excellence, 2009], patients who may have depression should be screened by asking two questions:

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

If patients answers 'yes' to either question further investigation is required, often by administering the PHQ-9 [Kroenke et al., 2001] or one of the questionnaires metnioned in the previous section. A general practitioner (GP) who is experienced in mental assessment can perform this assessment his/herself, though they can also refer the patient to an appropriate professional. Most patients with depression are treated in primary care. The GP considers the degree of functional impairment and duration of the episode, as well as factors that may have affected the development, course and severity of the depression

(e.g. history of depression, comorbid mental health or physical disorders, response to previous treatment, living conditions and social isolation).

In order to diagnose depression, a longitudinal assessment is needed and GPs tend to monitor patients and assess their depression symptoms over time. Depression diagnoses, symptoms and referrals are entered in a patient's medical records by using Read codes [Chisholm, 1990], which will be further explored in the next chapter. Prescriptions for antidepressants will also be coded in electronic medical records. GPs can also enter notes in free text areas (more on electronic medical records in Chapter 2).

1.3 Parental postnatal depression

Depression is a common mental disorder affecting 121 million people worldwide [WHO, 2011]. In the US, about 1 in 10 individuals older than 12 are taking antidepressant drugs, according to a recent report from the US Centers for Disease Control and Preventions (CDC) National Center for Health Statistics [Kuehn, 2011]. Women appear more likely than men to develop depression: a gender imbalance in prevalence, incidence and morbidity risk develops in adolescence and persists throughout adult life [Piccinelli and Wilkinson, 2000]. In the perinatal period, 10-15% of mothers are affected by depression [Cox et al., 1993, Davé et al., 2010, Kumar and Robson, 1984, O'Hara and Swain, 1996]. Although postnatal depression is generally thought of as a disorder affecting mothers, I will use the term 'postnatal' as a specifier of time of onset (relating to the first year after childbirth) and as such use it for depression in both mothers and fathers.

1.3.1 Maternal early depression

There is long history of research into maternal mental illness around childbirth. For centuries, 'female hysteria' was thought to be caused by disturbances of the uterus, such as during childbirth [King, 1993]. Louis Victor Marcé was the first to write a book[2] en-

[2]Although Louis Victor Marcé was the first to devote an either work to puerperal illness, there are earlier references. For instance, Gerard van Swieten, a Dutch physician, mentions puerperal sadness in his Commentaria in Hermanni Boerhaave aphorismos de cognoscendis et curandis morbis (page 601) from 1764. He writes that in the Dutch city of Haarlem, women were required by law to put a sign on their doors

tirely devoted to puerperal mental illness in 1858 [Marc, 1858]. In it, he attempted to estimate the number of women afflicted by 'puerperal madness' (la folie puerprale) by counting women who had become 'mad' after giving birth in hospital, and the number of women who had been admitted to asylums during pregnancy or shortly after childbirth. Although the numbers he found were very low (e.g. only 9 out of 3500 women in the General Lying-in Hospital in Westminster were identified as cases, while most other hospitals reported never having observed puerperal madness), Marcé did stress the influence of maternal mental illness on the child.

A large meta-analysis of the rates of postpartum depression found an average rate of 12.8% (95%CI: 12.3-13.4%) [O'Hara and Swain, 1996]. This meta-analysis also found, by including data from 59 studies on a total of 12,810 women, that the prevalence of early maternal depression varied with the method of assessment. Studies in which women had been assessed for depression using a questionnaire reported higher prevalence rates than studies using interviews. Women who had been assessed with the EPDS had depression rates of 18.0% (95%CI: 16.1-19.9%) on average, compared to 7.2% (95%CI: 3.7-10.7%) for women assessed by an interview based on DSM-III.

Studies have found little evidence for a biological basis of maternal postnatal depression, and the main risk factors are the same as those for major depressive disorders [Cooper and Murray, 1998]. These risk factors include lower social class, negative life events, marital difficulties, lack of social support, and a history of depression (particularly antenatal depression) [Cooper and Murray, 1998, Milgrom et al., 2008, O'Hara and Swain, 1996]. Some pregnancy-specific risk factors have also been identified, such as unplanned pregnancy, complications during pregnancy or childbirth, and not breastfeeding [Milgrom et al., 2008, Warner et al., 1996].

Rates of early depression for mothers are not necessarily higher than prevalence rates outside of the perinatal period [Cox et al., 1993]. However, the incidence of new

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after they had given birth. This would prevent 'officers of justice' from coming into their homes and giving them bad news (Haarlem was a city of sailors and merchants who travelled between Europe and Asia), which Van Swieten thought would lead to puerperal sadness. He recommended women to carefully avoid all emotions after childbirth.

depressive episodes might be higher in the first few weeks after delivery. Moreover, although the prevalence of depression is not increased, the effects of maternal depression on the child are thought be most potent during the first months postpartum (see section 1.4 on page 37 for more detail).

1.3.2 Fathers and early depression

Although most research on psychiatric morbidity during the perinatal period has focussed on mothers, there are some studies that have included fathers as well. As early as 1931, Zilboorg described several case studies of 'depressive reactions related to parenthood' [Zilboorg, 1931]. The fathers described in his article experienced severe depressive reactions resulting in hospitalisations, and Zilboorg classified them as manic-depressives. In the Freudian spirit of the time, he attributed their psychopathology to suppressed incestuous thoughts about their mothers (and occasionally sisters), hatred or jealousy towards their fathers, and passive homosexuality.

In the following decades, case studies on mental illness in men around the perinatal period appeared sporadically in the scientific literature [Ballard and Davies, 1996]. From the 1980s onwards, small studies started to assess psychiatric morbidity in fathers. Most of these were biased in that they assessed partners of mothers with severe mental illness, or partners of mothers who were being treated in mother-baby units. As such, these studies often found high rates of paternal morbidity, ranging from 40% to 50% [Harvey and McGrath, 1988, Lovestone and Kumar, 1993].

Paternal early depression has received more attention in recent years. A large meta-analysis estimated that 10.4% (95%CI: 8.5-12.7%) of fathers experienced depression during their partners' pregnancy or in the first year after childbirth [Paulson and Bazemore, 2010], which is slightly higher than the estimated 12-month prevalence of 5-7% for depression in men in general [Kessler RC, 2005, Kessler et al., 2003, 1993]. The study included information on 28,004 participants from 43 studies. The highest rate was observed in the 3- to 6-month postpartum period, with an estimated rate of 25.6% (95%CI: 17.3-36.1%) of fathers experiencing depression. However, there was a large amount of heterogeneity between studies, with estimates ranging from 0.7% [Thorpe et al., 1992] to 46.2% [Dudley et al., 2010], which is likely due to differences in study populations, types

of measurements (e.g. interview or questionnaire), and criteria used to define depression.

Studies that have followed parents up longitudinally tend to find lower estimates of paternal postnatal depression compared to depression in mothers. For instance, a study in Spain that followed up 769 parents from pregnancy to 12 months postpartum found that 3.4% and 4.0% of fathers were depressed at 3 and 12 months postpartum [Escribà-Agüir and Artazcoz, 2011]. A study using a UK primary care database (THIN) found a postnatal depression rate of 3.56 per 100 person-years for fathers [Davé et al., 2010]. These rates could be lower than the meta-analysis estimate due to fathers with depression being more likely to drop out of longitudinal studies, and because studies using diagnoses rather than questionnaires to define depression tend to find lower estimates.

The risk factors for early depression in fathers are similar to those for mothers: younger age, low income, low level of education, poor partner relationship quality, and worries about the economy and employment [Bergstrøm, 2013].

1.4 Intergenerational transmission of depression

As shown in section 1.3, parental depression in the first year postpartum is common in both parents. This section will explore different mechanisms for transmission of parental depression onto their children, and will look into potential intermediate child outcomes such as internalizing behaviour.

1.4.1 Developmental origins of health and disease: genes, epigenetics & environment

1.4.1.1 Developmental origins of health and disease

Developing organisms adapt themselves to their environment [Bateson et al., 2004]. This observation has been found in fields of research ranging from evolutionary ecology to medical epidemiology, leading to the theory of developmental programming [Barker et al., 1993]. During programming, environmental adversity is transmitted to the foetus and acts on specific tissues during sensitive periods in their development to change developmental trajectories and thus their organisation and function [Harris and Seckl, 2011].

According to this theory, a given genotype - the genetic constitution of an individual organism - can give rise to different phenotypes - the set of observable characteristics of an individual - depending on environmental conditions. Put more briefly: the impact of the environment experienced by one generation can shape the development and behaviour of the next.

The varied developmental pathways triggered by environmental events may be induced during sensitive, often brief, periods in development. Outside these sensitive periods an environmental influence that sets the characteristics of an individual may have little or no effect. If the effects of past conditions produce mismatches with current, changed conditions, developmental plasticity may have an adverse effect on survival and reproductive success.

In humans, the idea of developmental plasticity has been shown with regards to the relation between adult health and nutritional level during later development with phenotypes that were initiated during pregnancy. A pregnant woman in poor nutritional condition may unwittingly signal to her unborn baby that is about to enter a harsh world. If so, this 'weather forecast' from the mother's body may result in her baby being born with characteristics, such as a small body and a modified metabolism, that help it to cope with a shortage of food. When sufficiently high levels of nutrition are available after the development of a 'small' phenotype has been initiated, marginal benefits of rapid growth may offset the costs, but they may also trigger the health problems arising in later life. The bigger the disparity between the 'forecast' received in the womb and the level of nutrition available, the larger the health problems are thought to be.

Evidence from the Dutch famine of 1944-45 showed that glucose intolerance, a prodrome of diabetes type 2, is induced by maternal malnutrition during the final three months of pregnancy [Ravelli et al., 1998]. The study compared 702 people who were born between November 1943 and February 1947 in Amsterdam, and for who detailed prenatal and birth records were available. People who were born during or in the months immediately following the hunger winter of 1944-45 had decreased glucose tolerance. The effect of famine was especially important in people who became obese, further strengthening the idea of developmental plasticity.

1.4.1.2 Epigenetics: Glucocorticoids and the HPA-axis

Similarly, maternal stress during pregnancy can have permanent effects on the child by disrupting hormonal balances. Stress is mediated by the hypothalamic-pituitary-adrenal (HPA) axis, and cortisol - a glucocorticoid hormone produced by the adrenal cortex - is its main hormonal mediator. Some researchers believe that stress-induced HPA-axis activation can directly cause depressive symptoms [Pariante, 2003]. When a mother experiences stress during pregnancy, for instance as a consequence of antenatal depression, blood cortisol levels will increase and can affect the offset of the foetus' HPA axis as it is prepared for a life in a stressful world.

The foetus' HPA axis can be affected as certain glucocorticoid-sensitive genes can be activated or repressed by cortisol, which can lead to lasting epigenetic effects in placental and foetal glucocorticoid target tissues such as the brain [Harris and Seckl, 2011, Hogg et al., 2012].

Animal studies have shown how prenatal stress can alter the function of the HPA axis in offspring. However, as detailed in a review by Glover and colleagues [Glover et al., 2010], there is a lot of variation in the possible effects. Importantly, rodent experiments have also shown that the effects of prenatal stress can be moderated, and even reversed, by positive postnatal rearing [Maccari et al., 1995].

Studies assessing the link between prenatal stress and child outcomes in humans are rare and observational, as opposed to animal studies. Although this complicates the making of causal inferences, results from human studies are similar to experimental animal data, strengthening the belief in a causal relationship.

Several childhood outcomes have been linked to prenatal stress, ranging from attention deficit hyperactivity disorder (ADHD) to effects on cognitive development [Glover et al., 2010]. A number of studies have also assessed the link between prenatal stress and cortisol levels in children ranging in age from 1 week to 15 years. These studies consistently found that cortisol levels were increased for children of mothers who had experienced prenatal stress (either through depression, or exposure to stressful life events such as 9/11 or Chernobyl) [Glover et al., 2010]. Therefore, maternal stress due to depression in the prenatal period could be a possible mechanism for the transmission of depression.

1.4.1.3 Epigenetics: Antidepressants in pregnancy - the SSRI paradox

A second possible mechanism of transmission of depression from parents to offspring is the SSRI paradox: while these drugs are used to treat depression in adults, they could have the opposite effect when a foetus is exposed to it in utero. As SSRI use during pregnancy has increased in both the US [Huybrechts et al., 2013] and the UK [Petersen et al., 2011] this potential transmission mechanism could have become more important in recent years.

SSRIs can reach the foetus via the placenta and can thus have an effect on serotonin levels in the foetal brain during critical phases of neurodevelopment [Rampono et al., 2004]. The serotonin transporter, one of the targets of SSRIs, is transiently expressed in many brain areas during development, and blocking this transporter (one of the mechanisms of action of SSRIs) during development can cause wiring defects. Animal research suggests that SSRIs could have paradoxical effects when administered prenatally: rather than decreasing depression levels, it appears to increase them in rodents (see for example this review by Homberg and colleagues [Homberg et al., 2011]).

SSRI use in pregnancy has been linked to many outcomes: pregnancy complications, birth defects, persistent pulmonary hypertension, neurodevelopmental outcomes, and stress regulation [Olivier et al., 2011a]. However, it is difficult to distinguish the effects of antidepressants from the effects of the underlying depression in humans. Animal research has replicated many of the effects of prenatal SSRI exposure, particularly neurodevelopmental outcomes. Increases in internalizing behaviour have been found in early adulthood in humans, and anxiety- and depression-like behaviour has also been found to be increased in rodents exposed to prenatal SSRIs [Oberlander TF, 2010, Olivier et al., 2011b].

1.4.1.4 Environment: early brain development and parent-child attachment

A third mechanism for depression transmission is via environmental transmission through parenting behaviour. A depressed parent may interact with their infant in ways that disrupt the child's emotional and/or cognitive development.

A number of studies have assessed whether parental depression, maternal depression in particular, affects parent-child attachment. A meta-analysis based on seven studies found that 1-3 year old children of depressed mothers were less likely to show secure attachment, and more likely to show avoidant or disorganised forms of attachment compared to infants of non-depressed mothers [Martins and Gaffan, 2000]. However, the number of children included in each study was small, ranging from 26 to 99, and families were relatively well off, making the representativeness of the studies unclear.

A larger UK study that sampled 10,438 children found that parenting strategies were associated with child mental health [Vostanis et al., 2006]. The quality of parenting, and abusive parenting of young children in particular, has been shown to have lasting biological effects [Scott, 2012].

1.4.1.5 Is there a gene for depression?

A final important potential transmission mechanism is genetic susceptibility. Adoption studies have provided some support for a role of genetic factors in the intergenerational transmission of depression [Levinson, 2006]. In these studies adopted children share their genes with their biological parents, but they do not share their environment, and thus researchers are able to distinguish between the effects of the two. It seems that children whose biological parents had depression are more likely to become depressed themselves compared to adopted children of non-depressed parents.

Similarly, twin studies have been used that compare monozygotic twins (who are genetically almost entirely identical) to dizygotic twins (who share half their DNA on average). By comparing how often both siblings are depressed, it is possible to estimate the role of genetics: if monozygotic twins are more often both depressed, this is a sign that genes are important in depression. If, on the other hand, there is no difference between monozygotic and dizygotic twins, environmental factors or shared adversity are more important. From twin studies, heritability has been estimated to be about 40-50% in depression, and might be even higher for severe depression. The role of familial transmission is further strengthened by the increased risk of depression for first-degree family members of a person with depression. Compared to the general population, this group has two- to threefold increase in risk of depression.

Several specific genes have been linked to an increased risk of depression. Most notable is SLC6A4, a gene on chromosome 17 that encodes the serotonin transporter (5-HTT). The promotor region of this gene, known as the 5-HTT-linked polymorphic region (5-HTTLPR), comes in different lengths. The short version of this region is linked to a higher risk of depression, especially when an individual has inherited the short allele from both parents [Caspi et al., 2003]. The gene appears to increase the risk of depression after negative life events - a gene-environment interaction. However, a more recent meta-analysis shows only a small effect of the polymorphism on susceptibility to depression and the authors warn the effect could be an artifact [Clarke et al., 2010].

Some studies have found that environmental factors also play an important role [Lewis et al., 2011]. A study an assisted conception design[3] found that associations between parental and child and adolescent depression were equally strong between genetically related and genetically unrelated parent-child pairs.

1.4.2 Sensitive period versus chronic exposure

As detailed in the previous section, many of the proposed mechanisms for the intergenerational transmission of depression appear to depend on a sensitive period around the time a child is born. However, some studies have suggested that parental depression in the perinatal period on its own is not associated with adverse child outcomes, but rather it is chronic exposure to a depressed parent that could facilitate transmission of the disorder [Hammen et al., 2004].

However, research in this area is sparse and methodologically flawed. Parental depression throughout a child's life is likely to be associated with depression in the perinatal period and thus could be seen as a mediator or intermediate variable on the causal pathway from early parental depression to child outcomes (Figure 1.2). As described by Baron and Kenny in their seminal paper on mediation analysis [Baron and Kenny, 1986], the strict assumptions required for a mediation analysis where a mediator is simply added to a regression model are rarely valid. However, this method has been used in papers attempting to assess whether early or chronic parental depression is more important for

[3]The assisted conception design uses children that are conceived with the help of donor sperm, donor eggs or donor embryos. In this design, children share their genotype with one or neither parent.

transmission.

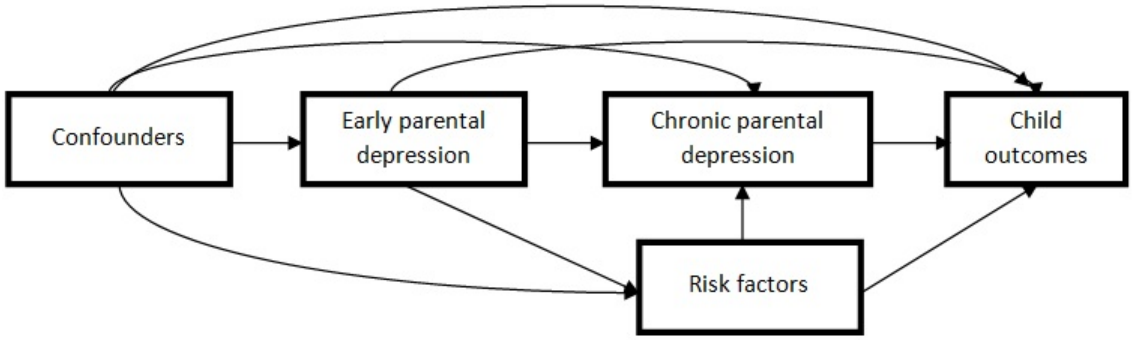


Figure 1.2: Causal diagram of the hypothesized effects of early parental depression on child outcomes

As chronic depression is on the causal pathway and potentially correlated with early parental depression (EPD), just adding chronic depression to a regression model assessing the effect of early parental depression on child outcomes can lead to biased results. In addition, mediation analysis requires special attention to possible confounders. In order to get an unbiased estimate of the direct effect (EPD to child outcomes) and indirect effect (EPD to child outcomes, via chronic parental depression) confounders of the association between the exposure and mediator, exposure and outcome, and mediator and outcome need to be considered. Unfortunately, the latter group of confounders (represented by risk factor in Figure 2) are often neglected as they were not explicitly mentioned in Baron and Kenny's paper despite an earlier paper by David Kenny stressed their importance [Judd and Kenny, 1981].

I will explore the effects of chronic exposure to depression and mediation analysis more in Section 5.2.2 on page 120 and Appendix D.1.

1.4.3 Childhood outcomes: internalizing behaviour

Early parental depression has been linked to many child outcomes [Grace et al., 2003]. Maternal postnatal depression has been associated with child cognitive development, behaviour, sleep, crying and motor behaviour. As the exposure (early parental depression) and outcome (adolescent depression) for my main analysis are at least 13 years apart in time, I will also explore internalizing behaviour in childhood as a potential intermediate

variable. I will introduce some of research on child outcomes in this section, but will come back to them in Section 5.2.1 on page 119.

1.4.3.1 Child behaviour problems

Child behaviour can be affected by parental depression as early as in the first few months of life. Larger studies, most notably the Avon Longitudinal Study on Parents And Children (ALSPAC) study, have tried to assess the effects of parental depression on child behaviour. ALSPAC has followed up over 14,000 families from the Avon area in the UK from pregnancy in the early '90s. The study found that behavioural problems at age 3.5 years were associated with both maternal and paternal early depression [Ramchandani et al., 2005a]. Maternal depression was particularly associated with emotional problems in girls (OR 2.24, 95% CI: 1.62-3.11) and conduct problems in boys (OR 2.18, 95% CI: 1.58-3.01), while paternal depression was linked to conduct problems (OR 2.66, 95% CI: 1.67-4.25) and hyperactivity (OR 2.06, 95% CI: 1.16-3.66) in boys. A review of the effects of parental psychiatric disorders on children's psychosocial development found that the effect of paternal and maternal depression were of similar magnitude [Ramchandani and Psychogiou, 2009]. However, paternal psychiatric disorders, depression in particular, appeared to have a larger effect on boys, while maternal depression was more likely to affect girls.

A small study including 48 fathers found that paternal negative mood was associated with infant fussiness at six months as measured by the Infant Characteristics Questionnaire [Davé et al., 2005]. However, men who were depressed at screening (4-6 weeks after childbirth) did not participate in the follow-up. Hence, none of the 17 fathers included in the final analysis linking negative mood to infant behaviour scored over the depression threshold.

1.4.3.2 Cognitive development

Child cognitive development has been tested extensively in a cohort of 59 women recruited in the Cambridge area by Prof Lynne Murray [Murray, 1992, Murray et al., 1993, 1996a,b, Sinclair and Murray, 1998]. At 9 and 18 months, children of mothers with postnatal depression (as assessed at 2-3 months postpartum by interview) performed worse on

Piaget's object concept task than children of non-depressed mothers [Murray, 1992]. Piaget's object concept task tests infants' abilities to recognise the independent existence of objects. In this study, objects were hidden under opaque plastic cups. Infants passed the test if they (tried to) recover the objects by removing the plastic cup, indicating they've progressed from the 'out of sight, out of mind' stage. At 9 months, 2 (13%) children of mothers with postnatal depression passed the object concept test, compared to 10 (59%) of children of non-depressed mothers ($p<0.04$). Results were similar at 18 months.

Follow-up studies found that the association between maternal depression and the child's cognitive development was mediated by mother's speech to her infant during play interactions at age 2-3 months [Murray et al., 1993], life adversity, infant sex [Murray et al., 1996a]. Mothers who were depressed at the time of speech assessment were much less infant-focussed than the non-depressed mothers and displayed more negative effect. Also, boys of mothers who had postnatal depression performed significantly more poorly than boys of non-depressed mothers, while there was no such effect for girls.

The children were reviewed again at age 5 years. At this time point, cognitive development was neither associated with maternal depression at any time point, nor with the length of maternal depression [Murray et al., 1996b]. Maternal postnatal depression was also unrelated to readiness for school, personal maturity, prosocial behaviour, adaptability, emotional intensity, and persistence at age 5 [Sinclair and Murray, 1998]. However, both postnatal and recent maternal depression were associated with significantly raised levels of child disturbance, particularly among boys and children from lower social class families.

A study from Germany found similar results [Kurstjens and Wolke, 2001]. The study followed 1,329 families from South Bavaria, Germany, from birth up to age six years and focussed on the effects of maternal depression on cognitive development of children. They found no significant main effects of depression severity, timing of onset, duration, or chronicity on the child's cognitive development. However, similar to the study by Murray et al., Kurstjens and Wolke found that cognitive development was affected by maternal depression when the depression was chronic, and for lower social class boys.

1.4.3.3 Clinical outcomes

Few studies have assessed the association between early parental depression and clinical child outcomes. Ramchandani and colleagues assessed the association between early parental anxiety - a measure closely related to depression - and recurrent abdominal pain (RAP) in school age children (6-7 years) [Ramchandani et al., 2006]. They found that both maternal and paternal anxiety were independently associated with RAP (OR 1.53, 95% CI: 1.24-1.89, and OR 1.38, 95% CI: 1.12-1.71, respectively). In an earlier study on the same cohort, it was shown that RAP is associated with anxiety in children, suggesting it is a psychosomatic symptom in children [Ramchandani et al., 2005b].

1.4.4 Adolescent depression

Depression is less common in children compared to adolescents or adults: prevalence rates range between 0.4% and 2.5% in children and between 0.4% and 8.3% in adolescents [Birmaher, 1996]. In prepubescent children, where prevalence rates are reported to be very low, boys appear more likely to be depressed than girls [Anderson et al., 1987, Cohen and Brook, 1987], although there is also some literature reporting no difference [Angold, 1992, Kashani et al., 1983]. However, between the ages of 11 and 13 this gender gap reverses and by the age of 15 girls are twice as likely to have experienced depression compared to boys [Angold, 1992, Angold et al., 1998, Cyranowski et al., 2000].

Although some studies suggest that there has been an increase, or even an epidemic, of childhood and adolescent depression [Collishaw et al., 2004], reviews show that this is not the case [Costello et al., 2006]. The apparent increase in childhood depression seems to be due to an increase in antidepressant prescriptions. However, rather than more children taking these drugs, prescriptions are for shorter lengths of time making, contributions to a inflation in the number of prescriptions but not the number of children taking them. Moreover, the prevalence of any disorder always involves some arbitrary decisions concerning where to place the cut points between sick and well. For depression this is particularly the case as it is defined by the presence of a certain number of symptoms which have changed repeatedly over the development of different versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM).

A multitude of factors can affect an adolescents vulnerability to depression (Fig-

ure 1.3).

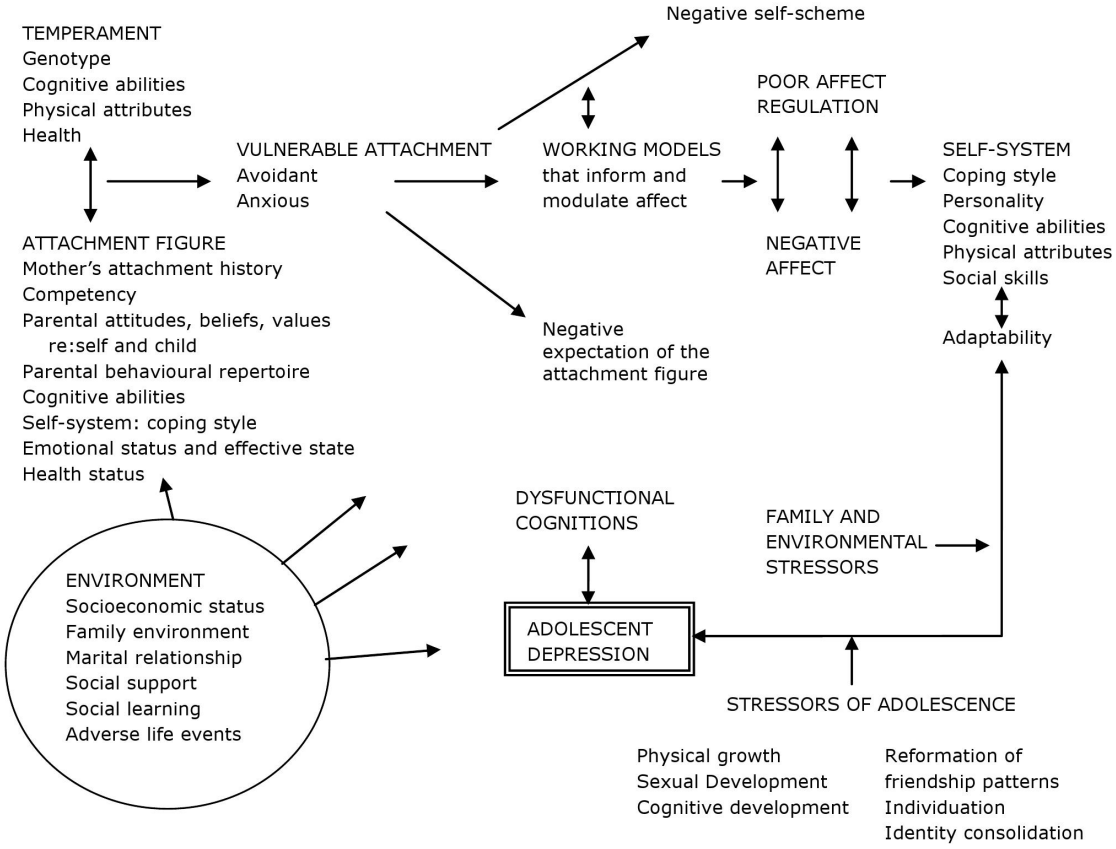


Figure 1.3: Factors affecting vulnerability to depression in adolescence. Adapted from The depressed child and adolescent [Goodyer, 2000].

A quarter of all lifetime cases of depression have started by age 19 [Kessler et al., 2005]. Moreover, internalizing disorders (anxiety and depression) in adolescence appear to be a risk factor for adult psychiatric outcomes. Using the 1946 British cohort, about 70% of adolescents who had internalizing disorder at both ages 13 and 15 had a mental disorder at age 36, 34, or 53, compared with about 25% of mentally healthy adolescents [Colman et al., 2007].

1.5 How does this chapter inform my thesis?

As detailed in this chapter, parental postnatal depression is common in both new mothers and fathers and many studies have shown that it can negatively affect children in the

short and long term. However, many questions remain to be answered. Although the prevalence of maternal and paternal depression during the first year postpartum has been studied separately, there appears to be no consensus on the prevalence of comorbid or comorbid early parental depression, despite the meta-analysis by Paulson and colleagues concluding that the two are correlated. Therefore, I have undertaken a systematic review of the literature (Chapter 3) to try to determine an estimate of the prevalence of comorbid parental depression, as well as its effects on child outcomes as research in this area seems sparse.

In addition, most studies examining parental depression and its effects on child outcomes are small and focussed on 'soft' non-clinical outcomes (with ALSPAC as a notable exception). Hence, I will use a large UK primary care database (as detailed in Chapter 2) to assess whether early parental depression has an effect on clinically relevant child outcomes. Finally, the few studies that have tried to assess whether the postnatal period is a sensitive period for the transmission of parental depression, or whether exposure to chronic depression is more likely to facilitate this have suffered from methodological flaws and small sample sizes. I will use novel methods for mediation analysis and structural equation modelling to assess this question.

Chapter 2

The Health Improvement Network primary care database

2.1 Objectives of the chapter

In this chapter, I will provide an overview of The Health Improvement Network (THIN) primary care database, which I have used as a data source for my thesis. I will go over the history of THIN, the data quality and structure, how I have identified diagnoses and prescriptions, limitations of THIN, and I why I used THIN as data source.

2.2 The Health Improvement Network (THIN) database characteristics

2.2.1 The history of THIN: five decades of primary care databases

The Health Improvement Network (THIN) is a large UK primary care database containing electronic medical records on approximately 6% of the UK population. The development of the database started in the mid-1970s with Dr Alan Dean (Figure 2.1). Dr Dean was a general practitioner (GP) from Essex who wanted to develop a program to computerise his records and become paperless [Health Service Journal, 1999]. With the

help of the IT staff from a shoe factory located near his practice he built such a program and started selling it to other practices in 1979.

At the end of the 1980s, the need for large databases to undertake pharmacoepidemiological research was highlighted by the Committee on the Safety of Medicines [Hall, 1992]. The two systems in place at the time in the UK, the Yellow card system and prescription event monitoring[1] [Rawson et al., 1990] were criticised for having a low response rates and being too slow to inform regulatory decisions. Large database of routinely collected data were being set up in the US (by insurers) and Canada at the time and with an increasing proportion of UK GPs working in computerised practices, a general practice research database seemed like the solution.

In 1987, Dr Alan Dean set up Value Added Information Medical Products Ltd (VAMP) with the aim to recruit 950 practices covering five million patients. With the help of Dr Gillian Hall, they started building the first primary care database with the aim to find a way to detect adverse drug reaction signals [Walley and Mantgani, 1997, Hall, 1992]. This first database was called the Vamp Research Databank (VRD). The UK database would have the added advantage of containing a representative sample of the population as the majority of the population is registered with a GP.

At the time Dr Gillian Hall started work on the VRD, under 100 practices had computerised medical records, and over 50% of those who used a computer, used home written programs [Gillian Hall, personal communication]. The development of a database was further complicated by the way GPs used computers. Dr Hall identified three 'phases' for GPs to convert from using paper medical records to computerised record. In the first phase, GPs use the computer system for prescriptions only; in the second phase, they also use it for recording consultation details; and finally, they will use it for storing all medical records, including secondary care outcomes and medical history. In order to

[1]The Yellow card system (which is still in place today) allowed doctors to report adverse events by filling out a yellow card at the back of the British National Formulary (BNF). Prescription Event Monitoring (PEM) identified all prescriptions by compiling lists from all pharmacies in England. From these lists, the drug of interest and individual patients prescribed this drug were identified. The prescribing doctor was then send a personalised questionnaire to ask about potential adverse events

contribute to analyses of the database, practices needed to be in phase three.

A second problem was data storage. Soon after GP practices started sending in data, the VRD started exceeding the available storage capacity at the time. In order to solve the problem, an computing engineer had to be flown in from California to daisy chain[2] several hard-drives together in other to be able to store the data from the ten initial practices that formed the VRD.

To incentivise others to join, GPs were offered free computer equipment in exchange for entering clinical data in a standard manner and providing anonymised data to VAMP (if practices chose not to provide data, the costs for computers and software was about £25,000). The initial database was compiled to be used in post-marketing studies. One such study, with Dr Alan Dean as co-author, examined the risk of suicide among people taking 10 commonly prescribed antidepressants [Jick et al., 1995]. At that time, data was available from 495 practices comprising 172,598 people who had at least one antidepressant prescription between 1988 and 1993.

In 1993 at the peak of VAMP's popularity with 6,000 GPs using it, Dr Dean sold the company to Reuters. Unfortunately, Reuters was only interested in the computer systems, not in the VRD database and was considering shutting the database down. However, Reuters donated the VRD 'for the public good' to the Department of Health, who renamed it the General Practice Research Database (GPRD) [Ogdie et al., 2012]. To allay GP anxiety the Department of Health would use the database to monitor their activity and link it to funding, the Office of National Statistics (ONS) was put in charge of the database. The GPRD moved again in 1999 from ONS to the Medicines and Healthcare products Regulatory Agency (MHRA) which still manages it today (although the name has changed to Clinical Practice Datalink - CPRD - in April 2012).

In 1994, EPIC, a new non-profit company set up by Dr Alan Dean, aquired a license to use the GPRD by the Department of Health. Meanwhile, VAMP had changed its name to In Practice Systems Ltd (INPS) and had bought back the practice management software from Reuters, calling it Vision. Despite the early setback with the VRD, INPS and EPIC teamed up in 2002, when EPIC's licence to the GPRD database expired, to form The

[2]Daisy chaining is a wiring scheme in which multiple devices are wired together in a sequence or ring to boost power, analog signals, or data storage capacity.

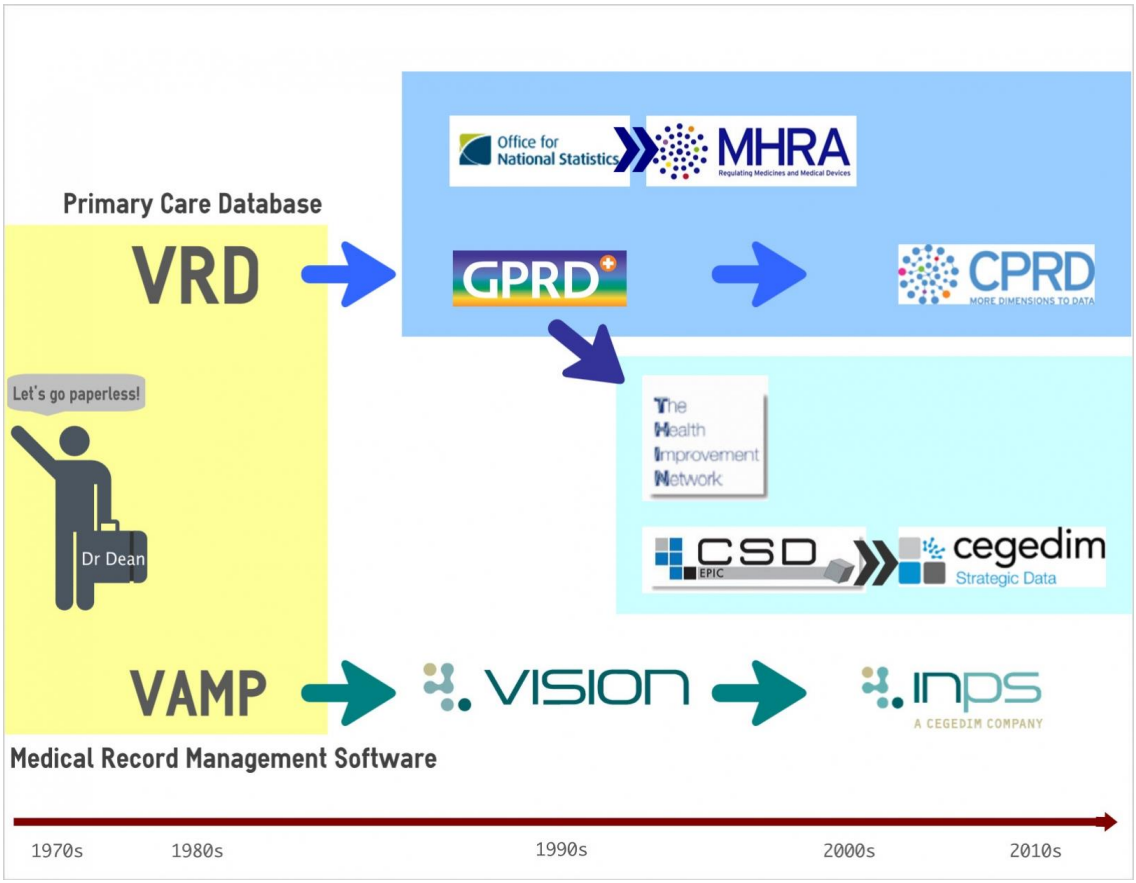


Figure 2.1: How THIN came to be. Yellow: VRD database (managers); blue: CPRD database (managers); green: THIN database (managers)

Health Improvement Network (THIN). The aim of this collaboration was to set up a new 'real life' database, while at the same time improving the quality of data recording by providing feedback and training to GPs. INPS dispersed and supported Vision software while EPIC managed data extraction and database use [Ogdie et al., 2012]. THIN started data collection in 2003, but data goes back to the 1980s for some practices. A final change happened in 2005 when Cedegim, the company owning INPS, acquired EPIC. EPIC was renamed to Cedegim Strategic Data (CSD) Medical Research UK.

2.2.2 THIN today

Apart from sharing a common history, THIN and the CPRD also share practices. Both databases collect similar data from practices using Vision software, and as a result, some practices appear in both databases [Lewis et al., 2007]. The most recent estimate, from

2009, is that 30% of GPRD practices also contribute to THIN [Ogdie et al., 2012].

When a practice first joins the THIN scheme, an initial Full Data Collection (FDC) is performed. This FDC includes all retrospective data available at the practice, going back to when the practice first started using Vision/VAMP software (1988 for the first practices) or switched to Vision, and is collected for THIN. Following this first data collection, incremental data are collected automatically and downloaded electronically each month. The data collection software used by Vision practices allows for data collection without interruption to the running of the GPs system. This method ensures minimal disruption to daily practice activities and maximises data security.

Each year, THIN GPs record information on 3-5 million patients, accounting for 5-7% of the population [Lewis et al., 2007]. The latest version of the database (updated to December 2012) included data on 559 practices, covering 11,350,933 patients, 3,802,018 of whom were 'active' patients who can be followed prospectively. This latest data cut covers 6% of the UK population [UK, 2012].

The overall majority of people living in the UK (the usually resident population) is registered with a GP: in April 2011, the NHS Patient Register contained records on 58,471,500 individuals in England and Wales. The Patient Register bases its counts on numbers reported by each Primary Care Trust (PCT). The 2011 Census, carried out on 27 March 2011, estimated the population to be 56,075,912 at that time (Office for National Statistics 2012). The difference between the two estimates (the NHS Patient Register estimate is 4.3% higher than the Census estimate) is likely due to both over and under coverage.

Patients could be counted twice if they are registered in multiple locations, which can happen temporarily when a patient is transferring GPs, or permanently if their new practice fails to identify a person as already being on the register and provides them with a new NHS number (e.g. if they spell their name differently). These so-called 'ghost patients' could also erroneously remain registered with their original practice if they do not notify their GP of their move. Furthermore, lags in the recording of births and deaths, immigrations and embarkations (especially if patients choose to stay registered in order to access healthcare in the UK) can influence the number of records in the Patient Register.

The number of individuals on the Patient Register has been slightly higher than

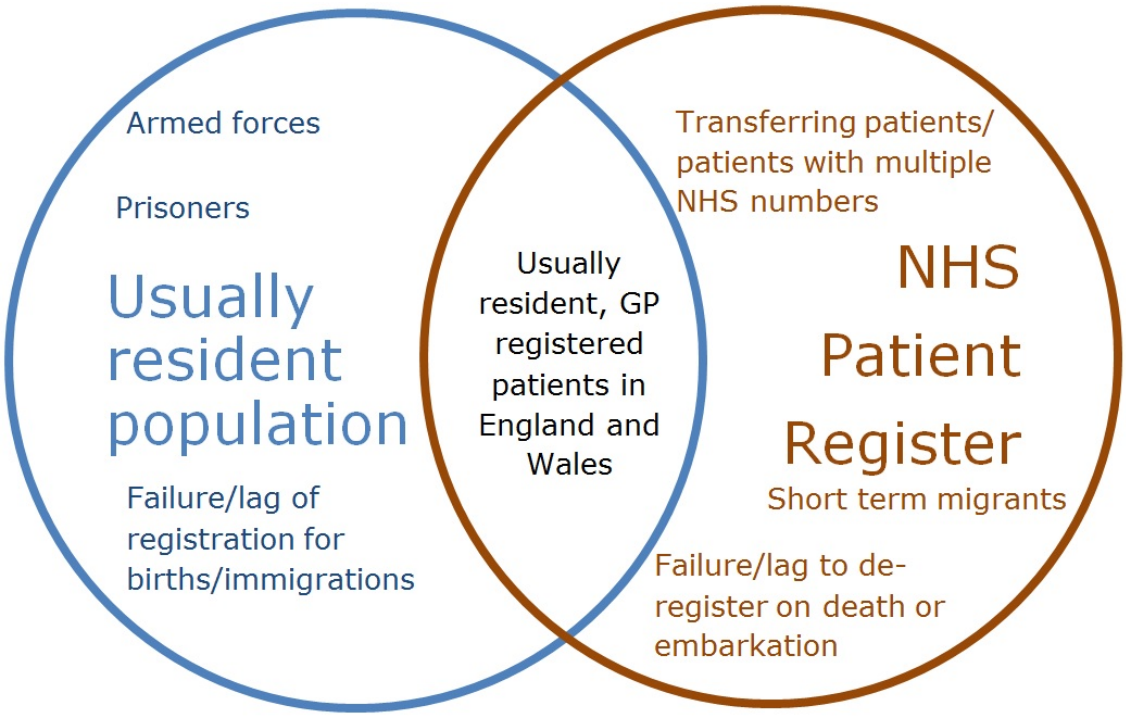


Figure 2.2: Differences between the usually resident population and the NHS Patient Register

estimates of the usually resident population in every year since 1961. Some groups of the usually resident population are known not to be registered with a GP practice, such as armed forces personnel, prisoners and non-registered immigrants. However, some people not included in the usually resident population such as short term migrants (for instance some students on language courses) might register with a GP and be recorded in the Patient Register (Figure 2.2). For the reasons outlined above, it is difficult to provide an accurate number on what proportion of the population is registered with a GP.

As an estimate of the theoretical proportion of the GP registered population, the armed forces made up 0.3% of the UK population on 1 April 2011[3], and prisoners accounted for 0.2%, also on 1 April 2011[4]. A study by the LSE estimated the number of

[3] 192.330 trained and untrained personnel (Defence Statistics 2013) / 63,182,175 UK population on 1 April 2011 according to Census data (Office for National Statistics 2013)

[4] 85,447 prisoners in England and Wales (Ministery of Justice 2012) / 56,075,912 England and Wales population on 1 April 2011 according to Census data (Office for National Statistics 2012)

illegal immigrants at 618,000 at the end of 2007 (estimate range: 417,000 - 863,000) (Gordon et al. 2009), making up 1.0% (0.7% - 1.4%) of the population[5]. Excluding these groups of people leads to an estimate that approximately 98.5% of the UK usually resident population is registered with a GP, suggesting that the GP-registered population is highly representative of the total UK population. It is likely that some other vulnerable populations, such as homeless people, are also less likely to be registered with a GP.

GPs use electronic medical records to document information about their patients' health and prescriptions. Data is collected on patient demographics (date of birth, date the patient registered with and left the practice, and a household identifier number), diagnoses (including details on hospital admissions, discharge medication and diagnosis), prescribing, additional health data (tests, laboratory results, lifestyle factors such as alcohol and smoking), free text comments, and socioeconomic data.

As shown in Figure 2.3, not all health events that occur in the community are recorded in primary care and hence in THIN. Health events need to be reported by patients to GPs, and GPs need to record them. Events could be lost if GPs do not record them, if patients do not deem events important enough to warrant a GP visit, or if they choose to go to a walk-in centre or hospital instead. In the case of hospital visits, the GP will often receive a discharge letter. However, discharge letters are now often received digitally and can be saved as (scanned) attachments or free text. As a result, these might not be directly available to researchers using THIN, unless participating practices also enter any diagnoses made directly into the patient's medical records.

Before data is available to researchers, it is quality checked (see section 2.3, page 56 for more details) and anonymised by CSD: date of birth is changed into year of birth (although children up to the age of 15 will have both year and month of birth available) and any names or addresses (from both patient records and free text comments) are removed. The data collection for THIN was approved by the NHS South-East Multi-centre Research Ethics Committee in 2003. In order to gain approval for individual studies, study protocols are reviewed by an Independent Scientific Review Committee (SCR) led by CSD Medical Research UK.

[5]Estimates based on a mid-2007 UK population estimate of 60,985,700 individuals (Office for National Statistics 2011)

The UCL Research Department Primary Care & Population Health has acquired a full license for access to THIN data for the purposes of conducting large-scale epidemiological, clinical and health care utilisation studies.

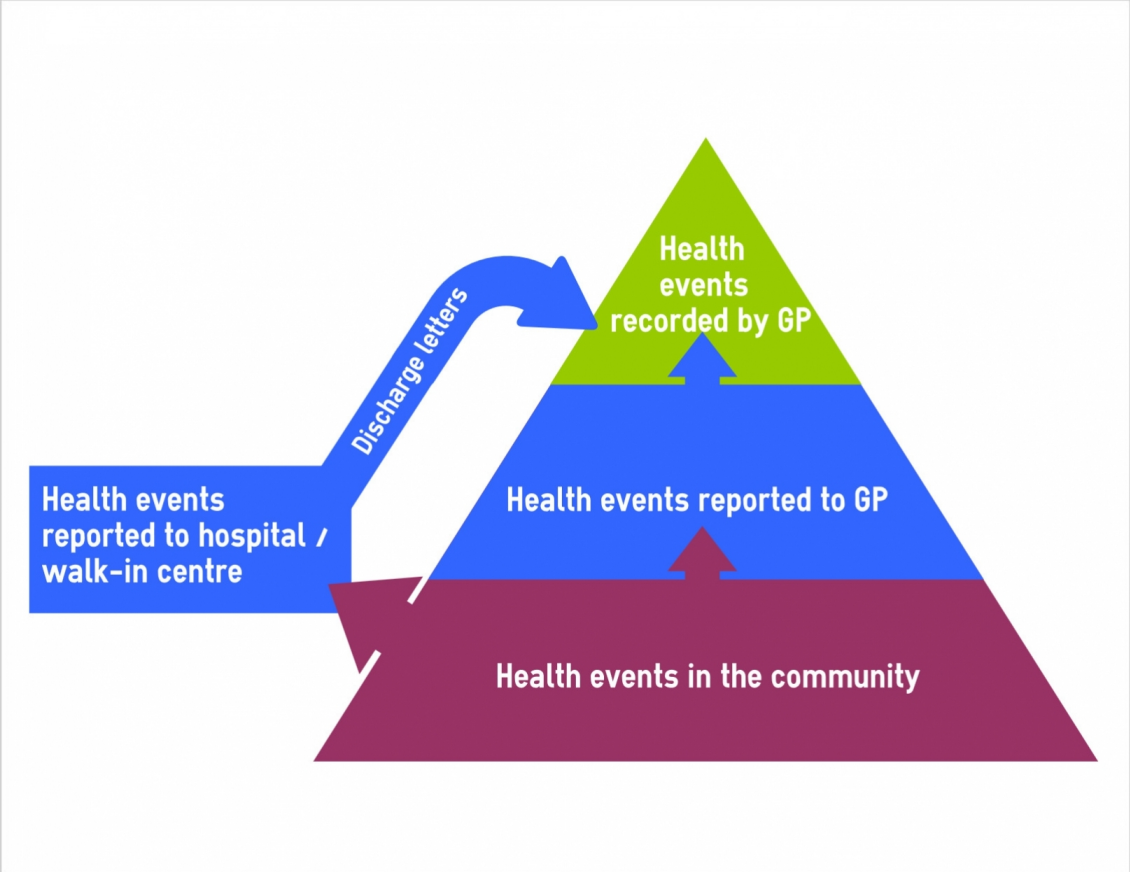


Figure 2.3: Recording of health events in THIN

2.3 Data quality and structure

2.3.1 Acceptable Mortality Reporting and Acceptable Computer Usage

For the first 100 practices that joined the THIN scheme, preliminary audits of consultations and prescriptions were compared to national figures. Incremental data collection undergoes consistency and integrity checks. This information is used to provide feedback to the GPs regarding UK quality metrics performances, medical history recording,

and comparison of prevalence of disease with national levels where available.

An extra check performed by CSD is the calculation of the Acceptable Mortality Reporting (AMR) date [Maguire et al., 2009]. The AMR date is the year from which the practice is deemed to be reporting all-cause mortality based on predicted numbers of deaths derived from National statistics given the practices's demographics (Figure 2.4).

When practices first switch to using electronic medical records, there might be a period when they use both the electronic record system and physical records. This would lead to an underestimate of the incidence of some health events.

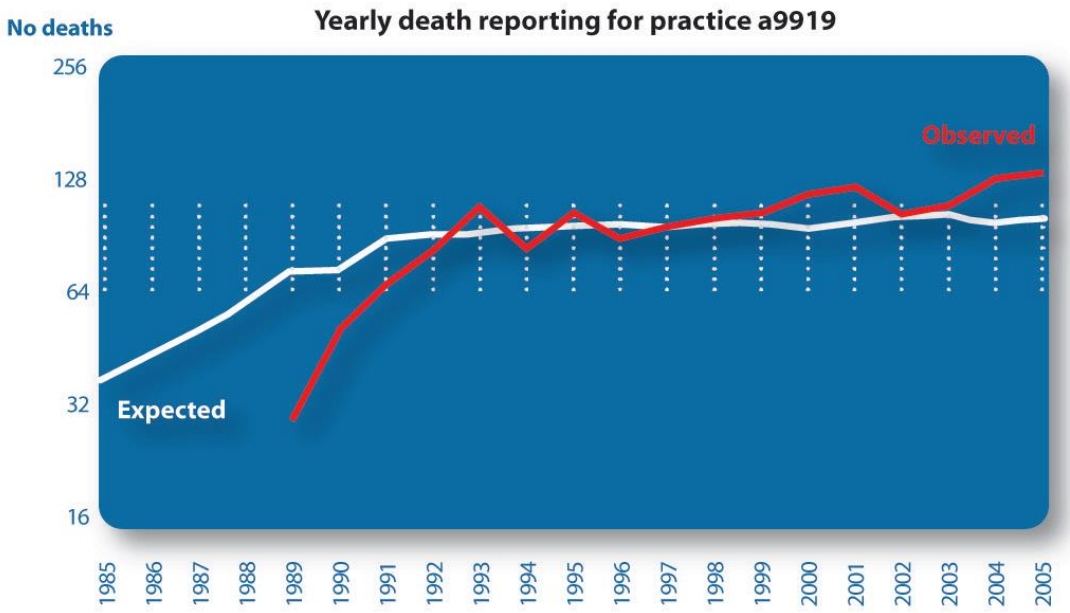


Figure 2.4: Example practice for determining the Acceptable Mortality Recording (AMR) year

Thus, practices might have started by using the electronic system for the most basic recording (e.g. registration, demographics, death) and continue to use paper-based recording for diagnoses and writing prescriptions. To correct for this, the Acceptable Computer Usage (ACU) date was developed by the research team at UCL [Horsfall et al., 2013]. The ACU date marks the date by which a practice was continuously entering on average at least two therapy records, one medical record and one additional health record per patient per year (see Section 2.3.2 on page 59 for information on THIN data files), and is 3.3 years later than the AMR date, on average. Applying the ACU date as a cut-off

for selecting high quality data resulted in incidence rates that were more comparable to external sources, as compared to just using the AMR date [Horsfall et al., 2013].

Table 2.1: Main file types of THIN data

File name	Information contained in file
Patient records	age, sex, registration date when entering the practice, and date when leaving the practice
Medical records	medical diagnoses, date of diagnosis, and location (e.g., GPs office, hospital, consultant) of the event and an option for adding free text; referrals to hospitals and specialists
Therapy records	all prescriptions along with the date issued, formulation, strength, quantity, and dosing instructions, and events leading to withdrawal of a drug or treatment
Additional Health Data (AHD)	vaccinations and prescription contraceptives; miscellaneous information such as smoking, height, weight, immunizations, pregnancy, birth, death, and laboratory results
Postcode Variable Indicators (PVI)	postcode linked area based socio-economic, ethnicity and environmental indices
Consultation records	date, time and duration (time patient record remained opened) of consultation
Staff records	gender and roles of staff who entered data

2.3.2 Data structure

THIN data is structured in seven standardised files that are available for each individual practice (Table 2.1), and one file containing basic information on each practice included in THIN.

Although the file types are intended to record different information, there is some redundancy between the files. For instance, suicides can be recorded in different places. It could be recorded in a patient's medical records using a diagnosis code, in the Additional Health Records which has a specific field for recording cause of death, or it could be recorded as free text. These different types of suicide records are entered in different sections of the Vision system, and it depends on a GP's personal preference where a record will be recorded. Because of this, it is important to consider multiple file types and codes when identifying cases and covariates, as explained in the next section.

2.4 Identifying cases and confounders

2.4.1 Diagnoses: Read codes in THIN

Diagnoses and symptoms are recorded using a system of diagnosis codes called Read codes [Booth, 1994, Chisholm, 1990]. The Read codes were developed by Dr James Read in the 1980s and are used in general practice in the UK. Read codes form a hierarchical system of codes, divided in chapters and structured similarly to the International Classification of Diseases (ICD).

Currently, there are just over 100,000 different Read codes. As a result, one diagnosis can usually be represented by several Read codes, ranging from very general to very specific. For instance, a search for the word 'depression' in Read code descriptions gives 130 different hits. Some of these codes are generic (e.g. 'Eu32z11: [X]Depression NOS')[6], while others are very specific (e.g. 'Eu32212: [X]Single episode major depression without psychotic symptoms'). As there are a variety of codes that could be used to describe the same condition, and which code is used is to some degree up to a GPs

[6]The '[X]' at the start of the Read code description indicates that this a Read code added after ICD-10 came out, and thus maps directly onto an ICD-10 code.

personal preference, it is preferable to use a code list to identify study populations.

A code list is a comprehensive set of condition-specific medical or drug codes which can be used by researchers to search patient medical/clinical and therapy records in primary care databases [Davé and Petersen, 2009]. Code lists are created by first identifying a list of key words that will be used to identify the disease or illness of interest. In the case of depression, words such as 'depressive', 'affective disorder', 'depressed', 'unipolar', and 'dysthymia' would need to be searched for as well in order to identify all relevant Read codes. Adding these key words to the initial search increases the yield to 319 Read codes.

However, some Read codes that relate to depression might not contain any of the key words. Therefore it is necessary to have a look at the identified Read codes and identify common stems. As the Read codes form a hierarchical system, codes relating to a similar disorder will have similar stems. By browsing through the Read codes looking for these common stems, codes such as 'Loss of interest in previously enjoyable activity' or 'Low mood' can be identified as well.

The final step of creating a code list is excluding irrelevant codes. As the key words used to identify relevant codes tend to be sensitive rather than specific, it is common that irrelevant codes are also included at this stage. For depression, this also leads to codes such as 'ECG: S-T depression' or 'Bone marrow depression' also being included. An example code-list and Stata do-file are included in Appendix C on page 202.

Apart from diagnoses and symptoms, Read codes are also used to record patient demographics (e.g. occupation, ethnicity or family structure), or administration (e.g. referrals, receipt of a hospital letter, or administered questionnaires). There is a group of Read codes that relates to different questionnaires such as the HAM-D or EPDS (see Section 1.2.1 on page 31). While these could be relevant when trying to identify patients with depression, they are distinct from diagnoses: a patient could have filled out the questionnaire and not have any symptoms of depression. The result of a questionnaire could either be the recording of a subsequent depression diagnosis (or no addition recording if the patient is diagnosed as not depressed) or the score on the questionnaire can be entered in the free text field. As free text is not available for all patients, these codes are generally also excluded.

Two systematic reviews have reviewed the validity of diagnoses in the GPRD [Herrett et al., 2010, Khan et al., 2010]. Both reviews conclude that most diagnoses are well recorded in electronic databases, with the exception of acute conditions. The review by Herrett and colleagues collected 212 papers that investigated 183 different diagnoses [Herrett et al., 2010]. Most papers (85%) used external data to validate diagnoses. On average 89% of cases were confirmed for the different types of diagnoses, though confirmation rates ranged from 24% to 100%. The second review found similar results. As this review had slightly more strict inclusion criteria, only 49 papers were included [Khan et al., 2010]. It found that most diagnoses were accurately recorded in electronic records, with exception of acute conditions. Also, rates of diabetes and musculoskeletal conditions were found to be underestimated.

2.4.2 Prescriptions in THIN

Prescriptions issued by GPs are recorded in THIN. However, there is no information available whether prescriptions were dispensed by pharmacies, or whether patients take their prescriptions.

Comparing prescription data in THIN to dispensing data from NHS Prescription Services showed that the mean practice redemption rate (the percentage of recorded prescription which were dispensed) was as high as 97.4% in 2008, with rates ranging from 89.9% to 113.9% [The NHS Information Centre and Services, 2011]. The study focussed on 145 practices covering over 1 million patients and using data from 2004 to 2008. Rates can be higher than 100% when prescriptions are redeemed that were not issued on the GPs computer, for instance during home visits. When the redemption rate is less than 100%, it indicates the GPs have issued prescriptions that were not redeemed by patients.

Redemption rates for antidepressants were slightly lower at 96.7% (ranging from 88.2% to 112.5%) in 2008. This high redemption rate is surprising as a systematic review of 12 studies has found that patients with depression were three times as likely as other patients to be non-compliant with their medication [DiMatteo M et al., 2000]. This could suggest that the non-compliance happens after redeeming a prescription.

In THIN, prescriptions were until recently coded using Multilex codes provided by First Databank (FDB). There are just under 75,000 drug codes (as of 2012), and each

drug code relates to a specific drug at a specific dose. On top of information about drug name and dose, there is also information about which British National Formulary (BNF) chapter the drug appears in. This is very useful information when creating drug code lists as these can be solely based on the relevant BNF chapter (e.g. chapter 4.3 Antidepressant drugs).

2.5 Limitations of THIN

Although THIN provides unique clinical information useful for epidemiological research on a large number of people, it also has some limitations. As mentioned in the previous section, THIN only contains information on prescriptions, not whether these were dispensed or whether patients take their medication. However, it is possible to get an indication of whether patients are adhering to their medication by looking at repeat prescriptions. If a patient receives a prescription for a drug that is intended to be taken long term (or at least for more than one prescription), you would expect the patient to come back for a repeat prescription. If a patient in this situation has only a single record of a prescription, this probably indicates that the patient did not adhere to the prescription. If there are multiple prescriptions (for instance, at least two within a certain time period), it is more likely that the drug is actually being dispensed and being used by the patient. Furthermore, THIN does not contain information on prescriptions that were issued in secondary care such as by a psychiatrist (although some information might be available in the free text as hospital discharge letters).

Secondly, patients are only followed as long as they stay registered with the same practice within THIN. If patients move to another practice not contributing to the database, they are lost to follow-up. However, it is possible that a few patients re-register with another practice that contributes data to THIN. In that case these patients may be counted twice, though this will be rare.

2.6 Why use THIN for this thesis?

To explore the intergenerational transmission of depression, a long follow-up time of at least 15 years is necessary. This follow-up time is difficult and extremely costly to achieve

in regular cohort studies, especially if the study is large. Hence, most epidemiological studies assessing the effects of postnatal depression on child outcomes are small and have short follow-up times. Moreover, as cohort studies tend to rely on questionnaires, child outcomes are usually 'soft' outcomes. Outcomes measured this way might not relate to diagnoses and could thus not have an important impact on a child's life.

With THIN, it is possible to follow a relatively large cohort of families over a prolonged period of time. With data up to 31 December 2011 available, children born before 1997 are eligible to be included in the THIN birth cohort I will use for my analysis. Over this time period, many GP practices will have used electronic health records for a number of years. Also, by using a primary care database, I can assess 'hard' diagnostic outcomes. Finally, loss-to-follow-up will be less of a problem in THIN compared to cohort studies. In cohort studies, families with a lower socioeconomic status tend to be more likely to drop out, while this will be less of an issue in THIN. However, families will be lost if they move and transfer out of a practice. Finally, a birth cohort linking mothers, fathers and their children has already been created in THIN [Davé et al., 2010].

In order to use THIN data, I have applied for and received scienitfic approval for all studies included in this thesis (Appendix G).

Part II

Parental and adolescent depression

In part II of my thesis, I explore my main exposure and outcome variables: comorbid early parental depression and adolescent depression. As discussed in Chapter 1, depression during the first year after birth is common in both mothers and fathers. Throughout my thesis I will use the term 'early depression' to signify parental depression in the first year after childbirth. I use this term in preference to 'postnatal' depression as I also include fathers' depression and some argue that fathers' depression is distinct from maternal postnatal depression that could be influenced by womens' physical and hormonal changes occuring after childbirth. As this discussion is beyond the scope of my thesis, I have chosen to use the term 'early depression' for both parents.

Several studies have found that depression in mothers and fathers is correlated [Dudley et al., 2001]: if one parent is depressed, the other is more likely to be depressed as well. A recent meta-analysis by Paulson and Bazemore found a moderately positive correlation between paternal and maternal depression (r=0.308; 95% CI: 0.228-0.384) [Paulson et al., 2006]. Similarly, a narrative review by Goodman found that one in four partners of postnatally depressed mothers were depressed themselves [Goodman, 2004]. Depression rates in fathers were significantly higher when mothers were severely depressed, with levels in up to 50%.

Many studies have found that maternal [Brennan et al., 2000, 2002, Hanington et al., 2011], and to a lesser extent, paternal postnatal depression [Goodman, 2004, Ramchandani et al., 2005a, 2008b] can have adverse effects on childhood outcomes. However, studies have generally only considered one depressed parent and ignored the potentially additive or multiplicative effects of comorbid parental depression. Theoretically, if one parent is depressed, the second non-depressed parent could form a 'buffer' to the child, providing the stimulation and affection the depressed parent is limited in giving. In the case of comorbid depression, where both parents experience depression simultaneously, the child could be deprived of this stimulation and affection and could experience more and more severe child outcomes.

However, few estimates of the prevalence of early comorbid parental depression are found in the literature. Therefore, I have performed a systematic review to estimate the prevalence and effects on childhood outcomes of early comorbid parental depression. This review forms Chapter 3.

In Chapter 4, I use THIN to explore childhood depression in more detail. As detailed in chapter 1, the prevalence of major depressive disorder is estimated to be approximately 2% in children and 4% to 8% in adolescents, with a male-to-female ratio of 1:1 during childhood and 1:2 during adolescence [Birmaher, 1996]. The risk of depression increases by a factor of 2 to 4 after puberty, particularly in females [Angold et al., 1998], and the cumulative incidence by age 18 is approximately 20% in community samples [Lewinsohn et al., 1998, Birmaher et al., 2007].

Depression is treated with psychological therapy or antidepressants. However, there have been doubts about the efficacy and safety of antidepressant use in children and adolescents, which I detail in Appendix B. Next, I describe trends in the recording of depression diagnoses, symptoms and antidepressant prescriptions in children and adolescents.

Chapter 3

Systematic review

3.1 Objectives of the chapter

The objectives of this review are to:

1. estimate the prevalence of comorbid postnatal depression during first year postpartum

2. assess the effects of comorbid parental postnatal depression on children

3.2 Methods

3.2.1 Criteria for considering studies for this review

3.2.1.1 Types of studies

Published and unpublished observational studies (cohort and cross-sectional studies) were included in this review if they reported the prevalence or incidence of comorbid parental postnatal depression. Studies were considered if they were published between January 1980 and December 2012.

3.2.1.2 Types of participants

Parents aged 15 to 50 years old, who had a primary diagnosis of depressive disorder according to DSM or ICD criteria assessed by a clinical interview, or who scored as

depressed on a validated questionnaire, during pregnancy or within 1 year of the birth of their child were included. Studies focussing solely on adolescent parents were excluded, as well as studies that used parents from high-risk populations as these groups of parents are likely to not be representative of the general population.

Parents who had suffered the loss of an infant, or parents of infants with chronic diseases were excluded from the current study as they are very likely to suffer from reactive depression in this situation which is distinct from depressive disorder. Studies including the effects on children were included for any type of effect and any age of the child (<18 years).

Types of outcome measures

1. Prevalence/incidence of depressive disorder according to DSM or ICD criteria

2. Prevalence/incidence of heightened risk of depression according to a validated questionnaire (e.g. Edinburgh Postnatal Depression Scale or Beck Depression Inventory), both as point prevalence or cumulative prevalence

3. Adverse outcomes in children

3.2.2 Search method for identification of studies

Computer searches for relevant studies were conducted on databases including PubMed, Web of Science, PsycINFO, CINAHL and EMBASE; and by consulting the reference lists of retrieved articles as well as relevant review articles and meta-analyses and a cited reference search of relevant articles.

The database search consisted of three terms: Outcome (depression), Subjects (both parents), and Timing (perinatal). The search strategies resulting from this method can be found in Table 3.1.

Table 3.1: Search strategies used in systematic review

	PubMed	Web of Science	PsycINFO	EMBASE	CINAHL
1	depression[MESH]	depress*	major depression/	major depression/	MH ”Depression, Post-partum”
2	depressive disorder[MESH]	dysthym*	postpartum depression/	puerperal depression/	MH ”Depression”
3	Depression, Post-partum[MESH]	”affective disorder”	depress$.ab	depression/	depression*
4	Puerperal Disorders[MESH]	”negative affect”	affective disorder$.ab	mood disorder/	dysthym*
5	1 OR 2 OR 3 OR 4	”mood disorder	mood disorder$.ab	depress$.af	affective disorder*
6	depress*	1 or 2 or 3 or 4 or 5	or/ 1-5	dysthym$.af	negative affect
7	dysthym*	paternal	paternal.ab	affective disorder$.af	mood disorder*
8	”affective disorder”	father*	father$.ab	mood disorder$.af	or/ 1-7
9	”negative affect”	7 or 8	fathers/	negative affect.af	MH ”fathers”
10	”mood disorder”	maternal	or/ 7-9	or/1-9	father*
11	6 OR 7 OR 8 OR 9 OR 10	mother*	maternal.ab	paternal.af	paternal
12	5 OR 11	10 or 11	mother$.ab	father$.af	or/ 9-11

continued on next page

Table 3.1: Search strategies used in systematic review

	PubMed	Web of Science	PsycINFO	EMBASE	CINAHL
13	fathers[MESH]	combined parental	mothers/	father/	MH ”mothers”
14	mothers[MESH]	(9 AND 12) OR 13	or/ 11-13	or/ 11-13	mother*
15	13 AND 14	postnatal	post?natal.ab	maternal.af	maternal
16	paternal	postpartum	post?partum.ab	mother$.af	or/ 13-15
17	father*	perinatal	peri?natal.ab	mother/	MH ”Postnatal Period”
18	16 OR 17	puerperal	postnatal/.ab	or/15-17	postnatal
19	maternal	antenatal	or/15-18	postnatal.af	postpartum
20	mother*	pregnancy	6 and 10 and 14 and 19	postpartum.af	perinatal
21	19 OR 20	15 or 16 or 17 or 18 or 19 or 10		perinatal.af	antenatal
22	”combined parental”	6 and 14 and 21		or/ 19-21	pregnancy
23	(18 AND 21) OR 22			10 and 14 and 18 and 22	or/ 17-22
24	15 OR 23				8 and 12 and 16 and 23
25	postnatal				

continued on next page

Table 3.1: Search strategies used in systematic review

	PubMed	Web of Science	PsycINFO	EMBASE	CINAHL
26	postpartum				
27	perinatal				
28	antenatal				
29	pregnancy				
30	25 OR 26 OR 27 OR 28 OR 29				
31	12 AND 24 AND 30				

3.2.3 Data collection and analysis

3.2.3.1 Selection of studies

I selected studies for inclusion in the review after employing the search strategy described previously. Where a title or abstract described a study eligible for inclusion, I obtained the full article and inspected it to assess relevance to this review based on the inclusion criteria. Study selection based on title and abstracts was performed independently by Shuk-Li Man and Jenny Woodman, full article inspection was checked by Ruth Blackburn, Jesca Brouwer and Hilary Davies.

3.2.3.2 Assessment of Study Quality

Studies were rated on the risk for selection bias (appropriate sampling method and clear inclusion/exclusion criteria 1 point each), representativeness of the study population (<60% of population in the same educational/socioeconomic group 1 point), response rate (adequate if >60% - 1 point), objectivity of the measurement instrument (validated questionnaire 1 point; or diagnostic interview/medical diagnosis 2 points), and reporting of ethical approval and funding disclosure (1 point). All assessment of the quality of studies was performed independently by reviewers (LW, RB, JB and HD). These quality measures were informed by the STROBE guidelines for observational studies [von et al., 2007].

3.2.3.3 Data extraction

Information on each study including quality characteristics and details regarding participants, comparisons, and outcomes was independently extracted by reviewers (LW, RB, JB and HD). The description of the included studies provides a context for discussing the reliability, internal and external validity of results.

I sought additional data from the principal authors of studies that appeared to meet the eligibility criteria when aspects of methodology were unclear, or where the data were missing, or were in a form unsuitable for meta-analysis. Study where the authors provided the necessary information were included.

Discrepancies in the study selection, study quality assessment and data extraction

phases were resolved by discussion or, if necessary, by a third reviewer.

3.2.3.4 Data analysis

Data analysis was undertaken using the meta-analytic methods available in Stata Statistical software (version 12.1, StataCorp).

3.3 Results: Prevalence of comorbid early parental depression

I identified 1554 studies, of which 690 were duplicates. Most remaining studies (n=761) were excluded because they were not applicable to the present systematic review (e.g. articles on other topics, depression only assessed in one parent, reviews or summaries, infant death, teen parents). Of those that were reviewed in full text (n=103), most were excluded because the diagnosis of depression was not ascertained (e.g. studies using reporting average questionnaire-based depression scores), while seven studies were not retrievable. Finally, 20 papers met the inclusion criteria for this systematic review (Figure 3.1) [Ballard et al., 1994, Bielawska-Batorowicz and Kossakowska-Petrycka, 2006, Currò et al., 2009, Davé et al., 2010, Escribà-Agüir and Artazcoz, 2011, Hanington et al., 2010, 2011, Kerstis et al., 2012, Lane et al., 1997, Muscat et al., 2012, Nishimura and Ohashi, 2010, Parfitt and Ayers, 2012, Paulson et al., 2006, 2009, Petitclerc et al., 2009, Ramchandani et al., 2005a, 2008b, Raskin et al., 1990, Soliday et al., 1999]. Of these studies, eight reported rates of comorbid depression at two or more time points and 11 reported a single observation. Apart from one study [Davé et al., 2010] that reported cumulative prevalence over the first year, all studies reported point prevalence rates.

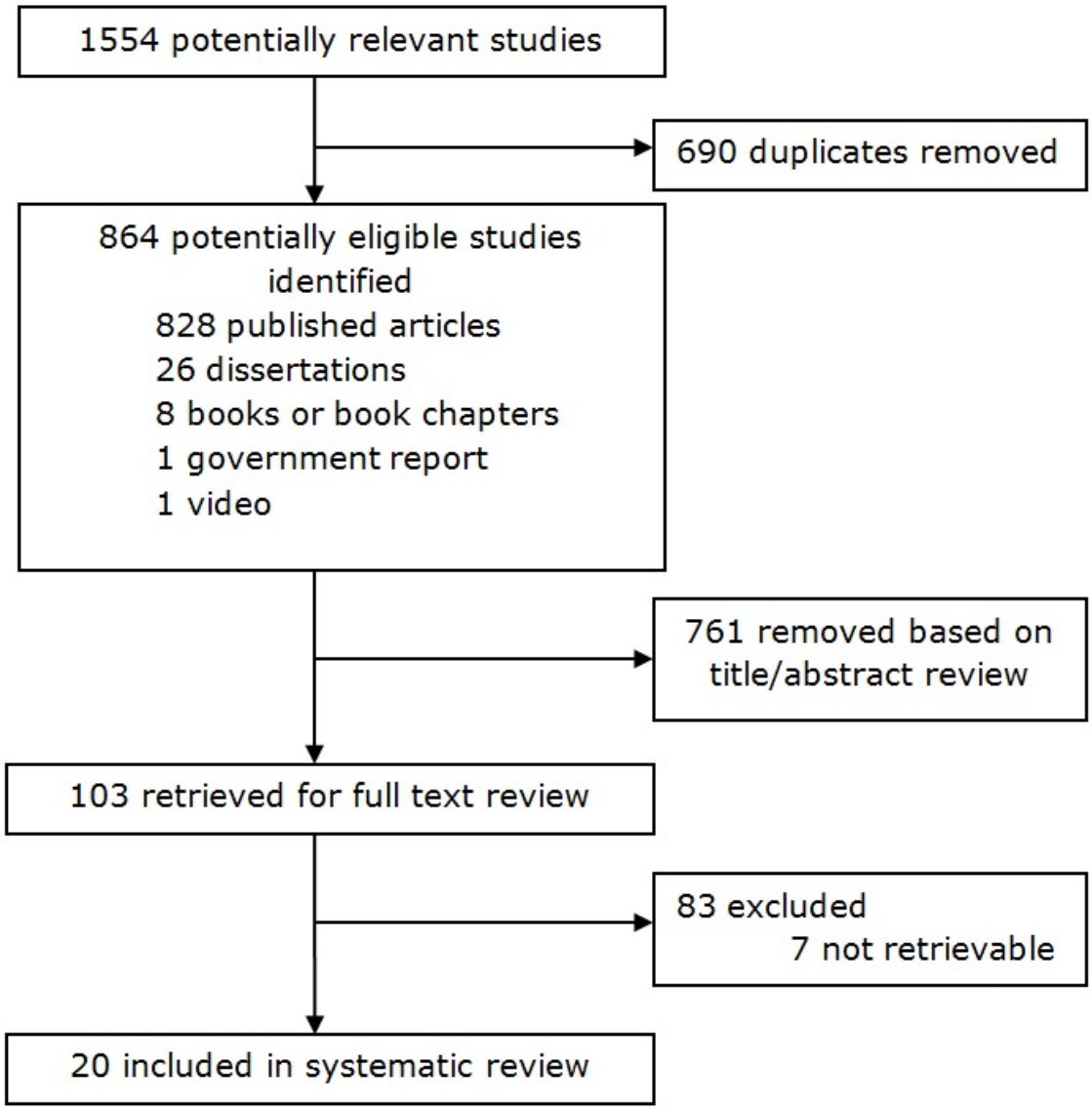
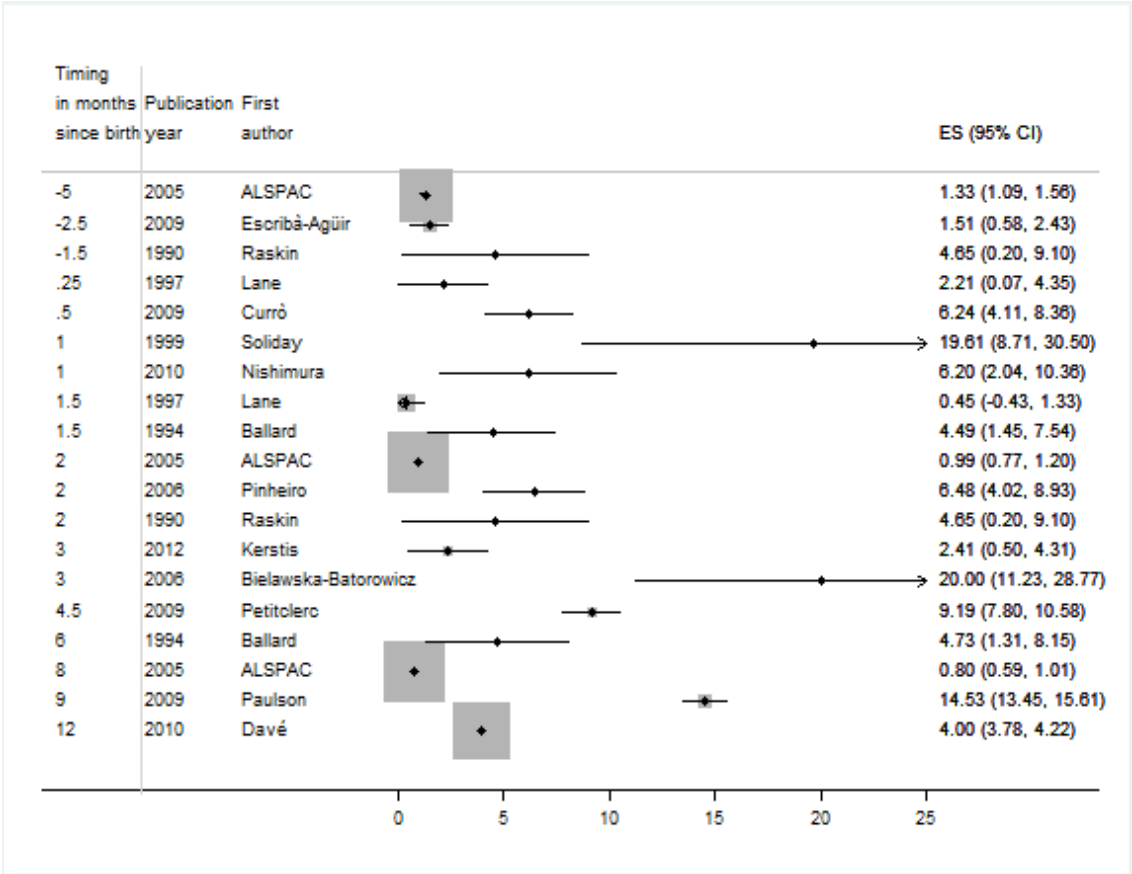


Figure 3.1: Study selection for inclusion in systematic review

Details on the characteristics of the 20 included studies are shown in Table 3.2. Studies originated from 10 different countries, with the United Kingdom contributing the most (n = 4 studies). Most studies used a validated self-report questionnaire as the primary case definition: The Edinburgh Postnatal Depression Scale (11 studies), the Center for Epidemiologic Studies Depression Scale (5 studies), and the Beck Depression Inventory (1 study). One study used a structured interview, and one used GP diagnoses. Sample sizes varied widely across studies (n = 40 - 72,861 couples), as did estimated rates of couple depression comorbidity (0 - 20%, Table 3.3). Rates of maternal depression ranged

from 4.5% to 39.2%, while rates for paternal depression were estimated between 0.9% and 27.5%.

Figure 3.2: Prevalence of comorbid early parental depression in the perinatal period. As the study by Paulson and Bazemore used 3 different cut-offs to determine depression, I chose the cut-off (CES-D>15) that was most commonly used by other studies to represent the study here. ES shows prevalence estimates with 95% confidence intervals, boxes represent study weights, studies that had prevalence rates of 0% are excluded



As studies used various instruments to measure depressive symptoms, at various time points, using different cut-off points (see Figure 3.2), it is not appropriate to summarise the results using a meta-analysis.

3.3.1 Study Quality

The quality of the included studies varied (Table 3.4 and Table 3.5). Most studies used appropriate sampling methods. However, Bielawska-Batorowicz and colleagues [Bielawska-Batorowicz and Kossakowska-Petrycka, 2006] used internet advertisements to recruit participants, which may be subject to selection bias as parents experiencing depression may be more likely to participate. Similarly, Soliday and colleagues [Soliday et al., 1999] used secondary recruitment or snowball sampling (i.e. participants recruited by other participants) to boost their sample size, again subject to selection bias. Two studies did not report on their sampling method [Raskin et al., 1990, Nishimura and Ohashi, 2010]. Most studies recruited participants in hospital after child birth.

Most studies (85%) reported on inclusion and exclusion criteria. Overall, studies were very inclusive, only excluding parents who did not speak the language used in the study questionnaires and excluding adolescent parents. Two studies did not report any inclusion/exclusion criteria [Raskin et al., 1990, Currò et al., 2009] , one study was unclear [Nishimura and Ohashi, 2010]. Eight study populations had limited educational or socioeconomic diversity, with 60% of participants at the same educational of SES level [Ballard et al., 1994, Currò et al., 2009, Kerstis et al., 2012, Parfitt and Ayers, 2012, Paulson et al., 2006, Raskin et al., 1990, Soliday et al., 1999].

Response and cohort retention rates were high (80%) in most samples, although few studies did not report on the number of people who were approached, so no response rates could be calculated. Moreover, some studies were cross-sectional so retention rates were not applicable to these studies.

All studies used validated measures of depression: validated questionnaires (18 studies), clinical interviews (1) and GP diagnoses (1). Although a few studies used the EPDS to measure depression in fathers before this questionnaire was validated for men, I have classified these as validated questionnaires as they used the cut-off score that was determined appropriate in the later validation. Only 7 (35%) of studies reported on receiving ethical approval and disclosed who funded the study.

Table 3.2: Characteristics of studies included in systematic review

First author, publication year	Country of study	Data source	Population included	Birth year(s)	Quality score
Ballard, 1994	England	Cross-sectional study recruiting married/cohabiting women from maternity hospital in Coventry	Maternity hospital	unclear	5
Bielawska-Batorowicz, 2009	Poland	Cross-sectional study recruiting couples from a maternity hospital in Lodz, Poland, and internet ads	Convenience sample	2002	3
Curro, 2009	Italy	Cross-sectional study recruiting women from a Pediatric Clinic	Hospital sample	2005	4
Dave, 2010	United Kingdom	The Health Improvement Network (THIN) UK primary care database	GP-registred population	1993-2007	8
Escrib-Agir, 2011	Spain	Cohort of women and partners attending a prenatal programme	Prenatal programme attendees	2005	6
Hanington, 2010	England	Avon Longitudinal Study of Parent and Children (ALSPAC) England, pregnancy cohort with follow-up through childhood	Population samle from SW England	1991-92	7

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Table 3.2: Characteristics of studies included in systematic review

First author, publication year	Country of study	Data source	Population included	Birth year(s)	Quality score
Hanington, 2011	England	Avon Longitudinal Study of Parent and Children (ALSPAC) England, pregnancy cohort with follow-up through childhood	Population samle from SW England	1991-92 s	6
Kerstis, 2012	Sweden	Cohort of parents attending child health centres (CHC)	Child Health Centre attendees	2004-06	5
Lane, 1997	Ireland	Cross-section of mothers from Dublin maternity hospital	Maternity hospital sample	unclear	4
Muscat, 2012	Australia	Parents attending general medical practices, antenatal classes, child health clinics and an early parenting centre in Brisbane	Community sample	unclear	5
Nishimura, 2010	Japan	Cross-section of mothers attending the 4 week postnatal health check at a general hospital or private clinic	Hospital/private clinic sample	2007	2
Parfitt, 2012	United Kingdom	Subsample from the longitudinal Sussex Journey to Parenthood Study	Population sample from SE England	unclear	5

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Table 3.2: Characteristics of studies included in systematic review

First author, publication year	Country of study	Data source	Population included	Birth year(s)	Quality score
Paulson, 2006	United States	The Early Childhood Longitudinal Study (ECLS), a national birth cohort	National probability sample of births	2001	5
Paulson, 2009	United States	The Early Childhood Longitudinal Study (ECLS), a national birth cohort	National probability sample of births	2001	5
Petitclerc, 2009	Canada	Quebec Longitudinal Study of Child Development (QLSCD), Quebec birth cohort	Sample of Quebec births	1997-98	6
Pinheiro, 2006	Brazil	Cross-section of births from urban area of Pelotas	Random sample of births	2004	4
Raskin, 1990	United States	Married primiparous couples attending childbirth preparation classes	Prenatal programme attendees	unclear	1
Soliday, 1999	unclear	Couples recruited from childbirth education classes, physician's offices, and recruited by participants	unclear	unclear	2

Table 3.3: Depression prevalence as recorded in studies. Studies are listed by time of parental depression assessment

Source (study location) and time of assessment	Depression measure (cut-off)	No. of couples (women)[a]	Depressed, No. (%)		
			Women	Men	Couples
ALSPAC, 2005, 2008, 2010, 2011 (UK)					
18 wks gestation	EPDS (>12)	8,972 (11,999)	1,667 (13.9)	396 (4.1)	119 (1.3)
Muscat, 2012 (Australia)					
27 wks gestation	EPDS (>12)	20 (35)	8 (22.9)	1 (4.0)	0 (0)
Escribà-Agüir, 2011 (Spain)					
29.5 wks gestation	EPDS (>13/10) [b]	664 (686)	71 (10.3)	43 (6.5)	10 (1.5)
Raskin, 1990 (US)					
34 wks gestation	CES-D (>15)	86	24 (27.9)	16 (18.6)	4 (4.7)
Lane, 1997 (Ireland)					
0.1 mo postpartum	EPDS (>12)	181 (289)	33 (11.4)	6 (3.3)	4 (2.2)
Currò, 2009 (Italy)					
0.5 mo postpartum	EPDS (>9/7)[b]	497 (1122)	298 (26.6)	63 (12.6)	31 (6.2)

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Table 3.3: Depression prevalence as recorded in studies. Studies are listed by time of parental depression assessment

Source (study location) and time of assessment	Depression measure (cut-off)	No. of couples (women)[a]	Depressed, No. (%)		
			Women	Men	Couples
Nishimura, 2010 (Japan)					
1 mo postpartum	EPDS (>8/7)[b]	129 (178)	50 (28.1)	17 (11.6)	[c] 8 (6.2)
1 mo postpartum	CES-D (>15)	129 (178)	43 (24.2)	11 (7.5)	
Soliday, 1999 (Canada)					
1 mo postpartum	CES-D (>15)	51	20 (39.2)	13 (25.5)	10 (19.6)
Ballard, 1994 (UK)					
1.5 mo postpartum	EPDS (>12)	178	49 (27.5)	16 (9.0)	8 (4.5)
Lane, 1997 (Ireland)					
1.5 mo postpartum	EPDS (>12)	223 (242)	24 (9.9)	2 (0.9)	1 (0.4)
ALSPAC, 2005, 2008, 2010, 2011 (UK)					
2 mo postpartum	EPDS (>12)	8113 (11575)	1175 (10.2)	291 (3.5)	80 (1.0)
Muscat, 2012 (Australia)					

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Table 3.3: Depression prevalence as recorded in studies. Studies are listed by time of parental depression assessment

Source (study location) and time of assessment	Depression measure (cut-off)	No. of couples (women)[a]	Depressed, No. (%)		
			Women	Men	Couples
2 mo postpartum	EPDS (>12)	20 (35)	8 (22.9)	3 (12.0)	0 (0)
Pinheiro, 2006 (Brazil)					
2 mo postpartum	BDI (>10)	386	91 (23.6)	46 (11.9)	25 (6.5)
2 mo postpartum	BDI (>18)	386	30 (7.8)	16 (4.1)	-
Raskin, 1990 (US)					
2 mo postpartum	CES-D (>15)	86	18 (20.9)	18 (20.9)	4 (4.7)
Bielawska-Batorowicz, 2006 (Poland)					
3 mo postpartum	EPDS (>12)	80	25 (31.2)	22 (27.5)	16 (20.0)
Kerstis, 2012 (Sweden)					
3 mo postpartum	EPDS (>9)	249 (260)	43 (16.5)	22 (27.5)	6 (2.4)
Petitclerc, 2009 (Canada)					

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Table 3.3: Depression prevalence as recorded in studies. Studies are listed by time of parental depression assessment

Source (study location) and time of assessment	Depression measure (cut-off)	No. of couples (women)[a]	Depressed, No. (%)		
			Women	Men	Couples
4.5 mo postpartum	CES-D (>75th centile)	1654 (1936)	520 (26.9)	417 (25.6)	152 (9.2)
Parfitt, 2012 (UK)					
5.4 mo postpartum	Birmingham Interview of Maternal Mental Health	40 (45)	5 (11.1)	3 (7.5)	0 (0)
Ballard, 1994 (UK)					
6 mo postpartum	EPDS (>12)	148	38 (25.7)	8 (5.4)	7 (4.7)
ALSPAC, 2005, 2008, 2010, 2011 (UK)					
8 mo postpartum	EPDS (>12)	6862 (11060)	968 (8.8)	206 (2.9)	55 (0.8)
Paulson, 2006, 2009 (US)					
9 mo postpartum	CES-D (>15)[d]	4109	1516 (36.9)	1205 (29.3)	597 (14.5)

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Table 3.3: Depression prevalence as recorded in studies. Studies are listed by time of parental depression assessment

Source (study location) and time of assessment	Depression measure (cut-off)	No. of couples (women)[a]	Depressed, No. (%)		
			Women	Men	Couples
9 mo postpartum	CES-D (>21)[d]	4109	551 (13.4)	397 (9.7)	105 (2.6)
9 mo postpartum	CES-D (>26)[d]	4109	186 (4.5)	150 (3.7)	25 (0.6)
Davé , 2010 (UK)					
12 mo postpartum	GP diagnosis	72861 (72306)	10072 (13.9)	4423 (6.1)	1263 (4.0)

[a] Numbers in parentheses represent the number of women who participated at each time point. If no separated number of women is reported, the number of female participants is equal to the number of participating couples

[b] First cut-off for women, second cut-off score for men

[c] Parents were classified as depressed if they scored above the cut-off on either or both questionnaires

[d] Authors used short-form of CES-D, scores 'translated' to regular CES-D

Table 3.4: Risk of bias summary: review authors judgements about each risk of bias item for each included study

	Sampling method (selection bias)	Clear inclusion/exclusion criteria (selection bias)	Educationally/socio-economically diverse population	Adequate response rate	Objective measurement of parental depression	Report ethical approval & funding disclosure
Ballard, 1994	+	+	-	+	+	-
Bielawska-Batorowicz, 2006	-	+	+	?	+	-
Currò, 2009	+	+	-	+	+	-
Davé, 2010	+	+	+	+	++	+
Escribà-Agüir, 2011	+	+	+	+	+	?
Hanington, 2010	+	+	+	+	+	+
Hanington, 2011	+	+	+	+	+	+
Kerstis, 2012	+	+	-	+	+	?
Lane, 1997	+	+	?	+	+	?
Muscat, 2012	+	+	+	?	+	+
Nishimura, 2010	?	?	+	-	+	?
Parfitt, 2012	+	+	-	?	++	+
Paulson, 2006	+	+	-	+	+	?
Paulson, 2009	+	+	-	+	+	?

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Table 3.4: Risk of bias summary: review authors judgements about each risk of bias item for each included study

	Sampling method (selection bias)	Clear inclusion/exclusion criteria (selection bias)	Educationally/socio-economically diverse population	Adequate response rate	Objective measurement of parental depression	Report ethical approval & funding disclosure
Petitclerc, 2009	+	+	+	+	+	?
Pinheiro, 2006	+	+	+	?	+	?
Ramchandani, 2005	+	+	+	+	+	+
Ramchandani, 2008	+	+	+	+	+	+
Raskin, 1990	?	-	-	?	+	?
Soliday, 1999	-	-	-	-	+	?

3.4 Results: Childhood outcomes

Two studies reported on the association between couple depression comorbidity and childhood outcomes (Table 3.6). One of these studies reported on couple depression prevalence [Paulson et al., 2006], while the second study only reports depression prevalence for mothers and fathers separately [Mezulis et al., 2004].

The study characteristics of the study conducted by Paulson and colleagues [Paulson et al., 2006] are represented in Tables 3.2-3.5. Paulson and colleagues found that couples

Table 3.5: Risk of bias overview: review authors judgements about each risk of bias item presented as percentages across all included studies. + means a study complies with that measure, ? means compliance could not be assessed by the information in the paper, - means the study does not comply

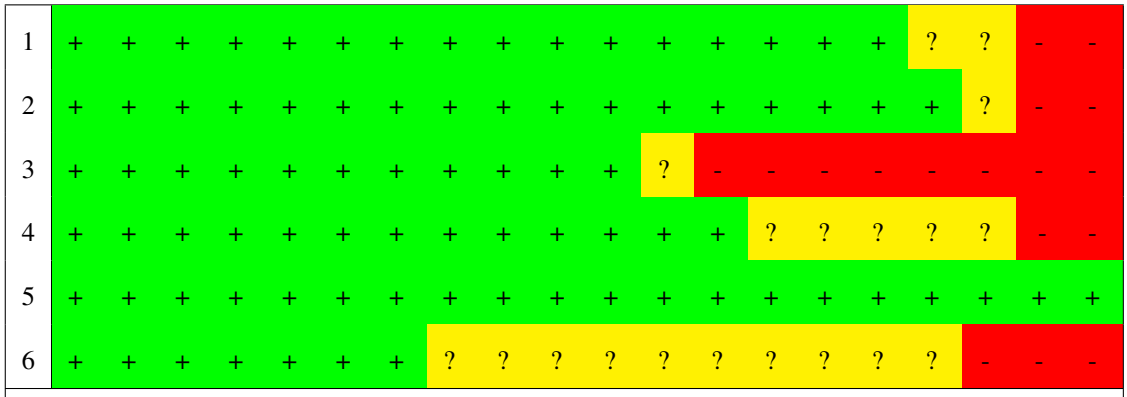


Table 3.6: Characteristics of studies included in child outcomes systematic review

Source (study location)	Child outcome measure	N of children	Child age at assessment
Paulson, 2006 (US)	Patient health behaviour Parent-child interaction	5089	9 months
Mezulis, 2004 (US)	Internalizing behaviour Externalizing behaviour	350	5 years

where both parents were depressed were less likely to follow anticipatory guidance recommendations on health behaviours compared to both couples where only one parent was depressed, and where both parents were non-depressed. Specifically, when both parents were depressed, the child was less likely to be put to sleep on his/her back (41% comorbid depressed versus 54% for both not depressed, $p<0.001$), was less likely to have ever been breastfed (64% comorbid depressed versus 74% for both not depressed, $p<0.001$), and was more likely to be put to bed without a bottle (62% comorbid depressed versus 75% for both not depressed, $p<0.001$), or awake (54% comorbid depressed versus 61% for both not depressed, $p<0.05$). Parent-child interaction behaviours were also affected as mothers were least likely to play peekaboo with their infants when both parents were depressed (85% comorbid depressed versus 88% for both not depressed, $p<0.01$), and fathers were least likely to play outdoor games (53% comorbid depressed versus 60% for both not depressed, $p<0.05$), or sing songs (29% comorbid depressed versus 35% for both not depressed, $p<0.10$) with their infants.

The study by Mezulis and colleagues [Mezulis et al., 2004] recruited women and their partners during pregnancy through US obstetric and hospital clinics and is part of the Wisconsin Maternity Leave and Health (WMLH) Project. To be included in the study, at least one member of the couple had to be working for pay or profit, and mothers were excluded if they were students, or unemployed and not looking for work. Of all eligible women, 75% agreed to participate, and 77% of women who participated were followed up to child age 5 years, compared to 64% of men.

The study by Mezulis used the CES-D questionnaire to assess depression in men and women at 1 month, 4 months, 12 months postpartum and when the child was in kindergarten, but also assessed mother's depression using the Diagnostic Interview Schedule (DIS). Women were depressed between 3.7% and 4.6% in the first year after childbirth according to the DIS, compared to between 5.9% and 11.6% as measured by the CES-D. Men were only scored using the CES-D and between 10.2% and 15.6% of fathers were depressed. Children's behaviour problems were measured when children were in kindergarten (age 5-6 years) with the Health and Behavior Questionnaire (HBQ) which was administered via the teacher by telephone interview. The mental health domain of the questionnaire used in this study focussed on internalizing (depression and anxiety symp-

toms) and externalizing behaviour (symptoms of conduct disorder, oppositional defiant disorder, overt aggression and attention deficits).

Mezulis and colleagues found that paternal depression during a child's infancy exacerbated the effect of maternal depression. Paternal depression had little effect on the children of non-depressed mothers. The highest levels of internalizing behaviours were found in children of parents where both were depressed (estimate not provided, $p<0.05$), especiallyin case when fathers spent a lot of time with the children. There were no effects on externalizing behaviour.

3.5 Discussion

Studies reporting on comorbid early parental depression showed a wide variety of prevalence rates, ranging from 0 to 20%. This can be explained by variations in the measurements instruments, cut-off scores, timing, and quality of the 20 included studies. A meta-analysis could hence not be performed. The larger, better quality studies estimated the prevalence of comorbid early parental depression between 0.8% and 4.0%. Only two studies measured child-related outcomes in families with comorbid depressed parents and found that these families were more likely to experience adverse outcomes compared to families with one depressed parent or no depressed parents.

Two studies included in my review found a comorbid early parental depression rate of 0% [Muscat et al., 2012, Parfitt and Ayers, 2012]. However, both studies were more limited by small sample sizes (20 and 40 couples), which could explain these results. In order to detect a prevalence rate of 4% (the higher end of the estimate based on the high quality studies) one would require a sample size of at least 1475 couples (if estimated with 95% power and a margin of error of 1%).

Two other studies found very high rates of comorbid parental depression (20% and 19.6%) [Soliday et al., 1999, Bielawska-Batorowicz and Kossakowska-Petrycka, 2006]. The first study used an internet advertisement that mentioned the study's aim to recruit couples. This may have biased the study participants to those with depression. The second study asked participating couples to recruit additional couples, a technique known as snowbal sampling. As couples would have been aware of the study aims at this time,

they could have been more likely to recommend the study to other couples whom they know were experiencing depression. If I only include studies with a sample size of at least 1475 couples, and exclude the two outliers, couple comorbidity ranged from 0.6% to 14.5%.

Overall, studies that assessed depression by using questionnaires appeared to find higher rates of depression compared to studies using a diagnostic interview or medical diagnosis. Since only two studies used interviews or diagnoses to assess depression, no formal analysis was performed to confirm this finding. However, the study by Mezulis and colleagues measured depression in mothers using both a diagnostic interview and the CES-D questionnaire and consistently found higher rates of depression when using the questionnaire (e.g. at 1 month postpartum, 4.6% of women were depressed according to the interview, compared to 11.6% based on the CES-D).

As shown in Figure 3.2, there were no clear time trends of couple depression over the first year postpartum. There is some indication that father's depression peaks in the period between 3-6 months after childbirth [Paulson and Bazemore, 2010], although I did not observe this for couple depression. However, due to the heterogeneity of the included studies, an existing time trend may have been obscured.

The relatively high rates of comorbid depressed parents could be explained by assortative mating: the tendency for individuals with similar phenotypes to mate more frequently than expected by chance. A meta-analysis has shown evidence for assortative mating in people with affective disorders, including depression [Mathews and Reus, 2001].

Couple depression comorbidity could be a significant public health concern if it leads to a higher likelihood of adverse events in children. It is well documented that adverse childhood experiences can have an impact on health outcomes in children (e.g. [Flaherty EG, 2013]), and that maternal and paternal depression individually can affect child outcomes (see Chapter 1). The two studies included in this review assessing child-related outcomes both found that these outcomes were increased in children of two depressed parents: these parents were less likely to follow guidance on health behaviours, and children were more likely to show internalizing behaviour.

This review was limited by the heterogeneity of studies reporting on couple de-

pression comorbidity (I^2=98.6%, p<0.001). This can be explained by the substantial differences in the measurement instrument and cut-off scores used and timing of measurement. It was hence inappropriate to perform a meta-analysis. Therefore, I am not able to provide a point estimate of the prevalence of early parental comorbid depression. Moreover, the point estimates from the individual studies could be biased by inappropriate sampling selections or non-representative populations. As couple comorbidity is not routinely assessed, this review is unable to compare couple depression rates to time outside the perinatal period. Finally, I was able to identify only two studies assessing the effects of couple depression on child outcomes, severely limiting the evidence base for drawing conclusions for this part of my review.

Despite these limitations, two conclusions can be drawn from this review. Firstly, a substantial number of couples experience comorbid depression during the first year after childbirth. Second, couple depression comorbidity appears to adversely affect child outcomes, more so than individual parental depression.

Future research should focus on families as a whole and examine the course of depression in both new parents as comorbid depression appears to exacerbate the effects of individual parental depressio [Paulson and Bazemore, 2010]. Further investigation of the long term outcomes of children of comorbid depressed parents, focussing on 'hard' clinical based outcomes rather than 'soft' questionnaire based outcomes is required.

3.6 How does this chapter inform my thesis?

Although I was not able to provide an overall estimate for the prevalence of early comorbid parental depression, the estimate from a previous THIN study [Davé et al., 2010] is in line with other studies, particularly the studies using data from another large UK birth cohort (ALSPAC) [Hanington et al., 2010, 2011, Ramchandani et al., 2005a, 2008b]. This finding shows that routinely collected health data is at least on par with the large UK birth cohort studies on this topic and that THIN is an appropriate data source to investigate parental depression.

Moreover, only two studies assessed child outcomes associated with early comorbid parental depression. These studies were limited in follow-up time, only assessing out-

comes in early childhood, but did find adverse effects of comorbid parental depression. As a significant number of couples does experience depression simultaneously in the first year after childbirth, a study focussed on long term clinical child outcomes, as I present in the next part of my thesis, is overdue. Using THIN, I will be able to assess clinical outcomes in both childhood and adolescence in a large and unselected population using information on both parents. This type of study has not been performed before and will provide novel inside into the effects of parental mental health on child outcomes.

As mentioned in this chapter, Shreya Davé has conducted a study on the prevalence of parental depression in THIN [Davé et al., 2010]. She found that overall, 4% of parents experienced depression in the same year. For mothers, 14% had a record of depression in the first year after childbirth, compared to 4% of fathers.

I have repeated her analysis on the updated cohort (as described in Chapter 5) and found that in 1994 - 1997, the years from which I will draw my cohort, rates for maternal depression were between 12% to 15% (Figure 3.3). For fathers, depression rates were around 1.5% (Figure 3.4). As described in the published THIN study [Davé et al., 2010], rates for paternal depression have increased over time, which explains why the rates I find in 1994 - 1997 are slightly lower compared to the rates drawing on data from 1993 - 2007.

Comorbid early depression was recorded for 0.5% of couples between 1994 - 1997, which is substantially lower than the 4% reported in the earlier THIN paper. Again, this will be at least partly due to the lower recording of paternal depression in that time period.

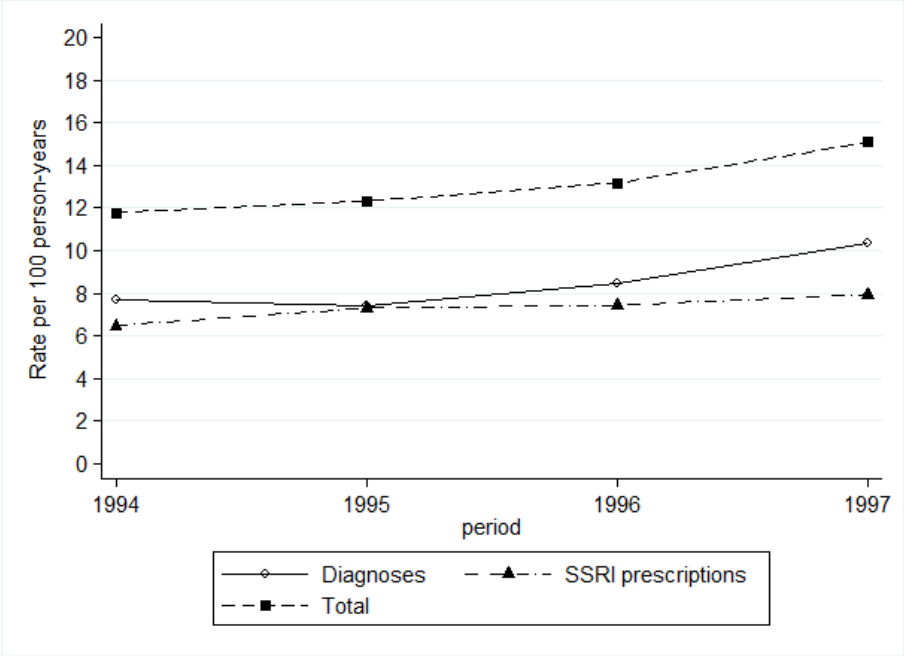


Figure 3.3: Early maternal depression as measured by depression diagnoses and antidepressant prescriptions

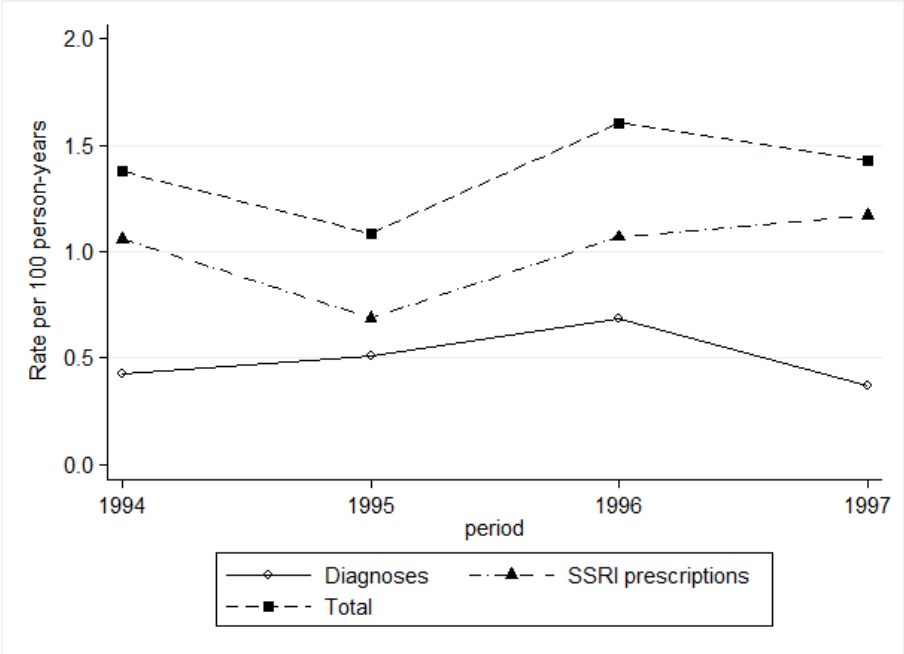


Figure 3.4: Early paternal depression as measured by depression diagnoses and antidepressant prescriptions

Chapter 4

Trends in childhood depression

4.1 Objectives of the chapter

In this chapter I aim to describe trends in the recording of depression diagnoses, symptoms and antidepressant prescriptions in primary care in the UK in children from 1995 to 2009, with a focus on the effects on the Committee for Safety of Medicines (CSM) advice in December 2003.

Adolescent depression is the outcome of my main analysis, presented in part III of this thesis. Therefore, I aim to describe how it is recorded, and any trends over time and by age in this chapter. A paper studying depression in adults in THIN has found that, over time, GPs have become more likely to record depression symptoms rather than depression diagnoses [Rait et al., 2009]. A similar study for people under the age of 18 has not been performed yet.

Apart from a trend towards symptom recording, depression recording could also be affected by a CSM advice issued in December 2003. This advice warned against the use of antidepressants (other than fluoxetine) in children and adolescents, as the balance of benefits and risks was deemed unfavourable. I will outline the treatment options available for depression in children and adolescents, provide a brief overview of the safety concerns, and evidence from trials and observational studies for these safety concerns.

Results from this chapter have been published in PLoS One (see Appendix F on page 232), and parts of the background and introduction were published in Significance

as a feature article that was runner-up in the annual writing competion organised by the Young Statisticians section of the Royal Statistical Society (Appendix F on page 250).

4.2 Introduction

4.2.1 Depression in children and adolescents: treatment options

There are several treatment options for depression in childhood and adolescence. The National Institute for Health and Clinical Excellence (NICE) guidelines on depression in children (aged 5 - 11 years) and young people (aged 12 years up to their 18th birthday) offer an overview of the available options [National Institute for Health and Clinical Excellence, 2005]. The recommendations for treatment are summarised in Table 4.1. In the NICE guidelines, it is stressed that psychological therapies ought to be the first line of treatment. Only children with moderate to severe depression who are unresponsive to psychological treatment should be treated with antidepressants, often in conjunction with psychological treatment. As there is limited evidence of the effectiveness of antidepressant treatment of young people, and especially children, NICE advises these should only be used very cautiously in this age group. However, a survey in a Child and Adolescent Mental Services (CAMHS) found that after publication of the NICE guidelines 28% of children and adolescents were receiving antidepressants without psychological treatment [Perera et al., 2007].

Selective serotonin reuptake inhibitors (SSRIs) were first developed in the 1970s [Wong et al., 1974]. At the time, depression was believed to be a rare disorder, while anxiety was much more frequent. As such, anxiolytics and tranquilizers such as benzodiazepines were the most frequently prescribed drugs. However, early in the 1980s it appeared that patients could develop dependence on these drugs, even on low or moderate doses, and suffer from withdrawal symptoms when benzodiazepines were discontinued. In the light of these findings, prescriptions for benzodiazepines decreased markedly and a market for antidepressants opened up.

Table 4.1: Recommended treatment for depression in children and adolescents, adapted from NICE guideline CG28

Depression severity	Recommended treatment
Mild depression (including dysthymia)	Watchful waiting Non-directive supportive therapy or group cognitive behavioural therapy/guided self-help
Moderate to severe depression	Brief psychological therapy ± fluoxetine
Depression unresponsive to treatment/ recurrent depression/psychotic depression	Intensive psychological therapy ± fluoxetine, sertraline, citalopram, augmentation with an antipsychotic

Selective serotonin reuptake inhibitors work upon the serotonin system in the central nervous system. Their main point of action is thought to be the inhibition of serotonin reuptake, making serotonin available for longer in the synapses between nerve cells, and making it more likely for the post-synaptic cells to become excited. They are deemed 'selective', as compared to the older tricyclic antidepressants (TCAs) which work on the serotonin, norepinephrine and dopamine systems, SSRIs work mainly on the serotonin system. They were found to be comparable to TCAs with regards to efficacy, although SSRIs did not seem as effective as TCAs in hospitalised patients [Anderson, 2000].

Antidepressants (ADs) are commonly prescribed to children and adolescents for depression, anxiety, and a variety of other disorders [Murray et al., 2004]. SSRIs, first marketed in the late 1980s, were prescribed to children for depression on the basis of effectiveness data from trials on adult psychiatric disorders coupled with other trial data demonstrating the ineffectiveness of TCAs [Stark and Hardison, 1985, Hazell et al., 2010, Keller et al., 2001, Emslie et al., 2002]. In the early 2000s, SSRIs became the preferred treatment for depression in children rather than TCAs [Paediatric Formulary Committee, 2010]. However, there are serious safety concerns regarding SSRIs, as detailed in Appendix B.

Up to now, time trends in antidepressant prescribing in children have been described for periods leading up to the CSM advice [Murray et al., 2004, 2005], and up to 2006, just 3 years after it was issued [Bergen et al., 2009]. Moreover, these studies only assessed antidepressant prescriptions, and did not take recording of depression diagnoses or symptoms into account. I therefore sat out to examine the full time trends over the time period for which information on depression (diagnoses, symptoms and antidepressant prescriptions) is available in THIN.

4.3 Methods: interrupted time series

4.3.1 Data source and population

4.3.1.1 Data source & study population

I identified a cohort of children aged up to 18 years who were registered with a General Practice which was a part of THIN for at least six months between January 1995 and December 2009. Children entered the cohort when they registered with a General Practice, or, the date when their practice joined the THIN scheme and met standards for acceptable levels of data recording. Children remained in the cohort until aged 18 years, transfer out of the practice, date of death or date of last data collection from the practice.

4.3.2 Outcomes and confounders

4.3.2.1 Depression and antidepressants

I examined entries made of diagnoses and symptoms of depression by examining Read codes. Depression diagnosis codes ranged from 'dysthymia' and 'mild depression' to 'recurrent severe major depression', but excluded codes that indicated other mental disorder such as psychosis or anxiety. Depression symptoms relate to codes indicating depression but are not certain enough to be classified as a diagnosis, such as symptoms of depression or 'C\O feeling depressed'. I also examined anti-depressants BNF codes prescribed by the general practitioner at appropriate therapeutic doses for the treatment of depression. I excluded antidepressant prescriptions for products dosed too high to be eligible for pre-

scription as an antidepressant. This led to the exclusion of high dose TCAs that were indicated for nocturnal enuresis. These code lists have been created and used in previous studies and were developed in line with the method described in chapter 2. The do-file used for creating this codelist and resulting codelist itself are detailed in Appendix C on page 202.

4.3.2.2 Potential confounders

I included information on age, gender and social deprivation score (Townsend scores) in my analysis as these are known to be associated with childhood depression and the distribution of these variables may change over the 15 year study period.

4.3.3 Statistical analysis

I described the baseline socio-demographic characteristics of the cohort using frequency tables. I calculated annual incidence rates and 95% confidence intervals (CI) for depression diagnoses, symptoms and antidepressant prescriptions by dividing the annual number of incident cases by the total person-years at risk (PYAR) for each year.

Incidence rate ratios adjusted for gender, age and quintiles of Townsend deprivation score) were estimated using a Poisson regression model. The analyses were adjusted for clustering at practice level.

A Lewis plot [Lewis et al., 2005] was used to explore the association between time since registration and incidence rates as prior diagnoses might be registered at or near the time of registration and these ought not to be included in the incidence rates. The Lewis plots revealed that there was an increased rate of depression diagnoses, symptoms and antidepressant prescribing in the first month after registration, after which the rate of recording dropped to a steady state. To correct for this, I started follow-up one month after registration. Unless otherwise specified, analyses were conducted in Stata, version 11.2 (Stata Corp, College Station, Texas).

4.3.4 Interrupted time series analysis

In order to assess the effects of the CSM advice on antidepressant prescribing, I used a segmented regression analysis [Wagner et al., 2002]. The general formula for using this

type of regression is as follows:

$$Y_t = \beta_0 + \beta_1 \times \text{time}_t + \beta_2 \times \text{intervention}_t + \beta_3 \times \text{time after intervention}_t + \epsilon_t$$

Here, Y_t is the outcome variable, in my case the incidence rate of depression in children, in year t; time is a continuous variable indicating time in years at time t from the start of the observation period; intervention is an indicator for time t occurring before (intervention = 0) or after (intervention = 1) the event of interest; and time after intervention is a continuous variable counting the number of years after the intervention at time t, coded 0 before the event of interest and (time - timing of intervention) after the event of interest. In this model, β_0 estimates the baseline level of the incidence rate at time zero; β_1 estimates the change in the incidence rate per person that occurs with each time increment before the intervention (i.e. the baseline trend); β_2 estimates the level change in the mean yearly outcome variable per person immediately after the intervention, that is, from the end of the preceding segment; and β_3 estimates the change in trend in the mean yearly number of records per person after the intervention, compared with the yearly trend before the intervention. The sum of β_1 and β_3 is the post-intervention slope.

In assessing the trends in incidence rates in depression recording in children, the advice issued by the CSM could be seen as the event or intervention of interest. However, doubt over the safety of SSRIs was raised a full year before the advice was issued by a BBC programme. Therefore, it would be possible that incidence rates of particularly antidepressant prescriptions changed before December 2003. To account for the uncertainty in the timing of the intervention, I used the Joinpoint regression program (version 3.5.1) from the Surveillance Research Program of the US National Cancer Institute to perform the segmented regression analysis [National Cancer Institute, 2011]. Joinpoint is statistical software for the analysis of trends using Joinpoint models. This analysis allows for identifying points where there is a change in the linear slope of the trend, rather than defining them yourself. The analysis starts with the minimum number of jointpoints (i.e., 0 joinpoints, which is a straight line), and tested whether one or more joinpoints (up to 4) were statistically significant and should be added to the model [Kim et al., 2000].

The models incorporates estimated variation for each point by using the standard error of the rate estimate. After identifying the existence of a change in the trend, a segmented regression is fitted and the result of the best model is shown graphically. Finally, the estimated annual percentage of change (APC) and its corresponding 95% CI is computed for each of those trends by fitting a regression line to the natural logarithm of the rates, using calendar year as a regression variable [Clegg et al., 2009].

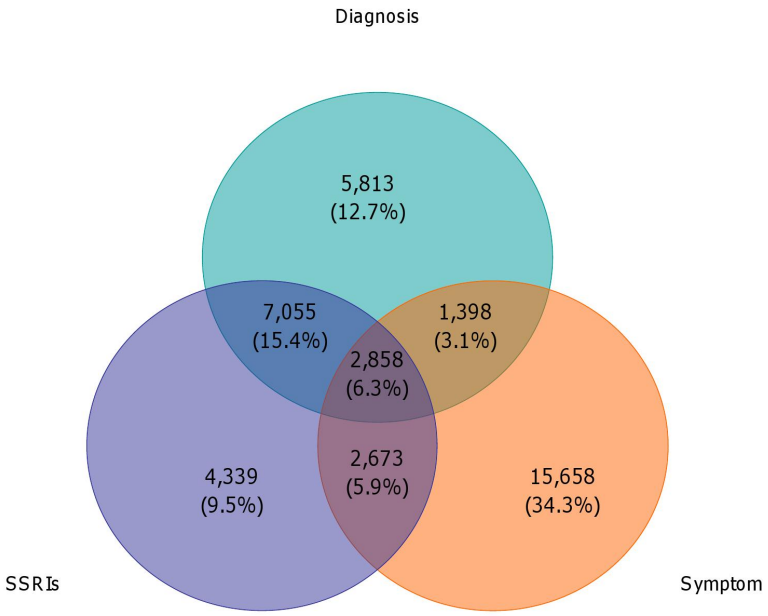


Figure 4.1: Venn diagram showing children with records of depression diagnosis, symptoms and/or antidepressants in THIN

4.4 Results: Trends in GP recording of childhood depression 1995 - 2009

In total, 1,502,753 children up to the age of 18 years were registered with their GP for at least one year in The Health Improvement Network (THIN) UK primary care database. Of these children, 45,723 (3%) children had at least one entry of a depressive symptom, diagnosis or antidepressant prescription. Of these children, 17,124 (38%) had a diagnosis of depression, 22,587 (49%) had a record of depressive symptoms, and 25,473 (56%)

were prescribed antidepressants. Most of these antidepressant prescriptions were for SSRIs: 16,925 (66%), with TCAs representing 7,777 (31%) and other antidepressants 771 (3%) of prescriptions (Table 4.2). Of the children receiving SSRIs, 4,339 (26%) were not diagnosed with depression or depression symptoms. Similarly, 7,211 (42%) of children diagnosed with depression were not prescribed antidepressants (Figure 4.1).

Table 4.2: Characteristics of first time users by antidepressant (AD). Values are numbers (column percentages) unless otherwise indicated

Characteristics	Individuals by AD drug group				
	SSRI	TCA	Other	MAOI	Any AD
Socio-demographic	(n=16,925)	(n=7,777)	(n=769)	(n=2)	(n=25,473)
Girls	12,142	4,680	488	1	17,311
	(71.7)	(60.2)	(63.5)	(50.0)	(68.0)
Deprivation quintile					
1 (most affluent)	3,252	1,631	144	1	5,028
	(19.2)	(21.0)	(18.7)	(50.0)	(19.7)
2	3,063	1,451	105	0	4,619
	(18.1)	(18.7)	(13.7)		(18.1)
3	3,456	1,646	139	0	5,241
	(20.4)	(21.2)	(18.1)		(20.6)
4	3,732	1,706	182	0	5,620
	(22.1)	(21.9)	(23.7)		(22.1)
5 (most deprived)	3,195	1,259	191	1	4,646
	(18.9)	(16.2)	(24.8)	(50.0)	(18.2)
Age groups					
3 - 10 years	179	1,577	7	0	1,764
	(1.1)	(20.3)	(0.9)		(6.9)
11 - 14 years	1,567	1,558	53	1	3,192
	(9.3)	(20.0)	(6.9)	(50.0)	(19.4)
15 - 18 years	15,179	4,642	709	1	20,652
	(89.7)	(59.7)	(92.2)	(50.0)	(80.7)

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; MAOI = mono-amine oxidase inhibitor; other ADs are: mirtazapine, venlafaxine, flupentixol, duloxetine, nefazodone and reboxetine

Rates for entries of diagnoses of depression increased from 2.2 (95% CI: 1.9 - 2.5) per 1,000 PYAR in 1995 to 3.0 (95% CI: 2.8 - 3.1) per 1,000 PYAR in 2002, then dropped to 2.0 (95% CI: 1.9 - 2.1) per 1,000 PYAR in 2005 and have since been relatively constant at around 2.0 per 1,000 PYAR (Figure 4.2). Rates for antidepressant prescribing show a similar pattern: they have gone up from 2.8 (95% CI: 2.4 - 3.1) per 1,000 PYAR in 1995 to 4.5 (95% CI: 4.3 - 4.6) per 1,000 PYAR in 2002, then dropped to rates similar to the initial 1995 rates, but have been increasing again since 2005. Recording of symptoms has seen a dramatic rise from 1.0 (95% CI: 0.8 - 1.2) in 1995 to 4.7 (95% CI: 4.5 - 4.8) per 1,000 PYAR in 2009.

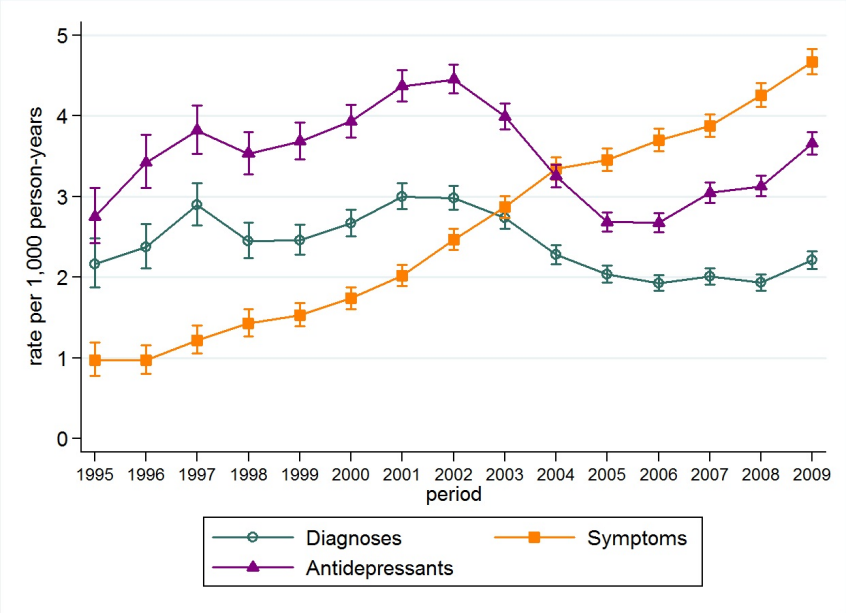


Figure 4.2: Trends in the incidence of childhood depression, symptoms and antidepressants from 1995 to 2010

TCAs were the most commonly prescribed antidepressant to children in 1995, but by 1999 SSRIs had overtaken them and have been the preferred drug type ever since (Figure 4.3). However, since 2003 there has been a sharp decline in SSRI prescriptions, with rates decreasing from 3.2 (95% CI: 3.0-3.3) per 1,000 PYAR in 2002 to 1.7 (95% CI: 1.7 - 1.8) per 1,000 PYAR in 2005. Since then, rates have gradually started increasing again. TCA prescription rates have gradually decreased since 1995, but stopped decreasing in 2006. Rates for MAOIs and other antidepressants were negligible.

In children aged 3 - 11 years, girls were less likely than boys to be diagnosed as depressed (IRR=0.79, 95% CI: 0.67 - 0.92), have depression symptoms recorded (IRR=0.90, 95% CI: 0.84 - 0.95) or be prescribed antidepressants (IRR=0.63, 95% CI: 0.58 - 0.69). In children aged 12 - 18 years, girls were more likely than boys to have been diagnosed as depressed (IRR=2.87, 95% CI: 2.77 - 2.97), have symptoms recorded (IRR=2.31, 95% CI: 2.23 - 2.39) or have been prescribed antidepressants (IRR=2.71, 95% CI: 2.63 - 2.80). The incidence rates in children in the younger age group (3 - 11 years old) were only a fraction of those in the older age group (12 - 18 years old, Figure 4.4).

Rates for all depression indicators increased with deprivation: children and adolescents in the most deprived quintile were twice as likely to be diagnosed as depressed (IRR=2.14, 95% CI: 2.03-2.26) or be prescribed antidepressants (IRR=1.91, 95% CI: 1.82-2.00) compared to children and adolescent in the least deprived quintile. For depression symptoms, there was an almost 50% increase of recording in the most deprived compared to the most affluent children and adolescents (IRR=1.43, 95% CI: 1.36-1.50).

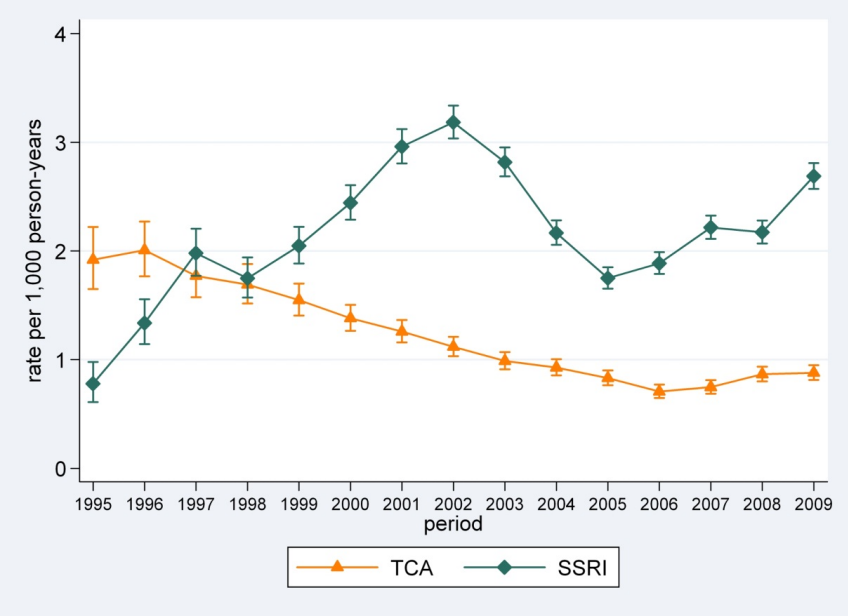


Figure 4.3: Rates of prescription of Tricyclic Antidepressants (TCA) and Selective Serotonin Reuptake Inhibitors (SSRI) in children

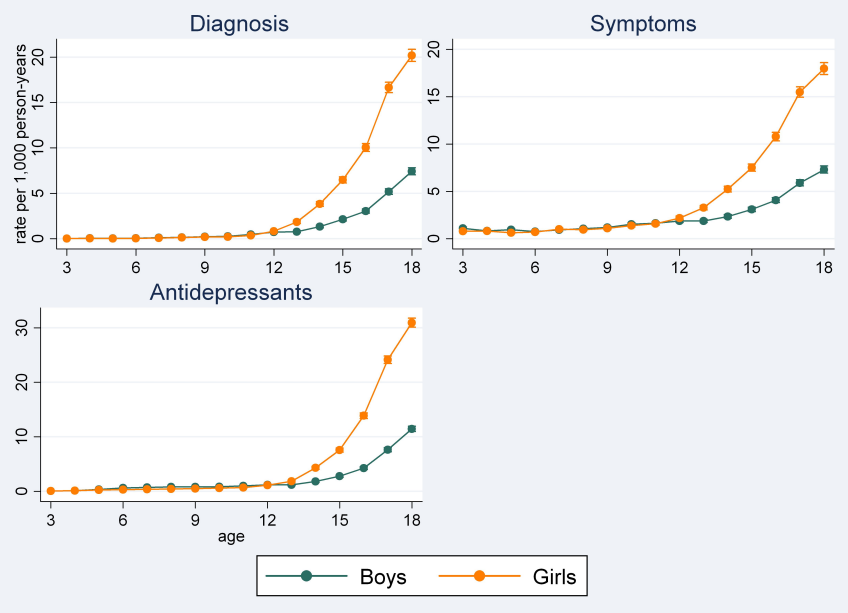


Figure 4.4: Incidence rates of depression diagnoses, symptoms and antidepressant prescriptions by age

Table 4.3: Incidence rate ratios (IRR) for diagnosis and symptoms of depression and antidepressant prescriptions stratified by gender, age group and deprivation

	Multivariable[a]: stratified by age group: 3 - 11 years		Multivariable[a]: stratified by age group: 12 - 18 years		Multivariable[a]: stratified by deprivation: Townsend 1 & 2[c]		Multivariable[a]: stratified by deprivation: Townsend 4 & 5[c]	
	IRR (95% CI)	P^b	IRR (95% CI)	P^b	IRR (95% CI)	P^b	IRR (95% CI)	P^b
Diagnosed depression								
Gender								
Boy	Reference		Reference		Reference		Reference	
Girl	0.79 (0.67-0.92)	0.003	2.87 (2.77-2.97)	< 0.001	2.58 (2.44-2.73)	< 0.001	2.93 (2.78-3.09)	< 0.001
Symptoms of depression								
Gender								
Boy	Reference		Reference		Reference		Reference	
Girl	0.90 (0.84-0.95)	0.001	2.31 (2.23-2.39)	< 0.001	1.78 (1.67-1.83)	< 0.001	2.12 (2.02-2.22)	< 0.001
Antidepressant prescription								
Gender								
Boy	Reference		Reference		Reference		Reference	
Girl	0.63 (0.58-0.69)	< 0.001	2.71 (2.63-2.80)	< 0.001	2.26 (2.16-2.36)	< 0.001	2.57 (2.47-2.69)	< 0.001

a. Adjusted for calendar year, gender, deprivation, age and for clustering by general practitioner practice using robust standard errors. b. P based on Wald test. c. A Townsend score of 1 or 2 represents the most affluent patients, while patients with a Townsend score of 4 or 5 live in the most deprived areas.

4.4.1 Segmented regression analysis

The Jointpoint analysis suggested for SSRIs as a group, there were two time points at which prescription rates changed: 2002 and 2005. Up to 2002 prescription rates for SSRIs had been significantly increasing nearly 16% from 1995 - 2002 (Table 4.3). However, between 2002 and 2005 the rates plateaued, followed by a significant increase of nearly 11% from 2005 to 2009 (Table 4.3).

Individual SSRIs followed a similar pattern: fluoxetine, citalopram, paroxetine and

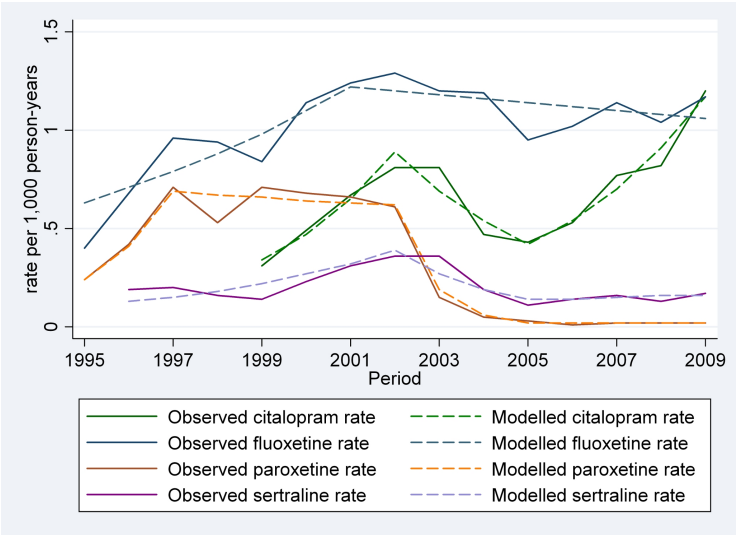
sertraline rates all were increasing from 1995 to the early 2000s before showing a temporary decrease, or stall, in prescription rates. Paroxetine was the only SSRI which showed a statistically significant decrease in prescription rates. Rates for citalopram and sertraline started increasing again in 2005, while rates for fluoxetine and paroxetine remained stable (Table 4.4 & Figure 4.5).

In contrast, rates for TCAs as a group showed a significant decrease between 1995 and 2006, after which there was no significant change. Rates for amitriptyline prescriptions showed a moderate decrease between 1995 and 2006, but started to increase after this point. Imipramine prescription rates showed a steady decline over the entire period.

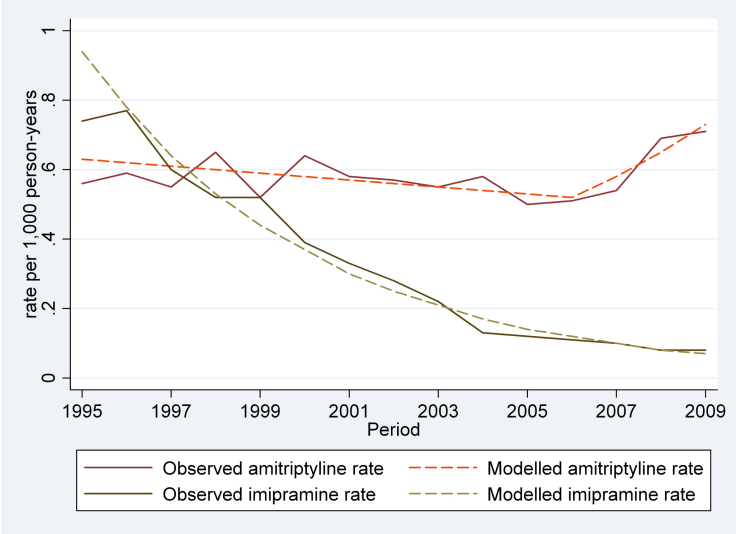
4.5 Discussion

4.5.1 Key Findings

This is the first large paediatric database study to compare depression diagnoses, symptoms and antidepressant prescriptions (and the effects the CSM advice) over a longer time period in the UK. I have found that prescription rates of SSRIs as a group decreased from 3.2 per 1,000 person-years in 2002 to 1.7 per 1,000 person-years in 2005. More specifically, rates for contra-indicated SSRIs, i.e. citalopram, paroxetine and sertraline, went down during that period, while rates for fluoxetine remained stable and rates for TCAs were not affected. The decline in prescription rates was sharpest for paroxetine. Rates for depression diagnoses entries decreased from 3.0 per 1,000 person-years in 2002 to 2.0 per 1,000 person years in 2005. Depression symptom recording saw a steady increase over the study period, increasing from 1.0 per 1,000 person-years in 1995 to 4.7 per 1,000 person-years in 2009. Finally, rates for SSRIs as group and citalopram in particular were increasing after 2005.



(a) SSRIs



(b) TCAs

Figure 4.5: Segmened regression trends for selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) as groups and individual drugs - y-axis differ between graphs.

Table 4.4: Annual percentage change (APC) for selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) as groups and individual drugs

	APC 1 (95% CI)	Period	APC 2 (95% CI)	Period	APC 3 (95% CI)	Period
SSRIs	15.8* (8.5-23.6)	1995-2002	-19.7 (-36.2-1.0)	2002-2005	10.6* (3.1-18.8)	2005-2009
fluoxetine	11.6 (-0.4-25.1)	1995-2001	-1.8 -4.8-1.3			2001-2009
citalopram[1]	37.7 (-4.7-98.9)	1999-2002	-22.0 (-51.1-45.4)	2002-2005	29.0* (14.4-45.4)	2005-2009
paroxetine[2]	67.9 (-27.1-286.9)	1995-1997	-2.2 (-12.2-9.1)	1997-2002	-69.1* (-84.2- -39.5)	2002-2005
sertraline[3]	20.5* (6.1-37.0)	1996-2002	-29.4 (-54.2-9.0)	2002-2005	4.3 (-11.3-22.6)	2005-2009
TCAs	-9.5* (-10.3- -8.7)			1995-2006	6.5 (1.0-12.2)	2006-2009
amitriptyline	-1.8 (-3.8-0.3))			1995-2006	11.9* (2.3-22.3)	2006-2009
imipramine	-17.1* (-18.6- -15.6)					1995-2009

*annual percentage change (APC) is statistically significant ($p < 0.05$) different from 0. [1]Observations start in 1999 for citalopram as prescription rates were negligible (< 10 prescriptions a year) before this year. [2]Observations stop in 2005 for paroxetine as it is only prescribed sporadically (< 5 prescriptions a year) after this time point. [3]Observations start in 1996 for sertraline as prescription rates were negligible (< 10 prescriptions a year) before this year.

The decrease in recording of both depression diagnoses and antidepressant prescriptions after 2002 could indicate caution on the part of GPs in diagnosing depression and prescribing antidepressants following the CSM advice. There appears to be a general consensus among GPs to not diagnose something that cannot be treated. In the case of childhood depression, the options for treatment are very limited: TCAs have not been proven to be effective in children, and have serious side effects; most SSRIs are contraindicated; and there are waiting lists for psychotherapy.

An audit in 2002 found that waiting times for specialist psychotherapy were 11.5

weeks on average for a first appointment, with 30% of patients waiting longer than 13 weeks. In 2003 an action plan was introduced, and in 2004 a re-audit found that the average wait for a first appointment had decreased to 6.7 weeks, with only 2.3% of patients waiting more than 13 weeks [Garry and Paley, 2006]. Over the last couple of years however, waiting lists have been increasing again: whereas 29% of primary care trusts (PCTs)[1] had waits of more than three months in 2009, this had increased to 41% in 2010 [magazine", 2011].

Moreover, GPs might prefer to record depression symptoms rather than recording a diagnosis of depression, which was also found in a THIN study assessing depression in adults [Rait et al., 2009]. The decrease in contra-indicated SSRIs as opposed to fluoxetine strengthens the possibility of a link with the CSM advice.

Although the Joinpoint program points to 2002 as the time point where SSRI rates changed, the observed data shows that rates did not decrease until after 2003, the year when the CSM advice was issued. However, prescription rates could have started decreasing prior to the CSM advice as information regarding the safety and effectiveness of SSRIs was circulating in the specialist community before the advice was issued and could have influenced changes in prescription recommendations. Similarly, the small dip in fluoxetine rates around 2005 was not statistically significant. This dip might be related to the requirement of the US Food and Drug Administration (FDA) to add a black box warning to all antidepressants, including fluoxetine and TCAs, about an increased risk of suicidal behaviour in 2004 [FDA, 2004].

The sharp decline in paroxetine prescription rates could be related to the advice by the MHRA against the prescribing of paroxetine specifically. This advice was issued in June 2003, preceding the overall SSRI advice in December of the same year. It followed a review of randomised controlled trials that showed higher rates of suicidal thought and behaviour (but not completed suicides) in patient who took paroxetine (25 out of 738; 3%), compared to those who took placebo (8 out of 647; 1%; p for difference = 0.01) [Waechter, 2003]. This might have led to patients and their parents being biased against taking paroxetine as a first line of treatment. Therefore, it is difficult to determ-

[1] A primary care trust (PCT) is a type of NHS trust, part of the National Health Service in England. PCTs commission primary, community and secondary care from providers.

ine whether the sharp decline in paroxetine prescriptions in primary care was due to a negative public opinion of the drug, or the advice issued by the CSM half a year later.

The increase in SSRI prescription rates after 2005 could indicate that concerns about a possible suicide risk associated with SSRIs have waned. Several studies failed to show an increased risk of suicide for SSRIs [Jick et al., 2004, Didham et al., 2005], or increases in suicide rates that coincided with decreases in SSRI prescription rates [Gibbons et al., 2007]. In the US, 2004 saw the largest single-year increase in suicide rates in adolescents aged 10 - 19 years [Bridge et al., 2007]. From 1990 to 2003 suicide rates had been decreased by 28%, but in 2004 they had increased with 15% from 6.78 to 7.32 per 100,000 people. This might have led GPs to revaluate prescribing SSRIs to children and adolescents, although doubt continue to exist regarding the safety and effectiveness of SSRIs [Hammad et al., 2006, Cepoiu et al., 2008].

4.5.2 Comparison to other studies

The antidepressant prescription rates I found are similar in size and trend to those found by a General Practice Research Database study which studied prescription rates from 1992 to 2001 [Murray et al., 2004]. I also found similar age and gender effects. My results also confirm findings by Murray et al. who found a decrease in SSRI prescribing in between 2003 and 2004, while prescribing rates for fluoxetine remained stable [Murray et al., 2005]. However, the study by Murray et al. did not assess data for individual drugs, apart from fluoxetine, whereas my study did take different SSRIs into account.

A study based on Australian data also found a decrease in antidepressant use in children, in particular of SSRIs [Dean et al., 2007]. They also saw a sharp rise of fluoxetine over time, which I did not find in the UK. This might be explained by sertraline being the most commonly prescribed antidepressant in Australia before the SSRI controversy started, whereas fluoxetine was already the drug of first choice in the UK before the CSM advice.

Previous research using THIN has shown that over time, GPs seemed to substitute depression diagnoses for depression symptoms: rates for depression diagnoses decreased while symptom recording increased. Meanwhile, the sum of depression diagnoses and symptom rates remained stable [Rait et al., 2009]. For children, there did not appear to be

a similar link between depression diagnosis and symptom recording. Rather, diagnoses followed the prescribing trend.

4.5.3 Main Strengths and Limitations

The main strength of this study is its sample size that enables examination of outcomes separately for girls and boys, and by drug. There is no clear reason to believe the results would differ for the entire population of UK children.

However, since these findings relate to clinical general practices data, a few children might have been missed if their depression was not severe enough to warrant a visit to a GP, or if they were diagnosed and managed in other settings. I believe that these data would have captured all adolescents in the NHS who are on antidepressant drug therapy as prescribing in the UK is predominantly managed by general practitioners. Moreover, a study on depression in adults found that although incidence rates in THIN are lower than depression rates found in epidemiological studies, associations with covariates such as gender and deprivation were similar [Rait et al., 2009]. Further, non-psychiatric physicians recognition of depression has been found to have a limited sensitivity, but a high specificity [Cepoiu et al., 2008, Kamphuis et al., 2011]. Childhood depression rates might have been underestimated in this study, but trends and associations with other variables are likely to be representative of the general population. Moreover, as I was specifically interested in the effects of the CSM advice in primary care settings, this limitation will have only a minimal effect on my results.

4.5.4 Conclusions

After 2002, general practitioners decreased their prescribing of contra-indicated SSRIs, particularly paroxetine. Rates for fluoxetine, the only SSRI not to be contra-indicated, remained stable. Both depression diagnoses and prescription rates decreased between 2002 and 2005, suggesting caution on the side of GPs. The timing and direction of these trends imply that GPs followed the CSM advice, although it cannot be ruled out that these trends resulted from the negative media attention SSRIs received around the same time. After 2005, rates for all antidepressants, except paroxetine, started to rise. This is in line with results from observational studies that found no increased risk of suicidal behaviour

with SSRIs. Further evidence is required on the risk of suicide for each SSRI using real time clinical data. Although not within the scope of this thesis, I have published an article exploring this association (Appendix F on page 241).

4.6 How does this chapter inform my thesis?

Depression in adolescents is recognised and treated in primary care, which will make it possible for me to use this as an outcome of my main analysis on the association between parental and adolescent depression. In addition, some children seem to be prescribed antidepressants in the absence of a depression diagnosis. I will consider these prescriptions as a marker of a depression diagnosis in cases where children do not have a diagnosis for any other potential antidepressant indication (e.g. eating disorders or anxiety).

For my main analysis (see chapter 7), I will include children born from 1994 onwards, and measure my main outcome, childhood depression as described in this chapter, in children aged 13 years or over. This means I will include children with a depression diagnosis or antidepressant prescription from 2007 onwards.

Figures 4.7 and 4.6 show the rates of depression diagnoses and antidepressant prescriptions in children aged 13 - 18 years old between 2007 and 2011, the age group and time period during which the outcome in my main analysis is measured.

Incidence rates for both depression diagnoses and antidepressant prescriptions were stable for this age group in this period for both boys and girls (Figure 4.6). However, rates were increasing with age and were, as expected, highest for girls aged 18 years (Figure 4.7).

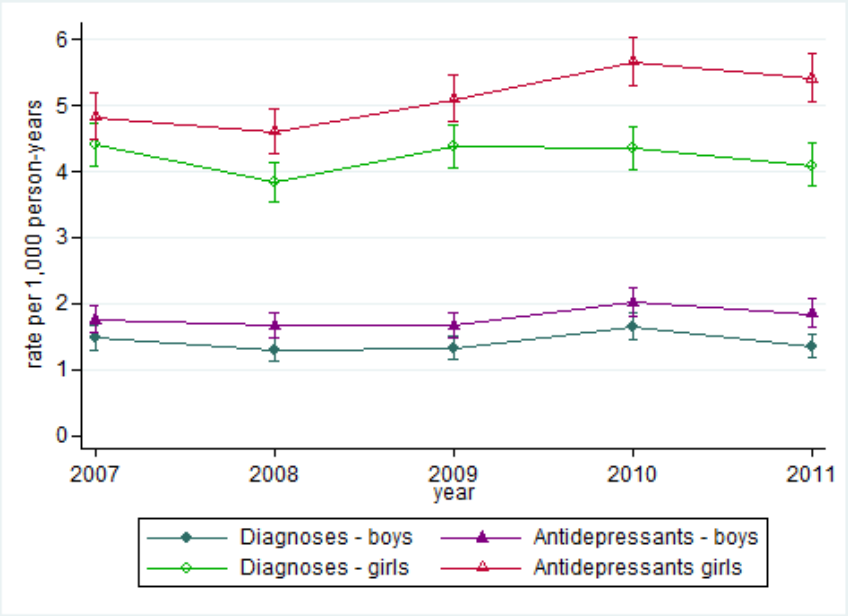


Figure 4.6: Rates of depression diagnoses and antidepressant prescriptions for children aged 13 - 18 years

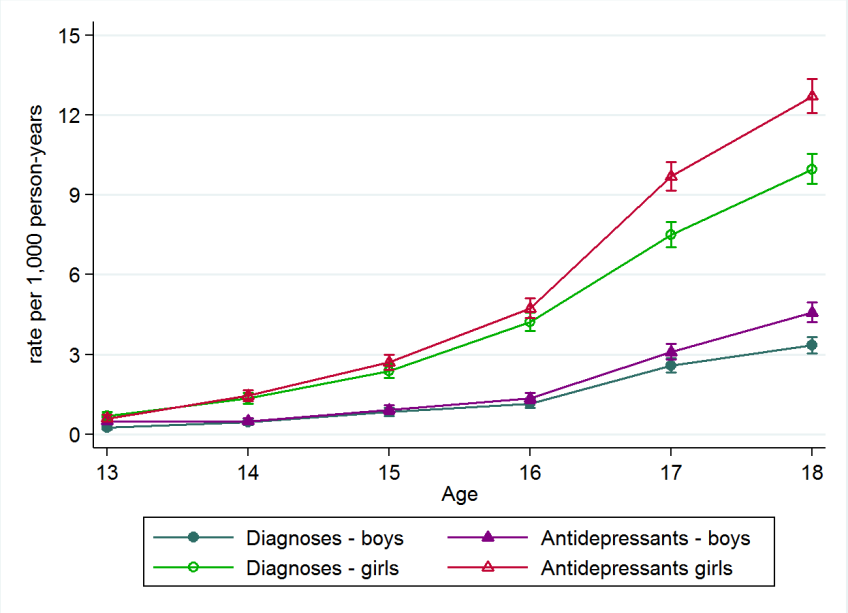


Figure 4.7: Rates of depression diagnoses and antidepressant prescriptions between 2007 - 2011

Part III

The association between parental and adolescent depression

In this part of my thesis, I will present my main analysis, a study involving a birth cohort nested within THIN. Birth cohorts are often used in life course epidemiology. This type of cohort study follows children from pregnancy or birth into childhood and sometimes even to adolescence or adulthood. In most birth cohorts, some information on the parents of the child is also available. Britain in particular has an impressive history of birth cohorts. Studies such as the National Survey of Health & Development (NSHD) have followed children from 1946 onwards. The NSHD has been called "the granddaddy of all cohort studies" because of its age and was set up by Dr James Douglas less than a year after the end of the Second World War. Over 13,000 women who gave birth in March 1946 were interviewed for the study and the children have been followed ever since.

Several other birth cohorts followed, such as the National Child Development Study (NCDS), set up in 1958, the 1970 British Cohort Study (BCS70) and the Millennium Cohort Study (MCS) that was established in 2000. Apart from national birth cohorts, there have also been regional studies, most notably the Avon Longitudinal Study of Parents and Children (ALSPAC).

Although these studies have proven invaluable for epidemiological research, they have their limitations. Children and parents are followed up at set time points with predefined questionnaires and/or examinations. At each assessment, only a limited amount of information can be collected. When participants are assessed more frequently or assessments are more invasive (e.g. more or longer questionnaires or a large range of medical tests), they will be more likely to drop out of the study. Moreover, the assessments themselves can influence the behaviour of study participants[2]. Therefore, cohort studies always have to try to find the right balance between retaining participants and extracting the desired information.

Another limitation of traditional birth cohorts is that they follow a specific generation

[2]This effect is known as the observer or Hawthorne effect, and is named after the Hawthorne Works factory. Hawthorne Works had commissioned a study between 1924 and 1932 to assess whether workers would become more productive in higher or lower levels of light. However, the workers' productivity allegedly increased both when lighting was increased, and when it was decreased. The researchers eventually found that knowing that their productivity was being assessed increased the workers' output.

of children. For instance, ALSPAC follows children born in 1991 or 1992. While the cohort has been able to delve into many important research questions, it has become dated already as children born in the early nineties will have had a very different exposure to for instance the internet compared to children who are born today. Moreover, because of the small time window of recruitment and different methods used in different cohorts, it is difficult to compare children from various birth cohorts to account for changes in children's environment.

Electronic health records can provide an alternative to traditional birth cohorts that is cheaper, collected continuously with minimal interference in participants' lives, and that is up-to-date. Although some detail might be lost in electronic health records compared to questionnaire-based cohort studies, the two study designs can be combined to achieve the best results. For instance, in THIN it is possible to go back to GPs with questionnaires (either for the GP or for selected patients) and ALSPAC is in the process of linking its data to the CPRD.

Chapter 5 will describe how I set up a family cohort in THIN and provide some descriptive statistics of the cohort. Following that chapter, I will explore whether internalizing behaviours, as described in section 1.4.3 on page 43, can be used as an early indicator in chapter 6. In this study, I will focus on sleep disorders. Finally, I will present the main analysis where I used structural equation modelling to assess the association between early comorbid parental and adolescent depression in chapter 7.

Chapter 5

The family cohort and study design

5.1 Objectives of the chapter

The main study for this part of my thesis consists of a family cohort nested within THIN. This chapter will detail how individuals are linked together to create a family cohort, how study variables are defined and will describe the characteristics of the family cohort.

The first family cohort in THIN was developed by Dr Irene Petersen and Dr Shreya Davé for a study assessing the incidence of depression in parents [Davé et al., 2010]. The cohort builds upon the pregnancy cohort developed by Dr Irene Petersen which was used to determine trends in the prescription of antibiotics [Petersen et al., 2010], antidepressants [Petersen et al., 2011] and antiepileptic drugs [Man et al., 2012] during pregnancy. It is also being used in ongoing studies to assess pregnancy outcomes associated with drug use in pregnancy.

5.2 Intermediate variables

As early parental depression and adolescent depression, the exposure and outcome for my main analysis, are far apart in time, I will also assess intermediate variables that could act as mediators. These variables, internalizing behaviour in children and recurrent or chronic depresion in parents, will be measured throughout children's lives and could potentially inform prevention targets.

5.2.1 Internalizing behaviour in children

As introduced in chapter 1, I plan to explore internalizing behaviour in children (see section 1.4.3 on page 43). This could prove important as about three quarters of adult mental disorders are extensions of juvenile disorders, approximately 50% of which could be diagnosed before the age of 15 [Kim-Cohen et al., 2003]. For depression, the study by Kim-Cohen and colleagues found that 84.5% of adults diagnosed with depression at age 26 years had a history of juvenile mental illness, which was first measured at age 11 years. Among those with a depressive disorder at age 26 years, anxiety, depression and conduct and/or oppositional defiant disorder have been the most common juvenile mental illnesses.

Child and adolescent psychopathology are categorised into two broad classes: internalizing and externalizing behaviour. Externalizing problems are characterised by behaviours that are harmful and disruptive to others (e.g. aggression and hyperactivity), whereas internalizing disorders signify a core disturbance in intropunitive emotions and moods (e.g. sorrow, guilt, fear, and worry) [Zahn-Waxler et al., 2000]. Internalizing behaviours in particular have been linked to later depressive disorders.

Anxiety, depression and sleep disorders have been classed as internalizing behaviours in children and adolescents and could be associated with later adolescent depression. Depression and anxiety are often comorbid in both children and adolescents [Brady and Kendall, 1992, Pine et al., 1998], and adults [Sartorius et al., 1996] and share some symptoms. Sleep disorders, insomnia in particular, are considered a symptom of depression, although they can also emerge as primary disorders. Therefore, I have selected these three internalizing behaviours.

Other potential internalizing behaviours, that are more often present in younger children, have been linked to early parental depression. A study in the ALSPAC cohort found that anxiety in both mothers and fathers predated the occurrence of recurrent abdominal pain (RAP) in children [Ramchandani et al., 2006]. The study had followed up almost 9,000 children up to age 6 3/4 years. RAP has been associated with depression and anxiety in children, as well as depression in their parents [Walker and Greene, 1989, Campo et al., 2001, 2004].

In addition, a population-based study in Finland found that both abdominal pain

and headaches in childhood (measured at age eight years) were associated with severe suicide attempts [Luntamo et al., 2013]. Headaches, particularly migraines, have been found to be comorbid with depression: patients with migraines are more likely to develop depression and patients with depression are more likely to develop migraines [Breslau et al., 2003, Anttila et al., 2004].

Finally, fatigue could be associated with depression. Adolescents with unexplained chronic fatigue score higher than controls for both anxiety and depression [Smith et al., 2003]. Moreover, tiredness is recognised as a symptom of depression.

5.2.2 Recurrent parental depression

Another important intermediate variable is recurrent parental depression. Parents who experience depression in the postnatal period are more likely to experience future episodes of depression. For instance, a study in Sweden found that women with a history of postpartum depressive symptoms were almost six times more likely to have recurrent depressive symptoms (OR = 5.82, 95% CI: 3.79 - 8.93) compared to those without symptoms [Josefsson and Sydsjö, 2007]. The study, which assessed mothers and children four years after childbirth, also found that both postpartum depression and current depression were associated with childrens' behavioural problems, although the association was stronger for current depression.

Other studies, not looking specifically at depression in the perinatal period, have also noted depression chronicity is important in the association between parental and adolescent depression. A study on a cohort of 816 women and their 15-year-old children in an Australian community attempted to quantify the influence of maternal depression history during the first ten years of life [Hammen and Brennan, 2003]. They found that adolescent depression at 15 years was twice as likely among offspring of mothers who were depressed at any time in their child's life as compared to offspring of never-depressed mothers. The association was stronger for mothers with more severe and/or longer depression episodes.

Conversely, the Early Prediction of Adolescent Depression Study found that children whose parents had experienced four or more episodes of depression were not more likely to have a diagnosis for a psychiatric disorder when depression severity was also

taken into account [Mars et al., 2012]. The OR for child disorders predicted by parental depression recurrence was 1.41 (95% CI: 0.80 - 2.47) compared to 1.81 (95% CI: 1.01 - 3.24) for depression severity. However, the confidence intervals for these estimates are quite wide, indicating uncertainty about the true effect of depression recurrence. As the sample only included 337 families, depression recurrence could still be associated with child outcomes, though this needs to be assessed in a larger sample.

5.3 THIN family cohort

5.3.1 Linkage: Families in THIN

Mothers and children were linked on the basis of delivery/birth months and family identifier codes in THIN. Linking each birth to the corresponding child involved matching the mother's delivery date to the child's month of birth and family identifier. Mother-child pairs were excluded from the cohort if the child could be linked to more than one mother or if the child first registered at their GP practice after nine months of age. To enter the cohort for this study, children must be born between 1 January 1994 and 31 December 1997 and must be registered for at least 15 years. Parents must be registered for at least one year, so that I could assess rates of early parental depression, but they could potentially leave the cohort after this time point.

Potential fathers were linked to mother-child dyads using an algorithm that has been explored in previous work on parental depression [Davé et al., 2010]. I selected males older than 15 years who had the same family identifier as the mother and child at the time of birth. The age difference between the mother and potential father was also restricted to 15 years in order to decrease the risk of erroneously selecting older sons (or in rare cases grandfathers) who live with the family as fathers of the child. Previous research has shown that, in THIN, 40% and 10% of households contained either no or >1 resident adult man, respectively, and these households were excluded as these were either single parent families, or families where the father had (thus far) failed to register with a GP, or registered with a different GP.

Because of my strict inclusion criteria, only traditional 'nuclear' families consisting of a mother and father with children were included in this cohort. Families with relat-

ives living at the same address, same sex couples or single parents (though only if they were single parents during the first year after childbirth) were not eligible for my cohort. For families where multiple children were registered, I randomly chose one child to be included in the THIN family cohort.

5.3.2 Variable definitions

The primary outcome variable of this study was adolescent depression in children aged 13 - 18 years (Table 5.1). This variable was based on different combinations of codes reflecting depression diagnoses, depression symptoms and prescribing of anti-depressants at the appropriate therapeutic dose for treatment of depression, as explored in chapter 4. Adolescents were considered to have depression if they had a diagnosis or antidepressant code in their records, or at least two records of depression symptoms within a month. Furthermore, for adolescents with a record of an antidepressant prescription, I excluded cases where adolescents had a diagnosis of an eating disorder or anxiety as antidepressants can also be prescribed for these indications.

Parental depression (both maternal and paternal) in the first postpartum year was identified using the same code lists for diagnoses and prescriptions (but not depression symptoms), with the addition of codes that specify postnatal depression. These code lists were created and used in previous studies [Davé et al., 2010] and were developed in line with methods described in chapter 2 and reviewed by a general practitioner (Prof Irwin Nazareth). For both parental and adolescent depression, I considered one prescription sufficient for a depression indication. For this study, I focussed on whether the patient was depressed and not whether they were treated for their depression. As such, I considered the decision of the GP to prescribe an antidepressant as indicative of depression (in the absence of an eating disorder or anxiety diagnosis).

I explored childhood internalizing behaviour between the ages of 5 and 13 years as a mediator. Internalizing behaviour is not measured directly in THIN. In order to estimate this latent variable, I used the following indicator variables: sleep disorders, anxiety disorders, recurrent abdominal pain or constipation, recurrent headaches or migraine, chronic fatigue, and depressive symptoms (Figure 5.1). For these indications, code lists were developed and reviewed by a general practitioner. For indicators relating

to physical symptoms (abdominal pain, headaches, fatigue, dysphagia) I excluded cases that were due to physical illness. Therefore, I excluded any cases where there was a diagnosis for an organic disease (e.g. inflammatory bowel disease in the case of abdominal pain) within a year of first presentation with symptoms.

Table 5.1: Timing of variable measurements

0 - 1 years	1 - 5 years	5 - 13 years	13 - 18 years
Early parental depression	Parental depression		
Covariates		Childhood internalizing behaviour	Adolescent depression

Information on Townsend scores, a measure for social deprivation as described in chapter 2, was extracted as this might act as a confounder in the association between parental and childhood depression. Negative life events (e.g. death of a parent or sibling, parental divorce) were explored as confounders as these are known to be strongly correlated to internalizing behaviour and depression.

I considered parental depression not within of the first year of life as an intermediate variable (or time-varying confounder) as parents with chronic or recurrent depression could impose a greater risk on their children developing depression in later life, either as an environmental influence or through direct genetic transmission. For each year of follow-up (measured by child age), I assessed whether each parent has a record of depression diagnosis or antidepressant prescription. The result is a cumulative depression score ranging from 0 (no episodes of depression) to 12 (parental depression in each year up to child age 12 years) for each parent.

Potential child abuse and neglect were considered as confounders, as it known that there is a strong association between maltreatment and later depression. Moreover, children of parents who were depressed in the antenatal period are four times more likely to be exposed to child abuse [Kotch et al., 1999, Pawlby et al., 2011]. To identify child maltreatment and neglect, I used a code list for suspected or potential child maltreatment and neglect developed by Jenny Woodman [Woodman et al., 2012].

Finally, I included parent behaviour during pregnancy and the first year postpartum that could influence both their risk of depression and the childs risk for later internalizing

behaviour. This included alcohol [Khadjesari et al., 2013] and illicit drug use, severe mental illness (e.g. schizophrenia and bipolar disorder), comorbidity, parental age and negative life events (divorce or death of parent/sibling). Other morbidities were assessed by assessing the number of prescriptions from different British National Formulary (BNF) chapters that a parent received during the first year after childbirth. Prescriptions for vaccinations, anaesthesia and contraceptives were excluded from this index.

5.4 THIN family cohort characteristics

In total 4,942 families were followed up for at least 15 years. Of these, 2,353 (48%) included families with a female child (Table 5.2). In general, a higher proportion of families in this cohort were more affluent than the general population, thus families with Townsend scores (score 1 or 2) made up 60% of the family cohort. However, a relatively larger proportion of families with depressed adolescents came from more deprived areas. Although there were few children with a record of the intermediate outcomes (recorded when the children were between 5 and 13 years) the proportion was generally higher in the group of children with adolescent depression.

The mean age at birth was 30.7 (sd: 4.7) years for mothers, and 33.1 (sd: 5.7) years for fathers. On average, mothers had received prescriptions from two different BNF chapters (median: 2, interquartile range: 1 - 3), while fathers received prescriptions from one (median: 1, interquartile range: 0 - 2) BNF chapters.

Covariates, recorded in the first year postpartum, were more prevalent in families where parents experienced depression, although prevalence was low overall (Table 5.3). Records of (suspected) child maltreatment and neglect were more common among families where at least one parent experienced depression. While only 2.8% of families with no record of early parental depression had a suspected child maltreatment record, 8.3%, 3.3% and 7.7% of families had a record if the mother, father or both parents experienced early depression, respectively.

Illicit drug use was recorded for only 7 families included in the THIN family cohort. Alcohol abuse, by either parent, was recorded most in families where the father had a record of early depression (7.8%) compared to 2.1% and 1.4% in families with no early

parental depression or maternal depression respectively.

Table 5.2: Child characteristics of the THIN family cohort

Baseline characteristics	Full cohort (4,942) Number (%)	Non-depressed adolescents (4,492) Number (%)	Depressed adolescents (250) Number (%)
Girls	2,353 (47.6)	2,182 (46.5)	171 (68.4)
Townsend score			
1 (most affluent)	1,849 (37.4)	1,759 (37.5)	90 (36.0)
2	1,119 (22.6)	1,072 (22.9)	47 (18.8)
3	938 (19.0)	895 (19.1)	43 (17.2)
4	641 (13.0)	600 (12.8)	41 (16.4)
5 (most deprived)	368 (7.5)	339 (7.2)	29 (11.6)
Missing	27 (0.6)	27 (0.6)	0 (0)
Intermediate outcomes		5 - 10 years	
Recurrent abdominal pain	71 (1.4)	64 (1.4)	7 (2.8)
Recurrent headaches/migraine	139 (2.8)	127 (2.7)	12 (4.8)
Tired all the time	58 (1.2)	54 (1.2)	4 (1.6)
Any psychosomatic symptoms	328 (6.6)	299 (6.4)	29 (11.6)
		10 - 13 years	
Sleep disorder	24 (0.5)	19 (0.4)	5 (2.0)
Anxiety	66 (1.3)	53 (1.1)	13 (5.2)
Depressive symptoms	41 (0.8)	29 (0.6)	12 (4.8)
Parental depression			
Maternal early depression	447 (9.0)	422 (9.0)	25 (10.0)
Paternal early depression	116 (2.4)	111 (2.4)	5 (2.0)
Comorbid early depression	26 (0.5)	25 (0.5)	2 (0.8)

Rates of parental depression (9.0% for mothers and 2.4% for fathers) recorded in the 1990s were lower than in families who had their children in the 2000s (13.9% for mothers and 3.7% for fathers). As shown in Figure 5.2, rates for paternal early depression have been increasing over time, which could explain the lower rates of paternal depression I found. A similar trend is found in maternal antidepressant rates (Figure 5.1): rates were lower in the early 1990s, when SSRIs had just arrived on the market, and steadily increased over time. Meanwhile, rates for maternal early depression rates declined, favouring the recording of maternal depression symptoms.

Table 5.3: Prevalence of covariates in the first year after birth

Early depression:	No	Maternal	Paternal	Comorbid
Child maltreatment & neglect	108 (2.5)	35 (8.3)	3 (3.3)	2 (7.7)
Illicit drug use	3 (0.1)	4 (1.0)	0 (0)	0 (0)
Alcohol abuse	93 (2.1)	6 (1.4)	7 (7.8)	0 (0)
Severe mental illness	30 (0.7)	11 (2.6)	5 (5.6)	1 (3.9)
Negative life events	742 (16.8)	126 (29.9)	18 (20.0)	10 (38.5)

Table 5.4: Prevalence of intermediate variables in children in the family cohort

Early depression:	No	Maternal	Paternal	Comorbid
	Number (%)	Number (%)	Number (%)	Number (%)
Recurrent abdominal pain	63 (1.4)	7 (1.7)	1 (1.1)	0
Recurrent headaches/migraine	120 (2.7)	16 (3.8)	3 (3.3)	0
Tired all the time	48 (1.1)	9 (2.1)	0	1 (3.9)
Any psychosomatic symptoms	279 (6.3)	43 (10.2)	5 (5.6)	1 (3.9)
Sleep disorders	19 (0.4)	5 (1.2)	0	0
Anxiety	52 (1.2)	13 (3.1)	1 (1.1)	0
Depressive symptoms	32 (0.7)	6 (1.4)	2 (2.2)	1 (3.9)

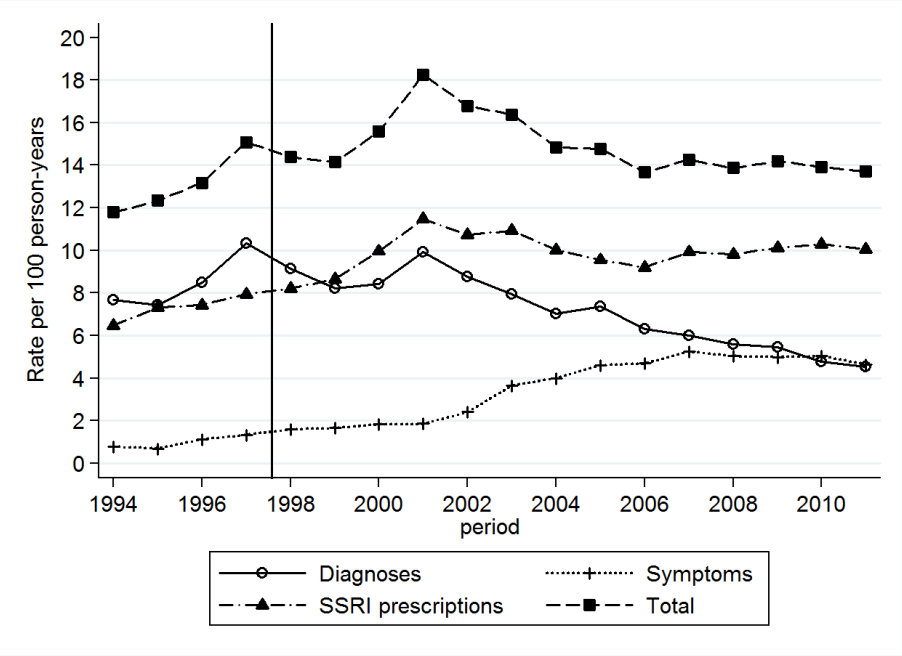


Figure 5.1: Early maternal depression rates from 1994 to 2011. Total represents the rates of diagnoses and/or prescriptions; line marks mothers potentially included in family cohort

As shown in Table 5.5, parents who experienced early depression are more likely to experience recurrence of depression compared to parents who were not depressed in the first year postpartum. While 69.2% of parents without early depression did not have a record of depression during follow-up, only 13.2% of mothers and 21.1% of fathers did not have a recurrence.

Table 5.5: Recurrent parental depression in the THIN family birth cohort

Early parental depression	No depression	Maternal	Paternal	Comorbid
	Number (%)	Number (%)	Number (%)	Number (%)
No recurrence mother	3,033 (69.2)	55 (13.2)	50 (55.6)	5 (20.0)
No recurrence father	3,462 (78.6)	271 (64.4)	19 (21.1)	6 (23.1)
N of episodes mother (5-95% centiles)	0.61 (0 - 11)	6.30 (0 - 16)	1.19 (0 - 6)	6.24 (0 - 16)
N of episodes father (5-95% centiles)	0.66 (0 - 4)	1.26 (0 - 7)	6.06 (0 - 17)	5.38 (0 - 17)

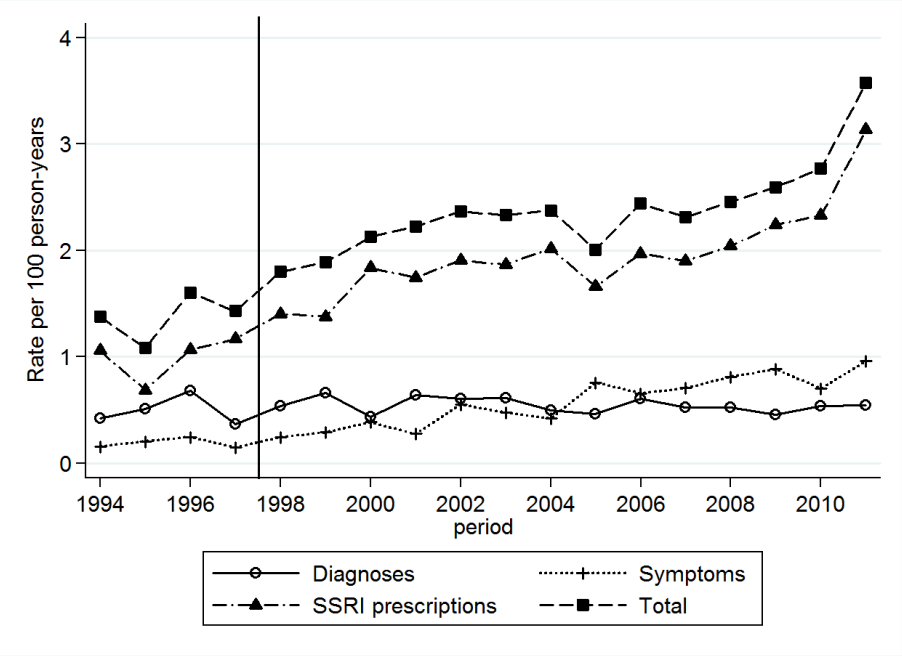


Figure 5.2: Early paternal depression rates from 1994 to 2011. Total represents the rates of diagnoses and/or prescriptions; line marks fathers potentially included in family cohort

Internalizing behaviour in children is described in Table 5.6. Overall, few children have a record of internalizing behaviour. Despite the small numbers, children of parents with early depression seem to have a slightly higher prevalence of internalizing behaviour.

Table 5.6: Intermediate variable characteristics of the THIN family cohort

Early parental depression	No depression	Maternal	Paternal	Comorbid
Intermediate child outcome	Number (%)	Number (%)	Number (%)	Number (%)
Recurrent abdominal pain or constipation	63 (1.4)	7 (1.7)	1 (1.1)	0
Recurrent headaches/migraine	120 (2.7)	16 (3.8)	3 (3.3)	0
Tired all the time	48 (1.1)	9 (2.1)	0	1 (3.9)
Any psychosomatic symptoms	279 (6.3)	43 (10.2)	5 (5.6)	1 (3.9)
Sleep disorders	19 (0.4)	5 (1.2)	0	0
Anxiety	52 (1.2)	13 (3.1)	1 (1.1)	0
Depressive symptoms	32 (0.7)	6 (1.4)	2 (2.2)	1 (3.9)

5.5 Sensitivity analyses

As I only included families with at least 15 years of follow-up in the main cohort, only a few families had information available before pregnancy. In addition, many parents move around the time they start a family, leading them to switch GP as well. For these reasons, I did not assess covariates or depression rates in families before birth. However, since many more families that have less than 15 years of follow-up are available, I could assess recording of these variables before birth in other families.

As a sensitivity analysis, I have explored depression rates and covariate prevalence in all families that have at least three years of follow-up available before the birth of the child included in the THIN family cohort (Table 5.7).

Early parental depression	No depression (71,090)	Maternal (10,732)	Paternal (2,935)	Comorbid (1,151)
Depression history of mother	7,142 (10.1)	4,540 (42.3)	232 (7.9)	249 (21.6)
Depression history of father	2,358 (3.3)	307 (2.9)	1,315 (44.8)	190 (16.5)
Comorbid depression history	657 (0.9)	457 (4.3)	349 (11.9)	481 (41.7)
Child maltreatment & neglect	7,589 (10.7)	1,413 (13.2)	396 (13.5)	195 (16.9)
Illicit drug use	427 (0.6)	193 (1.8)	99 (3.4)	87 (7.5)
Alcohol abuse	467 (0.7)	158 (1.5)	99 (3.4)	87 (7.5)
Severe mental illness	140 (0.2)	111 (1.0)	75 (2.6)	43 (3.7)
Negative life events	1,589 (2.2)	503 (4.7)	168 (5.7)	101 (8.7)

Table 5.7: Prevalence of covariates in the three years before birth

Covariates are more prevalent in families who experience early depression, and are more prevalent compared to the analysis including only the first year postpartum (Table 5.3).

	Townsend score					
Follow-up	1 (least deprived)	2	3	4	5 (most deprived)	missing
1-4 years	17,135	14,099	14,818	13,537	9,042	5,152
	(23.2%)	(19.1%)	(20.1%)	(18.3%)	(12.3%)	(7.0%)
5-9 years	13,611	9,672	8,437	6,855	4,110	1,452
	(30.8%)	(21.9%)	(19.1%)	(15.5%)	(9.3%)	(3.3%)
10-14 years	6,812	4,444	3,578	2,722	1,553	502
	(34.7%)	(22.7%)	(18.2%)	(13.9%)	(7.9%)	(2.6%)
15-19 years	2,372	1,492	1,253	916	570	101
	(35.4%)	(22.3%)	(18.7%)	(13.7%)	(8.5%)	(1.5%)

Table 5.8: Townsend scores by birth cohort follow-up

Finally, I examined cohort attrition. It is possible that certain families are more likely to move and deregister from a GP register practice, and thus be lost to follow-up. Table 5.8 show the distribution of Townsend scores in families followed up for 1-4 years, 5-9 years, 10-14 years and, the group included in my family cohort, 15-19 years. Families with higher Townsend scores (indicating low deprivation levels) are more likely to be follow-up for longer. Whereas 23% of the group with 1-4 years of follow-up had a Townsend score of 1, more than 1 in 3 families (35%) in the group with 15-19 years of follow-up was in the least deprived group. It is possible that part of this difference is explained by a lower proportion of missing values for Townsend scores, as this decreases with follow-up.

People who are more ill might be less likely to move, hence, I also examined co-morbidity scores in the groups with different lengths of follow-up. As shown in Table 5.9 comorbidity scores do not vary between groups of different follow-up.

Maternal comorbidity	Mean	Median	5-95% percentiles
1-4 years follow-up	2.79	2	1-6
5-9 years follow-up	2.78	2	1-6
10-14 years follow-up	2.74	2	1-6
15-19 years follow-up	2.84	3	1-6
Paternal comorbidity			
1-4 years follow-up	1.96	2	1-4
5-9 years follow-up	1.90	2	1-4
10-14 years follow-up	1.83	1	1-4
15-19 years follow-up	1.88	2	1-4

Table 5.9: Parental comorbidity scores by birth cohort follow-up

5.6 Discussion

With the methods used in previous studies, I was able to construct a family birth cohort within THIN following almost 5,000 families from birth to at least 15 years later. Mothers and children were linked using birth/delivery records and family identifier codes. Potential fathers were linked to mothers and children using the same family identifier code, and by restricting the potential age difference between fathers and mothers to 15 years.

Parents in the family cohort were older than the national average. In the 1991 census, the average age of all fathers in England and Wales at the birth of a child was 30.8 years, compared to 33.1 years in THIN [for National Statistics, 2013]. Similarly, the average age for mothers was 27.7 years in 1991 according to the Office for National Statistics (ONS) data, while the average age in the family cohort was 30.7 years. This could be explained by the relatively high proportion of more affluent families (60.0%) in the family cohort, as the average age was lower for more deprived families. In addition, it is likely that I have missed some of the first children in families, as families tend to move house around the time they start their families. As a result, the apparent age of new parents might be slightly higher than average.

Families who were less deprived were overrepresented in the family cohort, with 35% being in the least deprived Townsend score quintile, compared to 23% in a cohort of families followed-up for 1-4 years. As it is known that deprivation is associated with a higher depression risk, the missing data on more deprived families could have affected my findings, although it is difficult to predict in what direction they might have been altered. Ideally, I would have investigated the possible impact of missing data by performing a simulation study or multiple imputation, but that was beyond the scope of my work. Another consequence could be a lower number of patients with depression, which would lead to a loss of power to detect an association in the first place. There did not appear to be any difference between families with different follow-up times with regards to comorbidity scores.

Depression in parents might be underreported in the family cohort as these families had their children in the mid-nineties. Since then, it appears the theshold for depression recording by GPs, and/or the reporting by patients has changed. As shown in Figure 5.2, rates for paternal depression were lower for fathers between 1994 and 1997 compared to the later time period. Similarly, rates for antidepressant prescriptions for SSRIs, which I used to identify early parental depression, were lower in the mid-1990s. As described in appendix B, SSRIs had just come onto the market in this time and, understandably, new drugs are not readily prescribed to pregnant or lactating women. This might have led to some parents who did experience depression to be classified as non-early parental depression in my cohort. This could result in a underestimation of the effects of early parental depression on adolescent depression.

The cohort is likely to be representative of children in the UK. However, I may have introduced bias as families are lost to follow-up. This happens if they deregister from their GP practice (though not if one parent deregisters), which might happen when moving house. There are no reasons to assume this will make our cohort less representative of the UK population.

I made the assumption that patients received anti-depressant prescriptions solely for depression. Because prescriptions are not always directly linked to medical diagnoses in THIN, it is possible that patients in the cohort receive antidepressants for reasons other than depression. However, I only included antidepressants when they were prescribed

at the appropriate dose for depression treatment and excluded patients when they had a diagnosis for eating disorders or anxiety, therefore minimising the risk of including prescription for indications other than depression.

5.7 How will this chapter inform my thesis?

The family cohort I described in this chapter will be the cohort I use for my main analysis in Chapter 7. The cohort, consisting of 4,942 families, was constructed within THIN to create a representative cohort of UK families. However, families included in the cohort were more likely to be more affluent compared to general population. In a cohort including 1,224,100 children aged 5 - 18 years (which I used in Chapter 6), 14.0% and 19.1% of children had a Townsend score of 5 or 4 (scores representing the more deprived quintiles), respectively. In comparison, only 7.5% and 13.0% of families included in the family cohort had a score of 5 or 4.

The proportion of missing Townsend scores was slightly lower in the family cohort compared to the 5 - 18 years child cohort (0.6% versus 2.0%). This could be the result of the longer follow-up in the family cohort of at least 13 years, compared to 5 years on average for the 5 - 18 year child cohort. This longer follow-up period would provide a GP with more opportunities to record the postcode on which the Townsend score is based.

The proportion of girls and boys was similar with 48.0% girls in 5 - 18 years child cohort, and 47.6% girls in the family cohort.

A possible explanation for the lower proportion of more deprived families could be that these families are more likely to move and change GP practice and thus be lost to follow-up. As depression is positively associated with deprivation, this could mean that I will lose the part of the population who is most likely to experience my exposure and outcome of interest.

Chapter 6

Paediatric sleep disorders and adolescent depression

6.1 Objectives of the chapter

In this chapter I will present a study to assess the viability of my objective to assess whether internalizing behaviours in childhood can be used to identify children at risk of adolescent depression. Sleep disorders, insomnia in particular, have been linked to depression in adults. Moreover, it is a specific symptom used in both DSM-IV and ICD-10 to identify depressive disorders. As such, the feasibility study focusses on paediatric sleep disorders and their association with adolescent depression.

6.2 Sleep disorders in children

Sleep problems are common, affecting 25% to 40% of children and adolescents [Owens et al., 2005]. Disrupted or inadequate sleep has been shown to affect neurobehavioural functioning in school-age children [Sadeh et al., 2002] and is correlated with concurrent anxiety and depression [Gregory and O'Connor, 2002]. However, little is known about the incidence of sleep disorders (as opposed to sleep disruption) in school-age children (age 5-18 years) and their recognition and treatment in primary care [Ford and Kamerow, 1989, Ohayon, 2002]. The few studies that have attempted to assess sleep disorders

in children have been cross-sectional studies [Ipsiroglu et al., 2001, Meltzer et al., 2010, Mindell, 1993, Simonds and Parraga, 1982]; or have focussed on groups with particularly high rates of sleep disorders, such as children with epilepsy, autism spectrum disorders (ASD), and attention-deficit/hyperactivity disorders (ADHD) [Cortese et al., 2009, Jan et al., 2006].

There is also a lack of data on prescriptions of hypnotics issued to children with sleeping disorders in primary care. A US study looking at hospitalised children found that antihistamines were most commonly prescribed to children with sleeping problems (37% of prescriptions), followed by benzodiazepines (9%) and other hypnotic agents (3%) [Meltzer et al., 2007]. No medications have a UK market authorisation for treatment of paediatric sleeping disorders, and there are no guidelines regarding the use of these or other drugs for treatment of sleep disorders in children.

In adults, an association between sleep disorders, insomnia in particular, and depression has been found [Baglioni et al., 2011]. Adults with primary insomnia were two to three times as likely as people with no sleep difficulties to develop depression later in life. Insomnia and hypersomnia are recognised as symptoms for major depression disorder by the DSM. Whether this association also exists for children remains unclear.

This study aimed assess the association between paediatric sleep disorders and adolescent depression. I also briefly explore the incidence of sleep disorders and hypnotic prescriptions in children in UK primary care.

6.3 Methods

6.3.1 Study population

I used data from The Health Improvement Network (THIN) primary care database, as described in chapter 2. Children who were registered for at least one year with their GP between 1 January 1995 and 31 December 2011 were included in the cohort. They entered the cohort from the age of five, and left the cohort 30 June in the year they turned 19, deregistered from the practice, or died. I studied children from the age of five, as sleeping patterns are established by this age, and a similar sleep rhythm is imposed on all children as they enter primary school. Furthermore, most children will be able to sleep

through the night and will not need daytime naps unlike their younger counterparts (i.e. those under 5 years of age [Thiedke, 2001]).

6.3.2 Exposures and outcome

First, I examined trends in sleep disorders and hypnotic prescriptions by sex, deprivation, age and calendar year. Second, I examined indications that could be associated with recording of sleep disorders in young children. Finally, I examined the associations between sleep disorder and risk of depression.

The exposure of interest was sleep disorders. This variable is based on different combinations of codes reflecting insomnia (problems falling and staying asleep); hypersomnia (problems staying awake); sleep rhythm problems (problems sticking to a regular sleep schedule); and sleep-disruptive behaviours (unusual behaviours during sleep), following ICD-10 classification. Sleep disorders due to physical illness such as narcolepsy and sleep apnoea were excluded. A Read code list was created using the method previously described in section 2.4.1 on page 59, and evaluated by a GP (Irwin Nazareth).

To assess drug treatment, I created a drug code list based on the BNF for children, chapter 4.1 Hypnotics [Paediatric Formulary Committee, 2010]. I also included sedating antihistamines (BNF chapter 3.4.1) if they were prescribed within one month of a sleep disorder diagnosis.

I explore the association between sleep disorders and depression. Depression was identified by using Read code lists for depression diagnoses, symptoms and antidepressant prescriptions. These code lists have been developed for chapter 4.

6.3.3 Analysis

Incidence rates and 95% confidence intervals for each class of sleep disorders and hypnotics were calculated by calendar year, age, sex, and deprivation quintile using person-years-at-risk (PYAR) as the denominator. To assess temporal trends in the change in incidence per calendar year, incidence rate ratios (IRR) were calculated for each indicator using Poisson regression models, with adjustment for clustering at the practice level. I used fractional polynomial models to take account of non-linear time and age trends [Royston and Altman, 1994]. Each model contained a continuous variable for

time (by calendar year) and age, a binary variable for sex, and a categorical variable for deprivation quintile.

I examined statistical interactions between age, sex and deprivation and the analysis was accordingly stratified by those variables where there was an interaction. Comorbidity in young children (age <12 year) was assessed by calculating incidence rates for diagnosis of neurodevelopmental disorders such as autism spectrum disorder, ADHD, and epilepsy in children with and all children without a hypnotic prescription. I chose these neurodevelopmental disorders as children with these disorders have been found to have high rates of sleep disorders [Cortese et al., 2009, Jan et al., 2006]. I calculated incidence rate ratios adjusting for age, calendar year, sex, and deprivation quintile.

I longitudinally assessed the association between the different classes of sleep disorders and depression by comparing children with sleep disorders and a group of randomly selected children with no sleep disorders, but with similar distribution in terms of sex, deprivation quintile, year of birth and follow-up time. This comparison was done by using a multivariable time-to-event model (Cox proportional hazards model). The start of the follow-up was from the first diagnosis of a sleep disorder and a matched date for the children without sleep disorder. The analyses were adjusted for clustering using robust standard errors.

All data management and analyses were performed using Stata SE version 12.1 (StataCorp, College Station, TX).

6.4 Results

In total, 1,224,100 children aged 5-18 years were registered with a practice for at least one year between 1995 and 2011. Of these children, 19,518 (1.6%) had at least one record of a sleep disorder, and 9,816 (0.8%) had been prescribed hypnotics. Children with sleep disorders had a slightly longer follow-up period than children without (median: 7.4 years vs 5.0 years) and were more likely to be in the more deprived Townsend quintiles (Table 6.1).

Characteristic	Sleep disorders (19,518)	All children (1,224,100)
Girls (%)	10,409 (53.3)	588,049 (48.0)
Median age at entry (5^{th}-95^{th} centiles)	7.9 (5.0 - 16.5)	7.5 (5.0 - 16.8)
Median age at exit (5^{th}-95^{th} centiles)	18.5 (8.8 - 19.0)	15.5 (7.0 - 19.0)
Median time in study (5^{th}-95^{th} centiles)	7.4 (1.7 - 13.5)	5.0 (1.3 - 12.3)
Deprivation (Townsend score) (%)		
1 (least deprived)	4,116 (21.1)	300,290 (24.5)
2	3,445 (17.7)	247,677 (20.2)
3	3,991 (20.6)	246,245 (20.1)
4	4,315 (22.1)	234,191 (19.1)
5 (most deprived)	3,337 (17.1)	170,990 (14.0)
0 (missing)	314 (1.6)	24,707 (2.0)

Table 6.1: Study population characteristics. Values are numbers (column percentages) unless otherwise indicated

6.4.1 Trends in sleep disorders and hypnotic prescriptions

Of the children with sleep disorders, 12,745 (65%) had a record for insomnia, followed by children with a record of sleep disorder, not otherwise specified (2,504, 13%), sleep rhythm disorder (2,496, 13%), sleep disruptive behaviour (2,488, 13%), and hypersomnia (319, 2%). As numbers for hypersomnia were very low, these were excluded from further analyses.

Of the children with a diagnosed sleeping disorder, 4,267 (28.0%) were prescribed hypnotics. However, not all children prescribed a hypnotic had a record of sleeping disorder. Thus, of the 11,410 children with a prescription for a hypnotic, only 59.7% had a record of a sleeping disorder. Melatonin was the most prescribed hypnotic, with 49,633 (67%) of all prescriptions, followed by zopiclone and temazepam (7,481 and 4,056 prescriptions, respectively).

Insomnia is the most commonly diagnosed sleep disorder increasing from 10.6 (95% CI: 9.7 - 11.6) per 10,000 PYAR for children aged 5-12 years to 48.3 (95% CI: 46.2 - 50.4) per 10,000 PYAR for children age 18 years (Figure 6.1). Over time, rates for insomnia have increased from 10.7 (95% CI: 8.5 - 13.2) per 10,000 PYAR in 1995 to 24.6 (95% CI: 23.3 - 26.0) per 1,000 PYAR in 2011 (Figure 6.1).

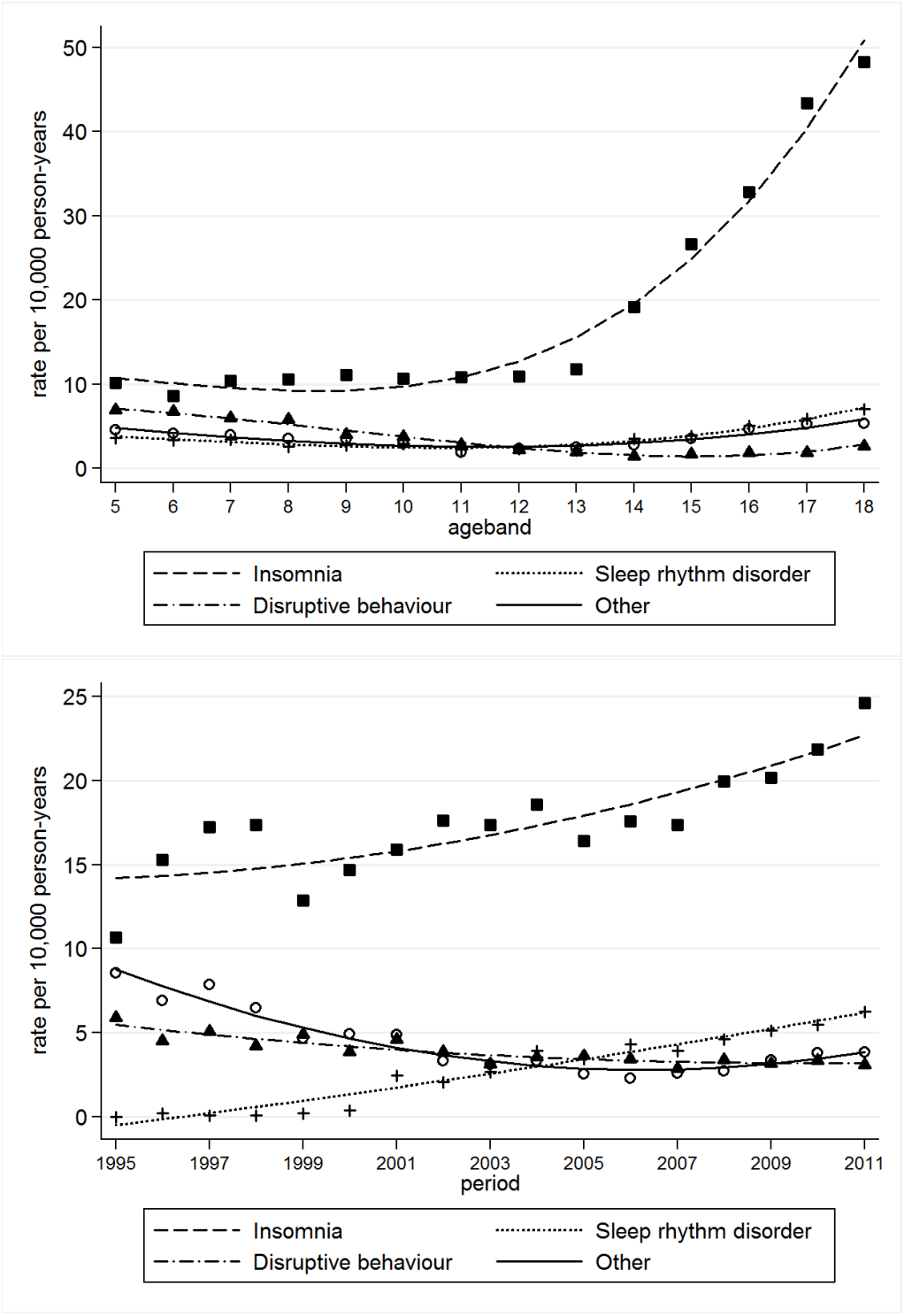
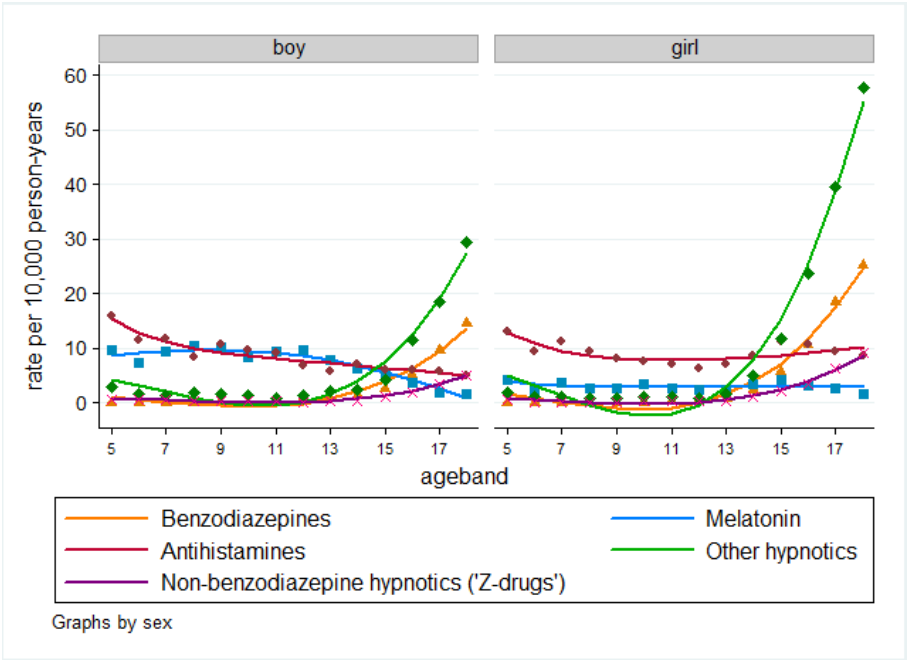
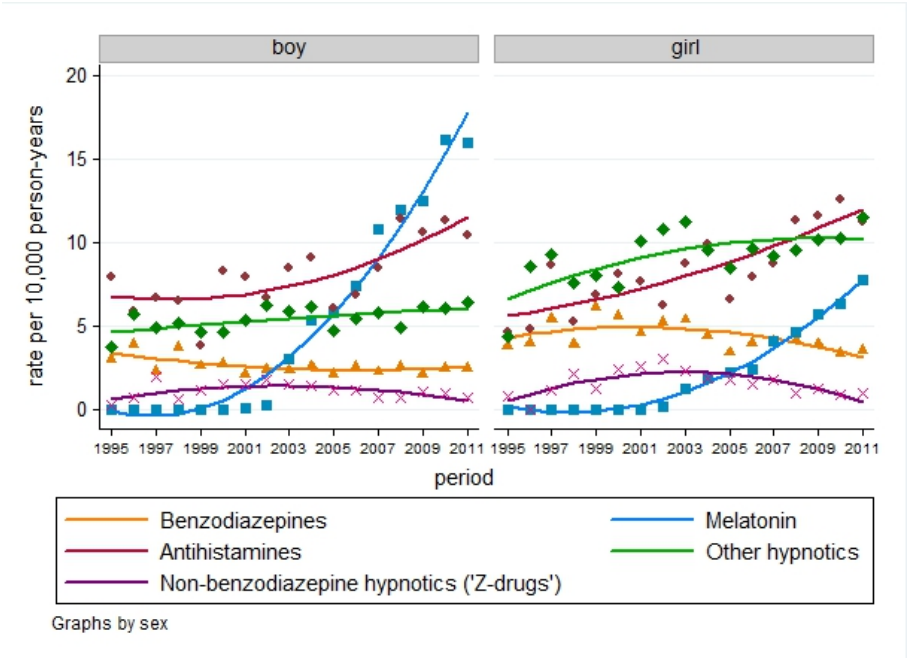


Figure 6.1: Incidence rates of insomnia, sleep disruptive behaviour, sleep rhythm disorder, and Not Otherwise Specified (NOS) sleep disorder by A) age and B) by calendar year. Dots represent data, line are fitted fractional polynomial models.

Sedating antihistamines are most commonly prescribed to children aged 5-14 years (rate: 9.2 (95% CI: 9.0 - 9.5) per 10,000 PYAR); while other hypnotics (chloral hydrate, triclofos sodium, chloral betaine, and clomethiazole) are most commonly prescribed to older adolescents (age 15-18 years, Figure 6.2). Melatonin was first prescribed to children in 2001. However, it became the most prescribed hypnotic for boys in 2006 (Figure 6.2) with 16.0 (95% CI: 14.5 - 17.5) incident prescriptions per 10,000 PYAR.



(a)



(b)

Figure 6.2: Incidence rates of prescriptions for hypnotics by A) age and B) by calendar year Non-benzodiazepine hypnotics are zaleplon, zolpidem and zopiclone, other hypnotics are chloral hydrate, triclofos sodium, chloral betaine, and clomethiazole Dots represent data, line are fitted fractional polynomial models.

Children under the age of 12 years with prescriptions for hypnotics were more likely to have epilepsy (16% versus 7%, respectively), autism spectrum disorder (32% versus 4%), or attention-deficit/hyperactivity disorder (52% versus 6%, Table 6.2).

	Children with hypnotic prescription	General population
Epilepsy	1,571 (16%)	85,687 (7%)
ASD	3,141 (32%)	48,964 (4%)
ADHD	5,104 (52%)	73,446 (6%)

Table 6.2: Prevalence of epilepsy, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD) in children aged <12 years with and without a record of a hypnotic prescription.

6.4.2 Sleep disorders and depression

Of the children with records of both sleep disorder and depression, 24% had a preceding diagnosis for depression, while 8% had a concurrent (within a month before or after prescription) depression diagnosis. I excluded these children from the rest of my analyses.

For children aged 5-12 years when they were first diagnosed with a sleep disorder, the hazard ratio for later adolescent depression (between 12-18 years) was 3.69 (95% CI: 2.90-4.70) for boys and 5.01 (3.84-6.54) for girls. For 13-18 year olds, the hazard ratio for developing adolescent depression at least a month later was 2.51 (2.36-2.67) for boys and 2.00 (1.93-2.09) for girls (Table 6.3). Young people (13-18 years) with sleeping disorder from the most deprived areas (Townsend quintile 5) were more likely to become depressed than those from the least deprived areas (Townsend quintile 1; HR: 1.62, 95% CI: 1.43-1.83 for boys, and 1.40, 95% CI: 1.05-1.60 for girls).

	5-12 year olds		13-18 year olds	
	Boys	Girls	Boys	Girls
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Sleep disorder	3.69 (2.90 - 4.70)	5.01 (3.84 - 6.54)	2.51 (2.36 - 2.67)	2.00 (1.93 - 2.09)
Townsend score				
1 (most affluent)	Reference	Reference	Reference	Reference
2	1.21 (0.82 - 1.79)	1.03 (0.67 - 1.58)	1.35 (1.21 - 1.51)	1.06 (0.99 - 1.13)
3	1.15 (0.75 - 1.76)	1.34 (0.88 - 2.04)	1.35 (1.20 - 1.50)	1.16 (1.08 - 1.24)
4	1.56 (1.02 - 2.40)	0.96 (0.60 - 1.54)	1.50 (1.34 - 1.67)	1.25 (1.17 - 1.34)
5 (most deprived)	1.48 (0.88 - 2.47)	1.10 (0.64 - 1.90)	1.62 (1.43 - 1.83)	1.40 (1.05 - 1.60)

Table 6.3: Hazard ratios for adolescent depression, by age group and sex

In line with the hazard ratios shown in Table 6.3, absolute rates for adolescent depression differed between children with and without a preceding sleep disorder. For younger children, aged 5-12 years, the absolute risk difference was small: 0.3% of children without a sleep disorder developed adolescent depression, compared to 1.2-1.3% of boys and girls with a sleep disorder (Table 6.4). For adolescent boys, a preceding sleep disorder increases the risk of adolescent depression from 4.6% to 12.1%, while the risk increases from 11.9% to 24.1% for girls.

	Children without a sleep disorder	Children with sleep disorder
Boys, 5-12 year old	2.96 (2.50 - 3.51)	11.66 (9.93 - 13.69)
Girls, 5-12 year old	2.56 (2.10 - 3.12)	13.33 (11.31 - 15.70)
Boys, 13-18 year old	45.99 (44.24 - 47.81)	121.07 (115.66 - 126.74)
Girls, 13-18 year old	119.12 (116.45 - 121.85)	241.00 (233.57 - 248.66)

Table 6.4: Rates of adolescent depression per 1,000 person-years in children with and without a preceding sleep disorder

6.5 Discussion

6.5.1 Key findings

Insomnia was the most commonly recorded paediatric sleep disorder in UK primary care, and was associated with adolescent depression. Children with a record of insomnia were at least twice as likely to develop adolescent depression compared to children without sleep disorders. Sedating antihistamines and melatonin were the most commonly prescribed hypnotics in primary care. Insomnia was the most commonly diagnosed sleep disorder in primary care across the entire 5 - 18 year age range, affecting 10.6 per 10,000 PYAR children from age 5 to age 12 years, and up to 48.3 per 10,000 PYAR for 18-year old children.

Some cross-sectional studies have found sleep problems in 25% to 40% of children and adolescents [Owens et al., 2005], which is much higher than my findings. This discrepancy indicates that while many children and adolescents may experience sleep problems, only few will have such severe sleep disorders that they will consult their GP.

Although there are no NICE guidelines on the treatment of paediatric sleep disorders, the British Association for Psychopharmacology (BAP) have reviewed the available treatment evidence and recommend behavioural therapy [Wilson et al., 2010]. The BAP made an exception for the prescription of melatonin for children who were not taking stimulants but were diagnosed with ADHD, for which there is some evidence of efficacy [Bendz and Scates, 2010], although a recent RCT found little benefit [Gringras et al., 2012]. However, melatonin has only been licensed for treatment of insomnia in adults over 55 years. There is still little information on its long-term effects and uncertainty regarding the effects on other circadian rhythms including endocrine or reproductive hormone secretion [Paediatric Formulary Committee, 2010].

Benzodiazepines and non-benzodiazepine hypnotics ('Z-drugs') were prescribed mainly to older adolescents and only in small quantities (median: 1 two-week prescription). As both benzodiazepines [Owen and Tyrer, 1983] and (to a lesser extend) non-benzodiazepine hypnotics [Hajak et al., 2003] can lead to dependence and withdrawal symptoms, these drugs should be prescribed with care.

6.5.2 Comparison to other studies

Studies in the US have found that antihistamines are the most commonly prescribed drugs to treat sleep disorders in children [Meltzer et al., 2007, Schnoes et al., 2006]. Similarly, I found that antihistamines were the most prescribed hypnotic between 1995 and 2011. However, in boys melatonin surpassed antihistamines as the most commonly prescribed hypnotic in 2006. A study of hospitalised children found that 6% had been prescribed medications for sleep [Meltzer et al., 2007]. Antihistamines were the most commonly prescribed drugs (36.6%), followed by benzodiazepines (19.4%).

Community child and adolescent psychiatrists from the East Midlands in the UK have been found to be increasing their prescribing of psychotropic medications in general, with two-thirds of consultants stating that they were using melatonin to treat sleep disturbance in children with ASD and ADHD [Doerry and Kent, 2003]. This is in line with my findings, as I find that younger children treated with hypnotics are more likely to have been diagnosed with neurodevelopmental disorders such as ASD, ADHD, and epilepsy.

A cross-sectional study on 823 US children found that children with sleep problems were almost 7 times as likely to show concurrent symptoms of anxiety and/or depression (OR=6.9, 95% CI: 4.1 11.4) [Johnson et al., 2000]. However, the association was not significant when assessing whether sleep problems at age 6 years affected depression/anxiety at age 11, although that might be due to small sample size. Another cross-sectional study on 4,494 US adolescents (age 12-18) found that insomnia symptoms were a risk factor for depression symptoms in young adulthood (OR=2.2, 95% CI: 1.34-3.58) [Roane and Taylor, 2008]. I demonstrated this effect longitudinally in this study.

A prospective longitudinal study in New Zealand found that persistent sleep problems between ages 5 and 9 years were not associated with depression at ages 21 or 26 (OR=0.99, 95% CI: 0.63-1.56), but were associated with anxiety (OR=1.60, 95% CI: 1.05-2.45) [Gregory et al., 2005]. However, despite focussing on more common sleep problems rather than sleep disorders, numbers of exposed children were still low. The lack of an association between paediatric sleep problems and later depression in this study could also indicate that sleep problems in prepubescent children are not related to depression. Although I found a strong association between more severe sleep dis-

orders and depression in my younger age group, this association could be confounded by the presence of neurodevelopmental disorders such as ADHD or other unmeasured confounders.

6.5.3 Strengths & limitations

In THIN, I had limited information on whether GPs referred children to behavioural or psychotherapy, or gave advice on sleep hygiene as this is poorly recorded in primary care. As such, I cannot assess whether GPs use non-pharmacological options as a first line of treatment. However, as I was primarily interested in the identification of paediatric sleep disorders in primary care and its association with depression, this should not affect the validity of my findings.

Second, I only have information on drug prescriptions, not whether they were dispensed by a pharmacy, or used by a patient. However, a validation study found that rates of prescriptions and dispensing in THIN were very closely associated [The NHS Information Centre and Services, 2011] (see also Chapter 2).

Finally, it is unclear whether the trends I observe in sleep disorders and hypnotic prescriptions over time indicate whether paediatric sleep disorders are increasing or whether the detection of the problem is on the rise. Diagnoses of sleep disorders in children and the issue of hypnotic prescriptions can occur in secondary care, and there is recent evidence of an increase in hypnotic prescribing by child and adolescent psychiatrists [Doerry and Kent, 2003].

6.6 How does this chapter inform my thesis?

My results suggest that there is a slight rise in paediatric sleep disorders diagnosed in primary care between 1995 - 2011, particularly insomnia. In addition, hypnotics are prescribed more commonly, with a distinct rise in the prescription of melatonin. Hence, I should be able to detect sleep disorder in the family cohort, although rates appear to be low.

Importantly, paediatric sleep disorders seem to be related to later adolescent depression, indicating that I can use them as an indicator for internalizing behaviour in my main analysis. As such, I have included sleep disorders, based on diagnoses and/or prescrip-

tions between as a type of internalizing behaviour in my main analysis, which will be detailed in the next chapter.

Chapter 7

Parental depression and adolescent depression

7.1 Objectives of the chapter

In this chapter of my thesis, I will explore the association between early comorbid parental depression and adolescent depression and assess to what extend this association is mediated by recurrent parental depression and childhood internalizing behaviour.

The classic approach to mediation analysis in epidemiologic research involves first regressing the outcome (Y) on the exposure (X) and any confounding factors (C) (Figure 7.1). Then, the potential mediator (M) will be added to the regression model and the estimates for the coefficients associated with the exposure (X) in the first and second regression model will be compared. If the coefficients for the first and second regression model differ, then some of the effect is thought to be influenced by the mediator.

This classic approach to mediation analysis of just including the mediator in the regression is subject to two important limitations: mediator-outcome confounding and exposure-mediator interactions (see appendix D.1).

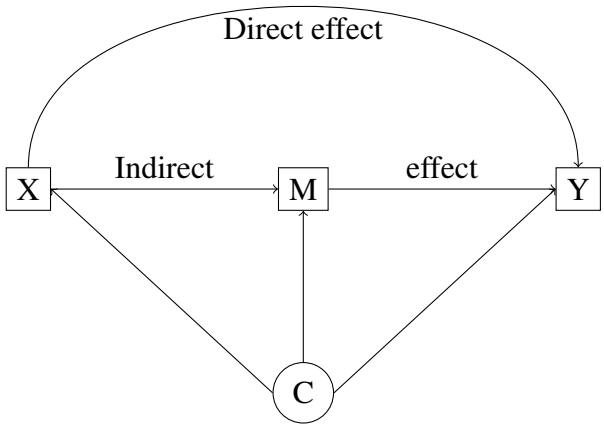


Figure 7.1: General mediation model

7.2 Introduction to structural equation modelling

Structural equation modelling (SEM) is a statistical technique that can be used to estimate and test causal relationships and adjust for mediator-outcome confounding as well as exposure-mediator interaction. SEM can estimate multiple outcomes and intermediate variables simultaneously, and construct latent variables, correcting for any correlations between them.

The term 'structural equation modelling' relays two important aspects of the method: a) that the causal processes under study are represented by a series of structural (i.e. regression) equations, and b) that these structural relations can be modelled pictorially to enable a clearer conceptualisation of the theory under study [Byrne, 2011].

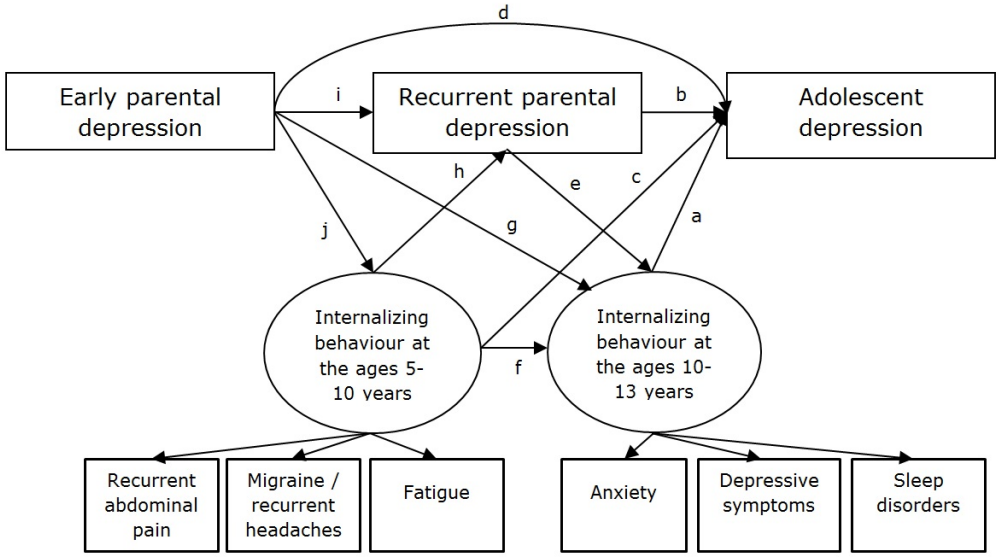


Figure 7.2: Theoretical associations (a-j) between early parental depression, recurrent parent depression between the ages of 1-13 years, internalizing behaviour between ages 5-10 years manifested by diagnoses for recurrent abdominal pain, migraine and fatigue, internalizing behaviour between ages 10-13 years manifested by diagnoses for anxiety, depressive symptoms and sleep disorders and adolescent depression between the ages of 13-18 years

The theoretical model for my study, as shown in Figure 7.2, explores the association between early comorbid parental depression and adolescent depression. I will use Cox regression to provide a raw estimate of this association. Then, I will estimate how much of this association (if there is one) is mediated by recurrent parental depression. I will assess this by comparing the direct and indirect effects, which is possible by using SEM as the simultaneous estimation of the regression equations allows for them to be adjusted for one another. Finally, I will assess whether internalizing behaviour is on the causal pathway, again by comparing direct and indirect effects of early parental depression on adolescent depression.

As mentioned in chapter 5, internalizing behaviour is not measured directly in THIN. However, individual aspects that could indicate internalizing behaviour are recorded in THIN. As there are many different types of behaviours and disorders that could poten-

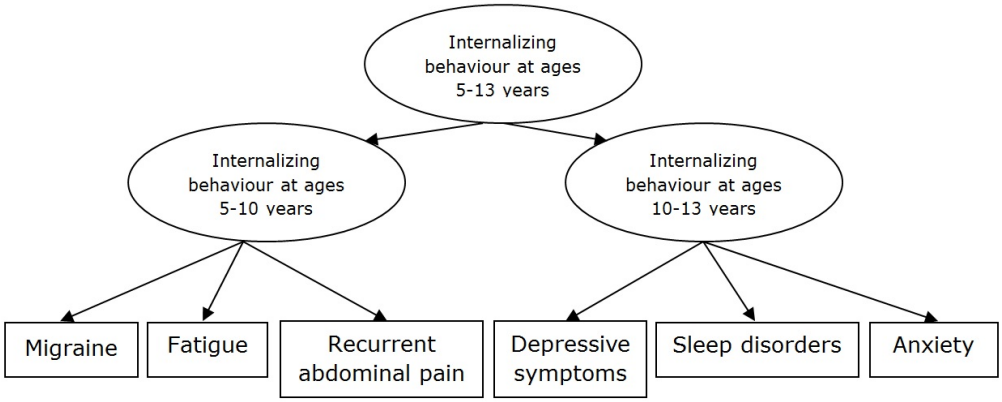


Figure 7.3: A theoretical measurement model for internalizing behaviour

tially be indicative of internalizing behaviour, I explore a measurement model to try to reduce the number of variables into one or more latent variables by using exploratory factor analysis (EFA) [Fabrigar et al., 1999, Gorsuch, 1983]. In Figure 7.3, the latent variable is represented by an oval, indicating that this is the variable that is to be estimated in the measurement model. The variables that are measured, the factors, are indicated by rectangles.

EFA is used to select indicators that measure the latent variable of interest and its goal is to explain a set of data in less than the total number of observations [Rabe-Hesketh and Skrondal, 2008]. Before using EFA, I will inspect the correlation matrix. EFA assumes that the selected factors are measuring the same concept, so there should be some correlation between the factors. If the majority of correlation are lower than 0.20, this could indicate that my selected factors are measuring different things and that EFA is not appropriate.

With EFA, each potential factor is assigned a factor loading. This loading indicates how strongly each factor is associated with the latent variable, and is used to determine which factors can be used to estimate the latent variable. Factors with a loading of $>$0.40 are considered acceptable, and ideally each factor would only load onto one latent variable.

To determine on the number of factors to include for each latent variable, I will assess the eigenvalues of the factors. The eigenvalue represents the total variance of each factor. I will use the Kaiser criterion to select the number of factors to include, which

means I will use factors with an eigenvalue >1 [Kaiser, 1958].

I will model the EFA using oblique factor rotation, as this type of factor rotation allows for the individual factors to be associated to one another.

After selecting the factors for the latent variable(s), I will use Exploratory Structural Equation Modelling (ESEM)[1] [Wall and Li, 2003, McArdle, 2009]. ESEM is a method that combines features of unrestrictive measurement models (EFA) with restrictive measurement models (confirmatory factor analysis CFA). ESEM allows part of the structural model to be exploratory, in the sense that no constraints are imposed on whether factor loadings should be fixed at 0, akin to CFA, while these latent factors are allowed to influence all manifest indicators according to a pre-defined structure. By using a multivariate structural model, I will be able to estimate direct and indirect effects simultaneously.

It is likely that not all factors I have identified as potential indicators of internalizing behaviour will be selected by EFA. If factors are shown not to load onto the latent variable(s), I will model them individually. If no latent variable constructs are appropriate, I will construct two binary variables indicating whether children experienced any indicators between ages 5-10 years (recurrent abdominal pain, migraine, and fatigue) or ages 10-13 years (anxiety, sleep disorders, depressive symptoms). Furthermore, instead of ESEM, I will use 'regular' SEM as latent variable constructs will not need to be confirmed. I will correct analysis for covariates mentioned in the previous chapter (Townsend deprivation quintile, maternal and paternal age at birth, birth year, child gender, potential child maltreatment or neglect, parental illicit drug use, alcohol abuse and comorbidity). I will not list the covariates in the diagrams for simplicity. However, their association with the outcome is shown in Appendix D.1.

All data management and exploratory analyses will be performed using Stata SE version 12.1 (StataCorp, College Station, TX). EFA and (E)SEM analyses will be performed

[1] ESEM is a combination between path analysis and confirmatory factor analysis, and as such provides a method for describing the assumed causal relationships between observed variables that are related themselves. Traditional multiple regression can run into problems with interpretation and multicollinearity when multiple predictor variables are considered, but this can be avoided with SEM. This method is particularly useful for analysing longitudinal repeated measures data.

using MPlus version 7.0 (Muthén & Muthén, 2012).

7.3 Model description

I will test and compare three different models. However, I will start by estimating the main effects of maternal, paternal and comorbid early depression using logistic regression with robust standard errors to adjust for clustering effect by practice. I hypothesise that children exposed to early parental depression will be at an increased risk of adolescent depression, and that children exposed to comorbid early depression will be at the highest risk. I will further explore the association between early parental and adolescent depression by comparing three risk models using structural equation modelling:

- Model 1 (parental depression model), in which the effect of parental early depression on adolescent depression is hypothesised to be mediated by recurrent parental depression during childhood.

- Model 2 (internalizing behaviour model), in which the effect of parental early depression on adolescent depression was hypothesised to be mediated by internalizing behaviour in children between the ages of 5 to 10 years and 10 to 13 years.

- Model 3 (integrated model), including direct effects of early parental depression on adolescent depression and mediating effects of both recurrent parental depression and internalizing behaviour.

The results will be depicted by path coefficients which are partial standardised regression coefficients that measure the effect of one variable on another, while controlling for all other variables prior in the model. Parameters are estimated using Full Maximum Likelihood methods, which allow a complete case analysis and provide unbiased and efficient parameter estimates if data (Townsend scores in this instance) are missing at random [Allison, 2001].

The exposure, outcome, mediators and covariates entered in the analysis are described in detail in previous chapters and summarised for one family in Figure 7.4).

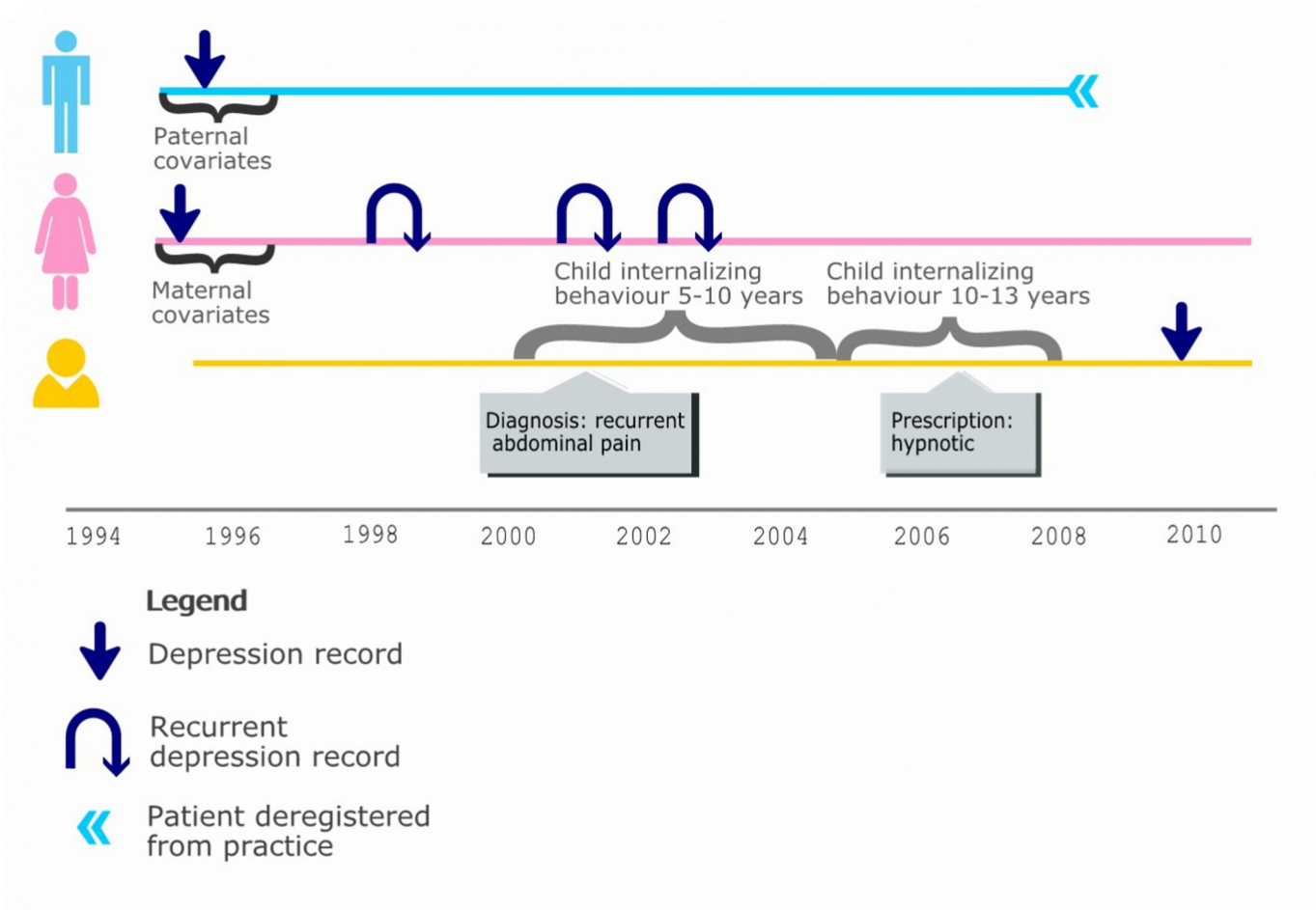


Figure 7.4: Variables entered in the main analysis. The blue line represents the father, pink is the mother, the child is the yellow line. The family depicted here is a random family who had both the exposure and outcome of interest recorded.

7.4 Results

I used the birth cohort consisting of 4,942 families and variable definitions as described in chapter 5 for this analysis. The overall results for the association between early parental depression and adolescent depression are described in Table 7.1. Early maternal depression increased the risk of adolescent depression twofold (fully adjusted OR: 2.04, 95% CI: 1.22 - 3.41), while paternal early depression does not appear to have an effect (OR: 0.38, 95% CI: 0.11 - 1.35). The effect of comorbid early parental depression does not reach statistical significance, although the effect estimate is similar to that of maternal early depression (OR: 2.02, 95% CI: 0.42 - 9.67).

Table 7.1: Odds Ratios for offspring depression in families with and without parental depression in 4,880 complete cases

		Model 1	Model 2	Model 3
Early depression	n cases (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Maternal only	447 (9.0%)	1.10 (0.71 - 1.71)	1.80 (1.09 - 2.970	2.04 (1.22 - 3.41)
Paternal only	116 (2.4%)	0.65 (0.20 - 2.08)	0.50 (0.15 - 1.68)	0.38 (0.11 - 1.35)
Comorbid	26 (0.5%)	1.64 (0.38 - 7.01)	1.99 (0.45 - 8.86)	2.02 (0.42 - 9.67)

Model 1: Univariate associations between early parental depression and adolescent depression

Model 2: Model 1 with adjustments for covariates (Townsend quintile, child birth year, possible maltreatment and neglect, illicit drug use, alcohol abuse, maternal and paternal age, comorbidity, and severe mental illness, child sex and negative life events as measured during the first year after birth)

Model 3: Model 2 with additional adjustment for recurrent parental depression

Each additional year during which a parent experiences a depression episode increases the risk of adolescent depression by 14% for mothers (OR: 1.14, 95% CI: 1.05 - 1.25), while the effect for fathers is not statistically significant (OR: 1.03, 95% CI: 0.98 - 1.08).

Table 7.2: Absolute number of adolescents with depression by parental depression

	Maternal early depression		Paternal early depression	
Child depression	n	%	n	%
No	229	5.1%	249	5.2%
Yes	25	5.6%	5	4.4%

As shown in Tables 7.2 and 7.3, the effect of early parental depression on adolescent depression appears small. Maternal early depression increases the outcome by 0.5%, while paternal early depression appears to results in slightly lower numbers (although numbers are small in this group).

Importantly, recurrent parental depression appears to have a stronger effect on adolescent outcome, more than doubling the number of the adolescents with depression in mother who have 5+ years with recurrences of depression compared to non-depressed mothers. The effect of early parental depression appears small, though the analysis is again limited by small numbers (figures for fathers' depression are not presented for the same reason).

Table 7.3: Absolute number of adolescents with depression by maternal early and recurrent depression

	No early maternal depression		Early maternal depression	
	n	%	n	%
No recurrence	99	4.0%	11	4.0%
1-4 recurrences	96	5.9%	12	9.7%
5+ recurrences	28	10.5%	2	7.4%

7.4.1 Exploratory Factor Analysis: measuring internalizing behaviour

First, I produced the correlation matrix shown in Table 7.4. As the majority of factors have a correlation of <0.20, factor analysis is not appropriate in this instance.

Table 7.4: Correlation matrix showing factor correlations

Correlation	1	2	3	4	5	6
1	1.00					
2	0.08	1.00				
3	0.04	0.06	1.00			
4	0.02	0.00	0.00	1.00		
5	0.02	0.02	0.00	0.03	1.00	
6	0.01	0.03	0.03	0.00	**0.42**	1.00

1) Recurrent abdominal pain

2) Recurrent headaches / migraine

3) Tired all the time

4) Sleep disorders

5) Anxiety

6) Depressive symptoms

Depressive symptoms and anxiety are moderately correlated (Pearson's ρ: 0.42, p<0.01). However, as this correlation is only just above the threshold of 0.40, I chose not to use latent variable modelling as a data reduction step, but rather construct two composite scores indicating internalizing behaviour between ages 5-10 years and 10-13 years. The prevalence of internalizing behaviour is similar for children of parents with no early parental depression compared to comorbidly-depressed parents (7.2% and 7.7%, respectively, Table 7.5). However, in families where only the mother experienced early depression, 51 (12.1%) children experienced internalizing behaviour. For internalizing behaviour between 10-13 years, prevalence rates were higher for all children with at least

one depressed parent, although the sample size was small.

Table 7.5: Prevalence of childhood internalizing behaviour (IB) by parental depression

Early parental depression	No depression	Maternal	Paternal	Comorbid
	(4,405)	(421)	(90)	(26)
IB 5 - 10 years (%)	316 (7.2)	51 (12.1)	5 (5.6)	2 (7.7)
IB 10 - 13 years (%)	83 (1.9)	18 (4.3)	3 (3.3)	1 (3.9)

7.4.2 Structural equation modelling

I fitted the hypothesised model as suggested in Figure 7.2 using SEM (see Appendix E for the Mplus code). The results of these analyses are shown in Figures 7.5, 7.6, and 7.7; pathways that have been set to 0 (in Figures 7.5 and 7.6) are not shown in order to make the figures more easily interpretable. Similarly, the models were adjusted for the covariates mentioned in Chapter 5 (Townsend quintile, child birth year, possible maltreatment and neglect, illicit drug use, alcohol abuse, maternal and paternal age, comorbidity, and severe mental illness, child sex and negative life events as measured during the first year after birth), but the related coefficients are not shown.

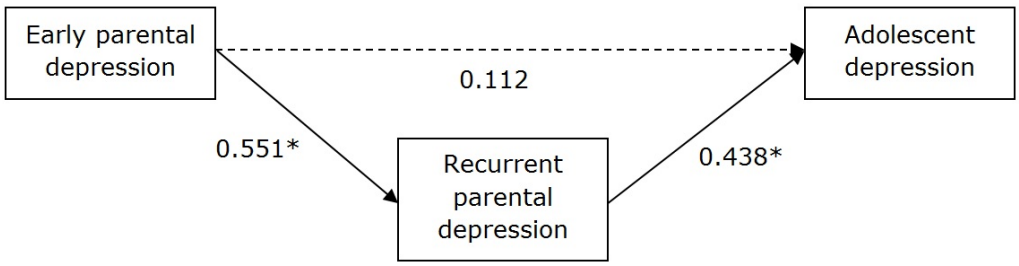


Figure 7.5: Model 1 (parental depression model). *p<0.01. Single-headed arrows reflect hypothesised relationships between variables. Regression coefficients are shown next to each path.

When focussing on the association between early parental depression and adolescent depression, mediated by recurrent parental depression (Figure 7.5) most of the association

appears due to the indirect pathway. Both the association between early parental depression and recurrent parental depression, and between recurrent depression and adolescent depression are statistically significant. Meanwhile, the association between early parental depression and adolescent depression is not statistically significant (p = 0.78).

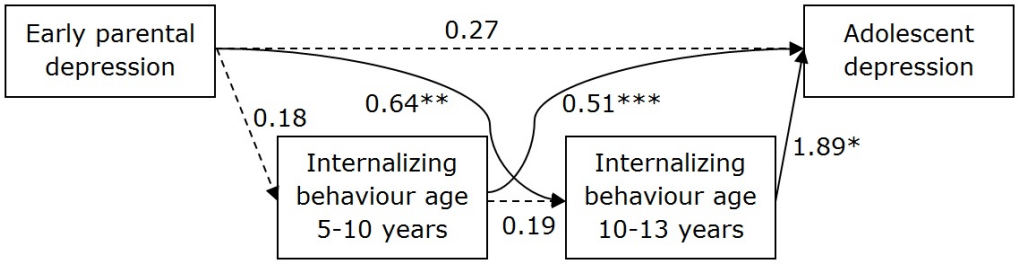


Figure 7.6: Model 2 (internalizing behaviour). *p<0.001, **p<0.01, ***p<0.05. Single-headed arrows reflect hypothesised relationships between variables. Regression coefficients are shown next to each path.

The association between early parental depression, internalizing behaviour and adolescent depression is explored in Figure 7.6. Internalizing behaviour between the ages of 10 to 13 is strongly associated with adolescent depression independent from parental effects, with a weaker but still statistically significant association for IB at 5 - 10 years.

Internalizing behaviour between the ages of 5 to 10 years is not associated with internalizing behaviour between the ages of 10 to 13 years. These results are in line with the results from the EFA (section 7.4.1, page 158), that suggested that the selected factors could not be reduced to one latent variable.

The regression coefficients from the integrated analysis are shown in Figure 7.7 and Table 7.6. Again, early parental depression does not seem to be associated directly with adolescent depression (OR: 1.06, 95% CI: 0.69 - 1.63). However, the indirect pathways via recurrent parental depression and internalizing behaviour are both statistically significant. It is interesting that early parental depression has a stronger effect on internalizing behaviour in early adolescence. This might be due to better ”specificity” of the symptoms at that developmental age.

Internalizing behaviour between the ages of 10-13 years (sleep disorders, anxiety and depressive symptoms) has the largest effect on adolescent depression (OR: 6.59, 95%

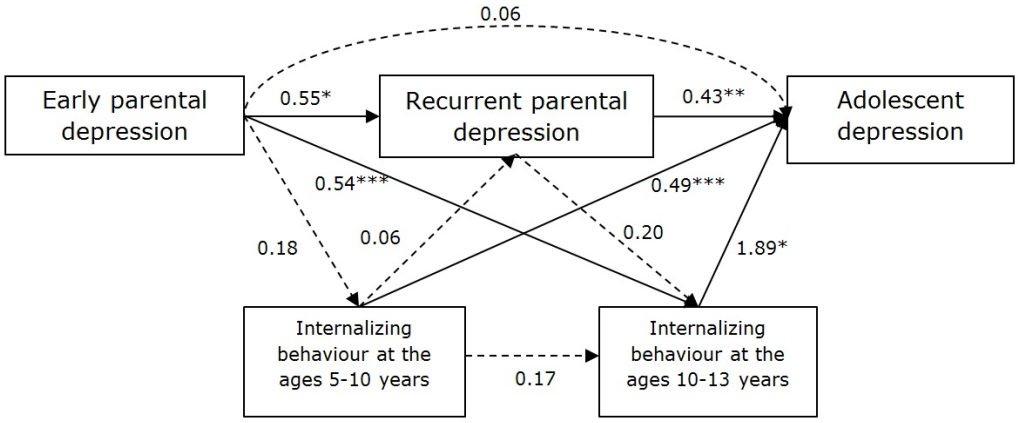


Figure 7.7: Model 3 (integrated model). *p<0.001, **p<0.01, ***p<0.05. Single-headed arrows reflect hypothesised relationships between variables. Regression coefficients are shown next to each path

CI: 3.91 - 11.09). To a lesser extent, internalizing behaviour between the ages of 5 to 10 years (recurrent abdominal pain, migraines and fatigue) also appears to increase the risk of adolescent depression (OR: 1.63, 95% CI: 1.08 - 2.45). However, the two variables are not associated with one another (OR: 1.17, 95% CI: 0.60 - 2.31). This might suggest they measure something slightly different, for instance somatisation and emotional disorders.

7.5 Sensitivity analysis

The risk associated with internalizing behaviour (IB) between the ages of 10-13 years was very large (OR: 6.59, 95% CI: 3.91 - 11.09). As this variable was a composite score comprising diagnoses and/or symptoms for sleep disorders, anxiety, and depressive symptoms, it is possible that this association is driven by only one of these disorders.

In Table 7.7, the associations between the individual components and adolescent depression are shown. While depressive symptoms seem to contribute much of the overall effect of internalizing behaviour (OR: 7.19, 95% CI: 2.91 - 17.79), the association of sleep disorders with adolescent depression is also large (OR: 6.09, 95% CI: 2.05 - 18.12). The effect of anxiety is smaller in comparison and not statistically significant (OR: 2.02, 95% CI: 0.85 - 4.62).

Table 7.6: Integrated model results; estimates, 95% CIs and *P* values

Parameter (letter in Figure 7.2)	Odds Ratios (95% CI)	*P* value	n (%)
Outcome: adolescent depression			
Internalizing behaviour at ages 10-13 years (a)	6.59 (3.91 - 11.09)	<0.001	105 (2.1%)
Recurrent parental depression (b)	1.54 (1.26 - 1.87)	<0.001	2,176 (44.3%)
Internalizing behaviour at ages 5-10 years (c)	1.63 (1.08 - 2.45)	0.02	372 (7.6%)
Early parental depression (d)	1.06 (0.69 - 1.63)	0.78	533 (10.9%)
Outcome: Internalizing behaviour at ages 10-13 years			
Recurrent parental depression (e)	1.22 (0.90 - 1.65)	0.20	55 (1.1%)
Internalizing behaviour at ages 5-10 years (f)	1.17 (0.60 - 2.31)	0.63	10 (0.2%)
Early parental depression (g)	1.72 (1.05 - 2.81)	0.03	22 (0.4%)
Recurrent parental depression			
Internalizing behaviour at ages 5-10 years (h)	1.07 (1.00 - 1.14)	0.06	188 (3.8%)
Early parental depression (i)	1.74 (1.65 - 1.84)	<0.001	244 (5.0%)
Internalizing behaviour at ages 5-10 years			
Early parental depression (j)	1.20 (0.89 - 1.62)	0.24	57 (1.2%)

Table 7.7: Sensitivity analysis: adolescent depression risk by type of internalizing behaviour

Internalizing behaviour type	OR (95% CI)
Sleep disorders	6.09 (2.05 - 18.12)
Anxiety	2.02 (0.82 - 4.62)
Depressive symptoms	7.19 (2.91 - 17.79)

Table 7.8: Sensitivity analysis: Integrated model results; estimates, 95% CIs and *P* values

Parameter (letter in Figure 7.2)	Whole population	Girls
	OR (95% CI)	OR (95% CI)
Outcome: adolescent depression		
Internalizing behaviour at ages 10-13 years (a)	6.51 (3.87 - 10.97)	2.96 (1.28 - 6.84)
Recurrent parental depression (b)	1.54 (1.26 - 1.88)	1.42 (1.11 - 1.81)
Internalizing behaviour at ages 5-10 years (c)	1.62 (1.07 - 2.43)	1.46 (0.89 - 2.40)
Early maternal depression (d)	1.11 (0.94 - 1.31)	0.99 (0.78 - 1.25)
Early paternal depression (d)	0.81 (0.59 - 1.12)	-
Outcome: Internalizing behaviour at ages 10-13 years		
Recurrent parental depression (e)	1.22 (0.90 - 1.65)	1.09 (0.67 - 1.79)
Internalizing behaviour at ages 5-10 years (f)	1.17 (0.60 - 2.28)	1.04 (0.36 - 3.02)
Early maternal depression (g)	1.25 (1.04 - 1.52)	1.24 (0.88 - 1.75)
Early paternal depression (g)	1.05 (0.74 - 1.51)	0.84 (0.21 - 3.29)
Recurrent parental depression		
Internalizing behaviour at ages 5-10 years (h)	1.07 (1.00 - 1.14)	1.04 (0.95 - 1.14)
Early maternal depression (i)	1.21 (1.18 - 1.23)	1.21 (1.17 - 1.25)
Early paternal depression (i)	1.19 (1.14 - 1.23)	1.18 (1.11 - 1.25)
Internalizing behaviour at ages 5-10 years		
Early maternal depression (j)	1.12 (1.00 - 1.26)	1.13 (0.96 - 1.32)
Early paternal depression (j)	0.86 (0.66 - 1.12)	0.95 (0.68 - 1.31)

Finally, I repeated the analysis using the integrated SEM model to separate out the effects of maternal and paternal depression individually, and to examine the outcome in boys and girls separately (Table 7.8). Similar to the results of the logistic regression, early maternal depression appears to have a stronger effect compared to paternal depression, although with smaller numbers, the effect does not reach statistical significance.

When the analysis is restricted to include only girls, the results are similar, although,

due to smaller numbers, confidence intervals are wider. I was not able to estimate the effect of paternal early depression on adolescent depression in girls due to low numbers. Similarly, I could not repeat the analysis for boys.

In order to assess potential sources of bias that could have influenced the classical mediation method, I performed counterfactual mediation analsysis. An explanation of this method, and the results, can be found in appendix D.3.

7.6 Discussion

Early parental depression increases the risk of adolescent depression, although the effect is mainly indirect through recurrent parental depression. Early internalizing behaviour at ages 5 to 13 years old could indicate that children are at risk of developing depression in adolescence. Comorbid parental depression, though rare in this cohort, did not significantly increase the risk of adolescent depression.

Initially, I aimed to use factor analysis as a data reduction step, using several indicators to measure one underlying structure I called 'childhood internalizing behaviour'. Several previous cohort studies assessing the effects of parental depression have used questionnaires assessing internalizing behaviour. However, there did not appear to an underlying structure to the factors I identified. Only anxiety and depression in children aged 10 to 13 years appeared to be moderately correlated.

It is possible that GPs only register one type of psychosomatic complaint in children's medical records. If children come back with different psychosomatic symptoms, they could be referred to mental health services rather than the GP treating the symptoms him or herself. Alternatively, it is possible that it is rare for children to have multiple psychosomatic symptoms that are above the threshold that would urge them, or their parents, to seek help for them. In this second case, it would be possible for questionnaires to pick internalizing behaviour up that does not interfere with daily life, but it would be hard to impossible to measure it in a primary care database.

The results from the SEM analysis suggested that internalizing behaviour between the ages of 10 and 13 years was more strongly associated with adolescent depression than internalizing behaviour between the ages of 5 and 10 years, and that the two were

not associated to one another. This latter finding is in agreement with the results from the exploratory factor analysis, which suggested the behaviours could not be reduced to one underlying structure. As the later internalizing behaviour was measured more closely in time to adolescent depression, it is not surprising that this measure was more closely associated with depression than the earlier measured internalizing behaviours. Moreover, the behaviours measured at ages 5 to 10 years could be partly due to physical rather than psychological causes, though I attempted to exclude those. It also is possible that the two groups of internalizing behavour measure something slightly different (somatisation and emotional disorders) and are part of different phenotypes leading to adolescent depression.

The sensitivity analysis on individual internalizing behaviours showed that the effect was not only due to the continuity of depressive symptoms in early adolescence to adolescent depression. Sleep disorders, as discussed in chapter 6, appear to be an important indicator of future emotional problems as well. The effect of anxiety at ages 10 to 13 was smaller and not statistically significant. However, anxiety could still be an important indicator for psychological disorders other than depression, such as generalised anxiety disorder. Moreover, depression and anxiety have high comorbidity and, especially in a younger population, are often indistinguishable.

It is likely that I have underestimated the prevalence of internalizing behaviour in children and adolescents. As these behaviours could present psychological problems, rather than disorders, and as such children might not have consulted their GP for them, or GPs could have chosen to not code them in patients' records. As I am likely to pick up only the most severe cases of internalizing behaviour, this underascertainment could have influenced the assocations reported, however, it is difficult to assess the direction of bias.

The final sensitivity analysis showed that the effects of early parental depression were strongest for maternal depression and for girls. Although other studies have found similar results, the lack of an effect for paternal depression and in boys could be due to a lack of men acknowledging their depressive symptoms and/or seeing their GP for them. Rates of early depression in fathers have been slowly rising over the years (chapter 5), as have the rates for adolescent depression in boys (chapter 4).

My effect estimates for early parental depression are similar to those found in the ALSPAC study [Pearson et al., 2013]. This British birth cohort, which includes 4,566 children born in the early nineties, found that antenatal (OR: 1.28, 95% CI: 1.08 - 1.51) and postnatal maternal depression symptoms (OR: 1.26, 95% CI: 1.06 - 1.50, though only for mothers with low education) were both risk factors for adolescent depression at age 18 years. These estimates were corrected for parental depression recurrence and similar to what I estimated the direct effect for maternal early depression to be (OR: 1.11). Moreover, the study by Pearson and colleagues did not find an effect of paternal early depression (OR: 0.9, 95%CI: 0.7 - 1.1), which I also did not find (OR: 0.81, 95% CI: 0.59 - 1.13).

Other, notably smaller, studies have found higher effect estimates. A study on a cohort of 93 dyads from Cambridge found that children of postnatally depressed mothers were 5 times (OR: 4.99, 95% CI: 1.68 - 14.70) as likely to experience depression by age 16 than children of non-depressed mothers [Murray et al., 2011]. This study also found very high absolute rates of adolescent depression, with 41.5% of children of depressed mothers experiencing depression themselves (in the control group, only 12.5% of children had experienced depression). As shown in chapters 4 and 5, adolescent depression rates are lower in THIN, potentially as depression is not always recognised in primary care and adolescents might not see their GP very often. Moreover, the confidence interval from the study by Murray and colleagues is very wide, though not overlapping with either my or ALSPACs estimate.

Other studies using the ALSPAC study found that paternal depression was independently associated with child development at age 3.5 years [Ramchandani et al., 2005a], recurrent abdominal pain at age 6 3/4 years [Ramchandani et al., 2006] and behavioural/emotional and psychiatric problems at age 7 [Ramchandani et al., 2008b,a]. However, in my analyses, paternal depression did not appear to be associated with internalizing behaviours in children, or adolescent depression. This difference could be due to ways these behaviours and problems were ascertained. Whereas I used primary care records, ALSPAC uses questionnaires which are more sensitive to subclinical symptoms. However, as mentioned earlier, a recent ALSPAC study did not find an association between early paternal depression and adolescent depression [Pearson et al., 2013], in line with

my results. This could indicate that early paternal depression has time-limited effects on child outcomes, although, as research into the effect of fathers mental health is only fairly recent, more research is needed.

I could not replicate the adverse effects of comorbid parental depression found by other studies in the THIN family cohort [Mezulis et al., 2004, Paulson et al., 2006]. This is likely due to the very small number of families with comorbid parental depression (26) in THIN, which caused the confidence intervals to be very wide. Combined with the previous research on these families, and the results from chapter 5 showing that problems related to adversity tend to cluster in these families, there is a hint that children in these families could be at a higher risk of psychiatric problems.

7.7 How does this chapter inform my thesis?

In part III of my thesis, I updated and extended a birth cohort within THIN, assessed whether sleep disorders could be used as an early indicator of adolescent depression, and assessed the association between early parental depression and adolescent depression using this cohort.

Updating the THIN family cohort to 2011 and including families based on family ID codes increased the cohort to 4,942 families with at least 15 years of follow-up. This cohort had slightly lower rates of early parental depression, possibly due to lower recognition and treatment of depression in the 1990s and families with depression being more likely to move house and drop out of the THIN cohort. Families with lower deprivation scores were also underrepresented.

Few children had a record of the internalizing behaviours I had previously selected. Rates for recurrent abdominal pain, headaches or migraine, fatigue, sleep disorder, anxiety and depressive symptoms ranged from 0.5% to 2.8% in the cohort. Rates were slightly higher for the 250 (5.1%) children who developed adolescent depression, but only marginally so.

Sleep disorders are associated with adolescent depression in THIN, and appear to double the risk of later adolescent depression. They could form an epiphenomenon of depression in early teenage years, or could be easier to report than depressive symptoms.

However, in younger children (aged 5 to 12 years) sleep disorders are almost exclusively recorded in children with neurodevelopmental disorders such as autism spectrum disorders, attention-deficit hyperactivity disorders or epilepsy. Therefore, sleep disorders might be an indicator for more general health problems in this group of children, rather than a specific indicator for adolescent depression.

Finally, early parental depression is associated with adolescent depression, though the association is mainly indirect via recurrent parental depression. Early internalizing behaviour at ages 5 to 13 years old could indicate that children are at risk of developing depression in adolescence. Comorbid parental depression, though rare in this cohort, did not significantly increase the risk of adolescent depression.

Part IV

Synthesis

Chapter 8

Summary, implications and conclusions

8.1 Summary

In this thesis, I examined the question whether children of parents who both had depression in the first year after childbirth (early comorbid parental depression) were more likely to develop depression in adolescence compared to children of non-depressed parents or families in whom only one parent was depressed.

In part I, I reviewed the literature on the intergenerational transmission of depression and introduced THIN, the UK primary care database I have used for the main analysis. In part II, I focussed on the exposure and outcome I used in my main analysis. I performed a systematic review on the prevalence of early comorbid parental depression and its effects on child outcomes. I also examined adolescent depression. Finally, in part III, I used THIN data to explore the association between early (comorbid) parental depression and adolescent depression in a family cohort.

As described in the introduction to my thesis, I aimed to answer my main research question by examining three subquestions:

- What is the prevalence of early comorbid parental depression?
- How has adolescent depression been recorded in UK primary care over time?
- What is the association between early comorbid parental depression and adolescent depression?

The next sections will summarise the results for each of these questions.

8.1.1 Prevalence of comorbid early parental depression

I found prevalence rates for comorbid early parental depression ranging from 0% to 20% in my systematic review (Chapter 3). The 20 studies that contributed to the review differed in their assessments depression using a range of questionnaires or different cut-off scores for the same questionnaire. Moreover, parental depression was assessed at different time points. Lastly, several studies potentially were affected by serious issues around selection bias. It was, hence, inappropriate to perform a meta-analysis to determine an overall estimate of the prevalence of comorbid early parental depression.

In the second part of my systematic review, I identified only two studies that had explored the effects of comorbid early parental depression on child outcomes. The first study [Paulson et al., 2006] found that parental health behaviour was worse when both parents were depressed compared to families with one depressed parent, or families where neither parent experienced depression.

The second study [Mezulis et al., 2004], found that internalizing behaviour by the age of 5 years was higher in children exposed to comorbid early parental depression. The effect was strongest for girls. They found no effect of parental depression, comorbid or single parent, on externalizing behaviour.

No studies looked beyond the age of five years, though several studies have tried to assess the effects of maternal early depression, and to a lesser extent, paternal early depression on mental health outcomes in adolescence. Several studies have found associations between early parental depression and adolescent depression, however it is unclear whether this is a causal association. As detailed in Chapter 1, several explanations have been offered for the apparent association between early parental depression and adolescent depression. Possible explanations include exposure to maternal stress hormones or antidepressants during pregnancy, lack of stimulation and impaired parenting during the first year of life, chronic exposure to depression, or inheritance of genetic susceptibility for depression.

8.1.2 Trends in childhood depression

Next, I assessed trends in the recording of childhood depression diagnoses, symptoms, and antidepressant prescriptions in primary care in the UK (Chapter 4). While rates of symptom recording steadily increased from the 1990s throughout the 2000s, diagnoses and antidepressant prescriptions showed a different pattern. Both were increasing from 1995 up to 2002 - 2003, after which they decreased suddenly. Depression diagnoses rates were stable after 2005, while antidepressant prescriptions increased again from 2005 to 2010, back to 2002 levels.

The decrease in both depression diagnoses rates and antidepressant prescription rates coincided with the MHRA warning against the prescription of SSRI antidepressants (accept for fluoxetine) in young people. Rates for paroxetine decreased most dramatically, leading to the drug being prescribed only sporadically after 2004. All other SSRIs were also affected by the warning, although to a lesser extent.

8.1.3 Early comorbid parental depression and adolescent depression

In this part of my thesis I attempted to address my main research question to examine whether children exposed to comorbid early parental depression are more likely to develop adolescent depression than children exposed to early parental depression in one parent, or no parental depression (Chapter 7). I used a cohort of almost 5,000 children (Chapter 5), their mothers and fathers who have been prospectively followed for at least 15 years in The Health Improvement (THIN) primary care database.

I found that children exposed to early comorbid parental depression are twice as likely to develop adolescent depression compared to children not exposed to parental depression. However, the effect was not statistically significant. Maternal early depression independently doubled the risk of adolescent depression, whereas paternal depression did not appear to have an effect on child depression, contrary to results from previous studies. However, other studies have not taken mediation by recurrent parental depression into account, or adjusted for it inappropriately.

The effect of early parental depression on adolescent depression was strongly mediated by recurrent parental depression. Parents who experienced early depression were much more likely to have subsequent depression episodes. It is appears that it is this

group, families with both early and subsequent parental depressive episodes, where children are at the highest risk of developing adolescent depression.

Moreover, parents who had experienced early depression were more likely than non-depressed parents to have a record of subsequent depression episodes. Of the parents who did not experience early depression, 31% of mothers and 22% of fathers remained had an episode of depression during the study period. Of the parents who did have records for early depression, 87% of mothers and 79% of fathers had a depression recurrence. Mothers with early depression had records of recurrence in six years on average (5-95% centiles: 0 - 16 years). Similarly, fathers with early depression had recurrence in six years on average (5-95% centiles: 0 - 17 years). This represents a large burden of exposure to depression for children in the group with parents experiencing both early and recurrent depression. Importantly, this burden has been mostly ignored by other studies focussing on the effects of early parental depression on later child outcomes.

These findings indicate that, opposed to previous research, early parental depression does not appear to have as definitive an effect on child outcomes as previously thought. Rather, it is the group of children exposed to continuous or recurrent depression (as opposed to just early parental depression) who are at high risk of developing adolescent depression. Whether this increase in risk is due to chronic exposure or genetic susceptibility remains a question to be answered.

I also examined symptoms that could indicate that children are at risk of developing adolescent depression. I started with a study in which I assessed sleep disorders in children and their association with adolescent depression (Chapter 6). There was a strong association between sleep disorders and depression, in both younger children (age 5 - 12 years) and adolescents (age 13 - 18 years). In the younger age group, sleep disorders were almost always accompanied by neurodevelopmental disorders such as autism, ADHD or epilepsy. Therefore, sleep disorders are probably not an appropriate indicator of internalizing behaviour in children aged 5 to 12 years. However, sleep disorders double the risk of subsequent adolescent depression for children aged 13 years and over. This suggests that sleep disorders can be used as an early indicator of depression. Also, it demonstrates there is potential to use other internalizing behaviours to find early indicators of depression, as I planned in my main analysis.

Next, I examined other internalizing behaviour symptoms between the ages of 5 - 10 years (recurrent abdominal pain, fatigue and recurrent headaches of migraine) and 10 - 13 years (sleep disorders, anxiety, depression symptoms). Internalizing behaviour between the ages of 10 - 13 years appeared to be strongly associated with adolescent depression (OR: 6.61, 95% CI: 3.92 - 11.12). Internalizing behaviour in children aged 5 - 10 years had a weaker, though still statistically significant effect (OR: 1.64, 95% CI: 1.09 - 2.25). Moreover, exposure to early parental depression doubled the risk of internalizing behaviour between the ages of 10 - 13 years (OR: 2.00, 95% CI: 1.30 - 3.08), suggesting that these behaviours (sleep disorders, depressive symptoms and anxiety) could be used to identify high-risk individuals.

8.2 Limitations

Despite the relatively large size and long and unobtrusive follow-up, my study has some important limitations.

In deciding on inclusion criteria and designing the algorithm to identify families within THIN, I was only able to include traditional families made of a mother, father and at least one child. Therefore, the results of my thesis might not be representative of modern or extended family types, such as single parents, families with grandparents living in or families with same-sex parents. However, the traditional family is the most common family type at birth and as a result, my cohort is largely representative of UK births.

Second, in using a primary care database, I could have missed some adolescents with depression. Adolescent are generally not very forthcoming with any mental health problems or depressive symptoms, and thus might have not contacted their family doctor themselves with their problems. This study would have hence only captured the more severe forms of depression.

Moreover, it is possible that parents who experienced mental illness themselves were more likely to recognise depression in their children compared to non-depressed parents. If this is the case, it could have lead me to overestimate the association between parental and offspring depression.

I could only estimate the prevalence of some important known confounders in my study. Child maltreatment and neglect [Woodman et al., 2012], alcohol abuse [Khadjesari et al., 2013] and illicit drug use are known to be underrecorded in primary care. GPs might have only recorded suspicions of these behaviours in the records of those children with more advanced manifestations of these behaviours.

8.3 Strengths

The strengths of my study lie in its large sample size and long follow-up. As more practices join UK primary care databases, and follow-up continues on existing practices, numbers will continue to grow in coming years, making the family cohort an extremely valuable resource for research into children's health. Compared to other birth cohorts, such as the ALSPAC study, which are used for similar studies, THIN provides excellent value for money. As it uses data that is routinely collected by GPs, this imposes a minimal intrusion on participants' lives.

Moreover, as opposed to cohort studies, the records present real-life data: health events are recorded when they happen in real time, rather than at set time points, risking recall bias. In addition, the information represents clinically relevant information, based on individuals decisions to consult their GP, rather than a response to a questionnaire. Although GPs are known to miss some depression diagnoses (sensitivity), the specificity of GP depression diagnoses is high, as described in Chapter 4.

Finally, I used appropriate methods to assess mediation by recurrent parental depression, a factor that has been ignored by many previous studies. Moreover, studies that did attempt to correct for the influence of recurrent parental depression did not take the limitations of classic mediation analysis into account and could therefore suffer from bias.

In analysing my data both using the classic methods, and SEM, I have found that results markedly differ. Whereas the classic mediation method did not identify recurrent parental depression as a mediator, SEM found it to be a very strong mediator. The indirect effect of early parental depression via recurrent depression on adolescent depression dominated the direct effect that was found using the classic analysis method. This finding

provides evidence that other studies could have been biased. Most notably this could have affected studies on the effects of early parental depression, although mediation analysis is performed in many other areas of epidemiological and psychological research as well.

8.4 Implications

Early parental depression doubles the risk of adolescent depression in offspring [Manning and Gregoire, 2009]. The effect is strongly mediated through chronic or recurrent parental depression rather than the postnatal period being a sensitive period for child development. This implies that parental mental health, especially over the long term, should be taken into account when assessing mental health problems in children and adolescents. This finding emphasises the importance the role of family doctors who, rather than just treat the patient, are involved and aware of the entire family and any problems that may arise. Primary care is key resource for children and young people with emotional difficulties and their families [Sayal et al., 2010].

However, few parents of children with mental health problems have expressed concerns about consulting GPs for these problems, including short appointments, continuity of care and trusting relationships with GPs [Sayal et al., 2010]. Concerns about embarrassment, stigma of mental health problems and being labelled or receiving a diagnosis further threw up barriers to primary care access. These barriers might be even more important in families where parents have experienced mental health problems themselves, as their contact and relationship with their GP could influence help-seeking behaviour for their children.

A large number of children are exposed to parental depression during their childhood: a study using THIN data estimated that up to the age of 12 years, 40% and 20% of children are exposed to at least one episode of maternal or paternal depression, respectively [Davé et al., 2010]. Because many parents who recover from an episode of depression continue to experience subclinical levels of depressive symptoms, children are often to exposed to depression and associated disruption in parenting for prolonged periods of time [Brennan et al., 2002]. In addition, depression can often become a chronic or recurrent illness [Mueller et al., 1999], leading children to become exposed multiple

times over.

It is possible that the postnatal period, as a sensitive period for child development, does not have a definitive effect as previous studies have suggested. Rather, the first year after child birth is a sensitive period for emotional disorders in parents. Parents who experience early depression in this stressful and life-changing period are much more likely to experience subsequent depressive episodes, as discussed in Chapter 5. The period after birth could serve as a depression 'stress test' for parents: parents who are susceptible to emotional disorders could be more likely to develop symptoms in this period in particular. If the postnatal period is a sensitive period for parents, this would also put less emphasis on possible long-lasting adverse effects for children originating in this period. This hypothesis would not replace the theory on a sensitive period for emotional development in children, rather it complement it and put more emphasis on development throughout a child's life.

Parental depression has been identified as one of the most potent risk factors for the development of adolescent depression: children of depressed parents have a two- to fourfold increased risk of developing depressive disorders [England et al., 2009]. In my thesis, I found a similar increase in risk. As adolescence is a period of formative biological and social transition [Blakemore and Mills, 2013], it is important to develop interventions for high-risk children, such as those exposed to a depressed parent (Figure 8.1).

Several papers have reported on such interventions, although a systematic review found that they have little overall effect [Calear and Christensen, 2010]. Beardslee and colleagues reported that parental depression was an important modifier of the effect of their Cognitive Behavioural Prevention (CBP) program [Beardslee et al., 2013]. Their large trial, which followed 316 participants for 33 months, included adolescents at high risk of depression. Youths were recruited if their parents had a history of depression or if they themselves had a history of depressive disorder or current depressive symptoms. While the CBP program significantly reduced the number of depressive episodes over the almost three years of follow-up for the group not exposed to parental depression, depression rates were similar for CBP and usual care for the youths whose parents were depressed at baseline.

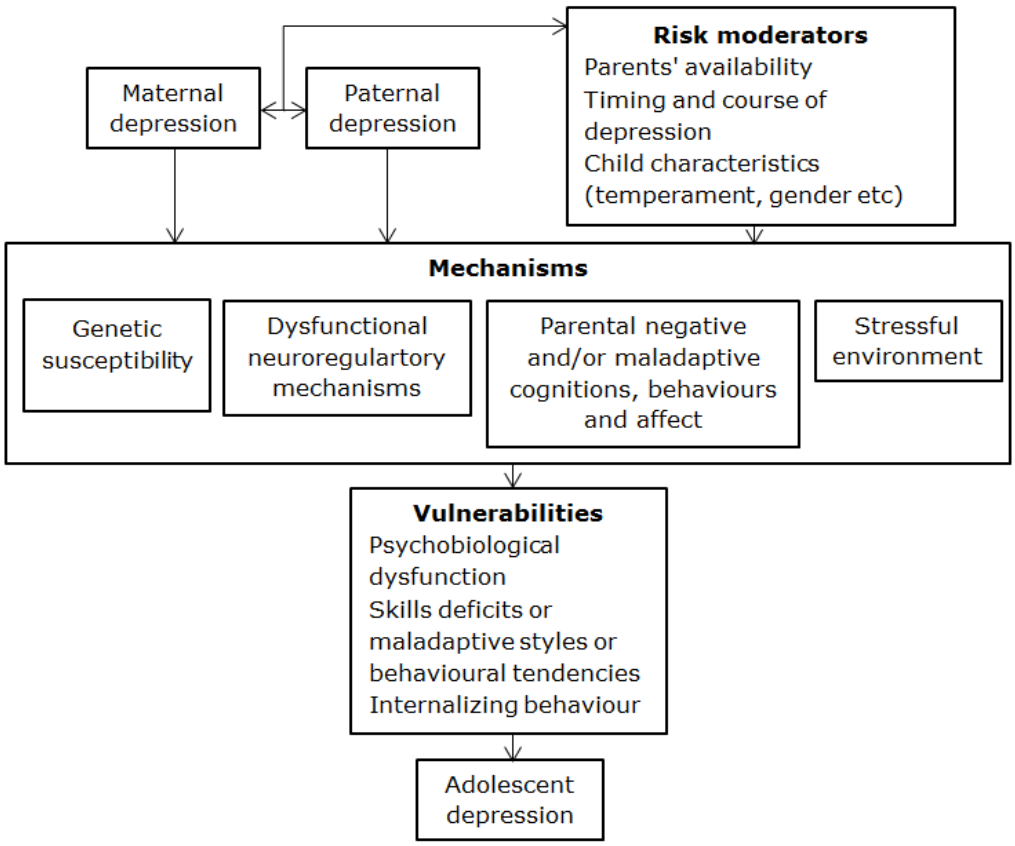


Figure 8.1: An integrative model of transmission of risk from depressed parents to offspring. Based on original Figure by Goodman and Gotlib [Goodman and Gotlib, 2002]

Attention should also be paid to adverse childhood experiences in a more general sense. As demonstrated in Chapter 5, parents who experience early depression are also more likely to engage in harmful drinking behaviour, illicit drug use, have records of potential child maltreatment or neglect and severe mental illness. These experiences are also known to have adverse effects on children's outcomes [Bellis et al., 2013] and should be considered in planning family or child treatment. The risk of developing a mental health problem is strongly increased by social disadvantage and adversity, both of which seem to cluster in families who also experience early depression.

These implications tie in with the recently published report by the Chief Medical Officer [Davies, 2013]. In this report, Dame Sally Davies recommends that children with long-term conditions, such as those with mental health disorders, should have a named GP who co-ordinates their disease management and stresses the importance of school

nurses, who could also play an important part in the prevention and recognition of mental health problems.

Finally, researchers should be aware of the limitations of classic mediation analysis (Appendix D.1). As shown in my study, results can be severely biased when mediation is not appropriately accounted for in statistical analysis. Methods such as structural equation modelling account for mediator-outcome confounding and exposure-mediator effect modification and give unbiased results. In addition, methods that are currently in development, such as counterfactual mediation analysis (Appendix D.3), can assess the presence of confounding and effect modification and will help identify cases where classic mediation analysis is inappropriate.

8.5 Future Research

Although I have attempted to address mediation by using structural equation modelling and counterfactual mediation analysis, some aspects of confounding may have been missed. There might be an important interplay between psychological problems in children and parental mental health which cannot be quantified by either of the methods and data used in this thesis. While parental depression could have an adverse influence on children's outcomes, the problems children are experiencing can also affect parental outcomes. This could lead to a feedback loop in which psychological problems reinforce themselves.

A potential way to deal with variables that are associated with each other in this way is the use of Marginal Structural Models (MSMs). MSMs were developed and are often used in HIV/AIDS treatment research. Treatment for HIV is dependent on disease severity as measured by a patient's CD4 [1] count. When a person's CD4 count drops below a specified threshold, an aggressive treatment is initiated. However, CD4 count can recover and increase to above the treatment threshold level. When this happens the aggressive treatment will be halted again. In this scenario, the exposure (HIV drugs)

[1] CD4 count measures the number of healthy CD4 T-cells, which are white blood cells that can be infected by HIV. When more CD4 T-cells are infected by HIV, the CD4 count decreases and the patient is at risk of developing AIDS.

and mediator (CD4 count) are involved in a feedback loop which traditional statistical methods struggle to adjust for.

MSMs are able to adjust effect estimates for these time-dependent confounders. This is achieved by using inverse probability weighting (IPW) to balance out the confounding at baseline [Sterne et al., 2005]. The weights are based on the inverse of each patient's probability of the treatment history they actually had, given their covariate history. If a majority of patients never reaches the threshold, this group will be given a low weight in the analysis, while rare patients - in terms of treatment regime and covariates - will receive higher weights. The weighted analysis creates a statistical pseudo-population in which the probability of being treated at each time point is unrelated to the measured prognostic factors, solving the problem of time-dependent confounding.

This method could be applied to my research, however, rather than weighting families for treatment probability, families would be weighted for parental depression probability. This means that THIN would have to contain enough information to construct a regression model to predict parental depression. As many of the factors that are associated with depression are available in THIN (e.g. history of depression, deprivation, alcohol/drug use), MSMs could be an interesting option for exploring the interplay between parental depression and child outcomes. However, in using only primary care data, information on important factors might still be missing. Therefore, linking primary care data to other data sources will important for making more complicated analyses work (see below for more on linking data).

Second, the effects of parental depression were most pronounced in girls in my study, who were more than twice as likely to develop depression compared to boys. Other studies have found similar results, although results did often not reach statistical significance due to small sample sizes. The lack of or reduction of an effect in boys could be due to boys expressing depression or mental illness differently. Studies that have assessed externalizing behaviour rather than internalizing behaviour (e.g. irritability or aggression) have found stronger effects in boys.

A recent study using data from the US National Comorbidity Survey Replication [Martin et al., 2013] found similar differences in between men and women. Rather than only looking at the traditional symptoms associated with depression, this study ex-

plored symptoms included in two new scales on alternative depression symptoms that were administered to a national sample of 5,692 individuals representative of the English speaking US population. The authors found that men reported higher levels of anger attacks/aggression, substance abuse and risk taking compared with women. When using the new scales, a higher proportion of men (26.3%) met the criteria for depression compared to women (21.9%). When both traditional and alternative scales were used, similar proportions of men and women met the criteria for depression (30.6% and 33.3%, respectively.

It would be interesting to try to assess externalizing behaviour in boys in primary care. The effects of parental depression on boys could lead to different symptoms compared to girls, such as higher rates of conduct problems, attention-deficit hyperactivity disorder, aggressive behaviour in children, and substance abuse in adolescents. In addition, it would be interesting to extend this study to hospital data in the Hospital Episodes Statistics (HES) database. The CPRD database is linked to HES and THIN is in the process of being linked. HES data contains information on emergency admissions, which could be used to assess suicide attempts in more detail than possible in THIN. Moreover, some data on psychiatric treatment is available in HES that could be used to look at mental illness in more detail.

In addition to exploring behaviours and symptoms that could indicate mental illness in boys, primary care and hospital data could also be further explored for behaviours that are indicative of future depressive illness. Although some of the internalizing behaviours in this study appear to be associated with adolescent depression (particularly anxiety and depressive symptoms), other indicators might exist. For instance, consulting behaviour or covariates associated with school or education could be associated with depression. With the recent approval of an Administrative Data Research Centre for England, based at UCL, and the Farr Institute, data linkage will receive a much needed boost and it might possible to link to other data sources such as educational data as well.

As mentioned in the limitations section, THIN has limited information on some of the more important confounders such as child maltreatment and neglect that are known to be associated with both parental depression and child outcomes. However, estimates of community prevalence of these, and other confounders are available, as are estimates of

their potential influence on child outcomes. These can be used in a sensitivity analysis to estimate the potential effect of these confounders on the overall effect estimate. As these methods are novel and I only heard about them at a conference in August 2013, I was not able to apply them in my thesis.

An example of this method for sensitivity analyses is given in a paper by Palmsten and colleagues [Palmsten et al., 2013]. In their paper, they assessed the risk of postpartum haemorrhage associated with SSRI and non-SSRI antidepressants using US claims data. Although their dataset is one of the largest databases containing information on pregnancies and detailed information on antidepressant prescriptions, it lacks important confounders such as obesity. Therefore, the researchers used information from the National Health and Nutrition Examination Survey (NHANES) to estimate the prevalence of obesity in women using SSRI, non-SSRI or no antidepressants. Relative risks for the association between obesity and postpartum haemorrhage were estimated between 1.5 and 2.0, based on existing literature. In using this external information, the authors were able to perform robustness checks on their effect estimates and found that estimates moved slightly towards the null, though remained statistically significant.

8.6 Conclusion

In conclusion, children whose parents experience early depression are twice as likely to develop depression as adolescents compared to children of non-depressed parents, although parental depression over childrens life course has an important mediating effect. The effect appears similar for families where one or two parents experience early depression, although the numbers of families with comorbid early depression were too small to draw firm conclusions.

In addition, internalizing behaviours in childhood seem to be intermediate variables on the causal pathway from early parental depression to adolescent depression and could potentially be used to identify children at high risk of developing depression. However, as this thesis only focussed on internalizing behaviour, which was recorded in only a few instances, further research is needed to explore other potential indicators. Externalizing behaviour and education records could provide more insight in the aetiology of adolescent

depression from a population health perspective.

These results suggest a family-based approach, involving both parents and children, to prevent adolescent depression. Further research is needed to identify appropriate interventions.

Appendix A

Research profile

A.1 Funding

I received a PhD training fellowship from the National Institute for Health Research (NIHR) School for Primary Care Research (SPCR) to cover research and training costs for this PhD project. I received additional scholarship funds to attend the International Society of Pharmacoepidemiology (ISPE) annual conference in Barcelona, Spain, in August 2012, and in Montreal, Canada, in August 2013. Finally, I was a co-applicant for public engagment grant from the UCL Volunteering Services Unit to set up London Science Buskers, a group of postgraduate students at UCL who are trying to take their science to the street.

A.2 Collaboration and data sharing

All analyses included in this thesis were performed by me. However, my supervisors helped in refining the research questions, analysis plans and interpretation of the data. For Chapter 3 I had the help of Ruth Muscat, a librarian at the Royal Free Medical School Library, who helped me operationalise the search question for my systematic review and identify additional databases to search. I also had the help of Shuk-Li Man, Jenny Woodman, Jesca Brouwer, Hilary Davies and Ruth Blackburn in selecting studies to include in my review and data extraction.

In order to identify some of the covariates for my main analysis, I used code-lists

and algorithms developed by other THIN team members at UCL. The Read code list for identifying (suspected) child maltreatment and neglect was developed by Jenny Woodman. Hilary Davies developed the Read and drug code lists to identify illicit drug use in THIN. Algorithms for defining alcohol abuse and comorbidity scores were developed by Dr Louise Marston. Read codes for identifying severe mental illness were developed by Dr Sarah Hardoon. Finally, Laura Horsfall developed the algorithm for determining dates for Acceptable Computer Usage (ACU) in individual GP practices.

The birth cohort nested in THIN was developed by my supervisor, Dr Irene Petersen, and was extended to include fathers by Dr Shreya Davé. I used this cohort as the basis for the family cohort included in my thesis, but updated it to the most recent data and extended the matching algorithm to be able to include more families.

Finally, Dr Nadia Micali from the UCL Department of Neurosciences & Mental Health advised on the analysis plan for the structural equation modelling analysis.

A.3 Software

As described in the relevant chapters, I used Stata (versions 11.2-12.1) and MPlus (version 7.1) for statistical analysis in my thesis. All graphs included in my thesis were produced using Stata and, where necessary, adapted using GIMP 2.0 image editing software.

Figures 1.2, 1.3, 2.2, 3.1, 4.1, 7.2, 7.3, 7.5, 7.6, 7.7, and 8.1 were drawn using Microsoft Word, and Figures 2.1, 2.3, and 7.4 were produced using easel.ly, a free website providing basic data visualisation tools.

This thesis was compiled using LaTeX.

A.4 Conference posters and presentations

I have presented parts of my thesis at local, national and international conferences. Parts of Chapter 4 were presented as poster presentations at the Society for Academic Primary Care (SAPC) annual conference in Bristol, 2011; the European Drug Utilization Research Group (EuroDURG) conference in Antwerp, Belgium, 2011; and the ISPE annual conference in Barcelona, 2012.

I presented analyses based on Chapter 6 at the NIHR SPCR conference in London in 2012; at the European Epidemiology Congress (EuroEpi) in Aarhus, Denmark, 2013; and at the ISPE annual conference in Montreal, Canada, 2013.

A.5 Courses

Thanks to the generous fellowship I received from the NIHR SPCR, I was able to attend several short courses that proved essential to finishing my PhD project. Particularly helpful were courses run by the London School of Hygiene and Tropical Medicine (Systematic Reviews and Meta-analyses of Health Research - ran by Katherine Ker and Pablo Perel; Causal Inference in Epidemiology: Recent Methodological Developments - ran by Prof Bianca de Stavola, Prof Simon Cousens, and Rhian Daniel; Factor Analysis and Structural Equation Modelling: and Introduction Using Stata and MPlus - ran by Prof Bianca de Stavola and Dr George Ploubidis).

I attended a course on Missing Data in Mental Health Research at the University of Cambridge, ran by Prof Ian White and Prof Sabine Landau. I also attended pre-conference courses in pharmacoepidemiology and methodology at both the ISPE annual conferences I attended, and at EuroEpi. The UCL grad school have also provided me with a lot of useful courses ranging from inproving my presentation skills, via thesis formatting to writing about science for the general public.

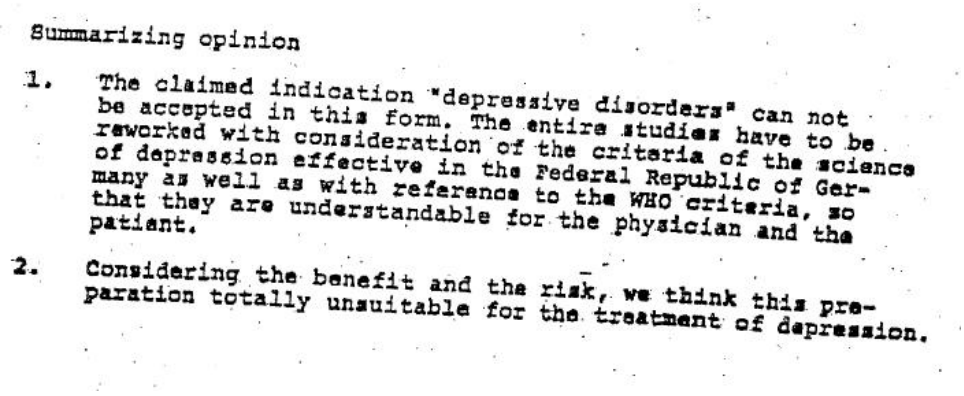
Finally, I have been involved in the Introduction to Primary Care Databases course run by my department, Primary Care and Population Health. I have given lectures on creating codelists, and an introduction to Stata Programming. I have also taught on the Use of Evidence module for medical students at UCL. This teaching consists of leading five working groups of second year medical students on systematic reviews and basic statistics.

Appendix B

A short history of safety concerns regarding antidepressants

Since the development of SSRIs there have been concerns about the safety of these drugs. In 1984, the West-German Regulatory Agency, the Bundesgesundheidsamt (BGA), rejected fluoxetine, one of the first SSRIs to go to market, as being "totally unsuitable for treating depression" (Figure B.1). Six years later, in 1990, the BGA would approve fluoxetine for depression, but not after a further two rejections due to concerns about the possibility of fluoxetine increasing the risk of suicide. It was approved for the US market by the Food and Drug Authority (FDA) in December 1987, and in November 1988 for the UK market for treatment of depression disorder.

Soon after its introduction, case reports about patients developing suicidal tendencies started to emerge [Teicher et al., 1993, Papp and Gorman, 1990]. In 1991, the FDA organised an advisory meeting to review the evidence available at the time for a link between fluoxetine and suicidal behaviour in adult patients [Mann et al., 2005]. Although data on other SSRIs was available at the time, they were not yet licensed and thus not included in this meeting. Concerns were raised following case reports of few patients who had exhibited suicidal behaviour upon initiation of treatment with the SSRI fluoxetine, as well as some cases involving TCAs. However, the FDA did not find evidence of an increased risk of suicidal behaviour in individuals taking these drugs. Rather, they found the apparent association was due to confounding by indicating: the few individual



Summarizing opinion

1. The claimed indication "depressive disorders" can not be accepted in this form. The entire studies have to be reworked with consideration of the criteria of the science of depression effective in the Federal Republic of Germany as well as with referance to the WHO criteria, so that they are understandable for the physician and the patiant.

2. Considering the benefit and the risk, we think this preparation totally unsuitable for the treatment of depression.

Figure B.1: Summarising opinion of the German Bundesgesundheidsamt (West-German Drug Regulatory Agency) concerning Fluctin (fluoxetine) in a fax dated 25 May 1984 to Eli Lilly

patients who worsened on taking antidepressants were severely depressed and would have progressed to suicidal behaviour with or without the drugs. Or put in other words: it was the disease rather than the drug. The FDA did advise Lilly, the pharmaceutical company that produced fluoxetine, to run a challenge-dechallenge-rechallenge trial[1] to rule out any drug effect, but although protocols were drawn up, the trial was never executed.

Despite the FDA's ruling, doubts about the effectiveness and adverse events related to SSRIs remained. During the 1990s, several law suits were filed against Lilly for holding back vital information about a possible link between their drug Prozac (fluoxetine) and suicidal behaviour. Lilly argued that fluoxetine, the most researched drug in history, was not to blame. Fourteen of these were settled, and the one law suit that did go to trial was won by Lilly.

In 2002, the BBC investigative programme Panorama revealed that pharmaceutical companies had been withholding negative trial results on multiple SSRIs [Cowen, 2002]. In a programme called 'The Secrets of Seroxat', aired in October 2002, they high-

[1]Challenge-dechallenge-rechallenge (CDR) is a medical testing protocol in which a medicine or drug is administered, withdrawn, and then re-administered, while being monitored for adverse effects at each stage. During the withdraw phase, the medication is allowed to wash out of the system in order to determine what effect the medication is having on an individual.

lighted the case of paroxetine (brand name: Seroxat), which according to the programme caused severe withdrawal symptoms, as well as the suicides of several patients. Following the programme and resulting negative media attention, the Medicines and Healthcare products Regulatory Agency (MHRA) decided to review the efficacy and adverse advents associated with paroxetine. The review was extended to include all antidepressants a few months later.

During its investigation, the MHRA demanded that pharmaceutical companies provide all available data. It reanalysed published and unpublished data on paroxetine, and found that the drug failed to demonstrate significant beneficial effects, and was associated with a small increase in suicidal behaviour and ideation [Committee on Safety of Medicines, 2003]. As a result, it released an advice against the prescription of paroxetine to children and young people under the age of 18 in June 2003 [Waechter, 2003]. This was followed by a broader advice in December of the same year, advising against the initiation of treatment with SSRIs for childhood depression [Healy, 2003, Gunnell et al., 2005]. Fluoxetine, the only drug which is licensed to treat depression in children in the UK, was exempted from this advice following a favourable balance of benefits and risk.

While the UK was first to issue an advice against prescription of SSRIs, Europe and the US followed suit over the next years with similar cautions. The FDA issued a black box warning[2] in October 2004 for all antidepressants (including TCAs and other antidepressants as well), warning about an increase in the risk of suicidality in paediatric patients taking these drugs [FDA, 2004]. In 2007 the black box warning was extended to 18-24 year olds (Figure B.2). The European Medicines Evaluation Agency (EMEA) issued a warning in April 2005. After an extensive review by the Committee for Medicinal Products for Human use (CMPH), they warned against the prescription of SSRIs and

[2]In the United States, a black box warning is a type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning indicates that the drug carries a significant risk of serious or even life-threatening adverse effects. The FDA can require a pharmaceutical company to place a black box warning on the labelling of a prescription drug, or in literature describing it. It is the strongest warning by the FDA that a medication can carry whilst remaining on the market.

serotonin-norepinephrine reuptake inhibitors (SNRIs) in children. While both the FDA and the EMEA included fluoxetine in their warnings, the MHRA did not as it deemed the benefits greater than the risk for this particular drug [National Institute for Health and Clinical Excellence, 2005, Whittington et al., 2004].

Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert established name] or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Insert Drug Name] is not approved for use in pediatric patients. [The previous sentence would be replaced with the sentence, below, for the following drugs: Prozac: Prozac is approved for use in pediatric patients with MDD and obsessive compulsive disorder (OCD). Zoloft: Zoloft is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD). Fluvoxamine: Fluvoxamine is not approved for use in pediatric patients except for patients with obsessive compulsive disorder (OCD).] (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

Figure B.2: Text of the updated black box warning issued by the FDA in August 2007

The evidence suggesting an increased rate of suicidal behaviour and intentional self harm associated with SSRIs is limited and inconsistent. In adolescents and young adults, RCTs indicate an increase in the risk of suicidal behaviour [Hammad et al., 2006]. However, the results from trial data should be interpreted with caution. Randomised controlled trials were not primarily designed to measure suicidal behaviour, rather these data were collected as a part of adverse event monitoring. It would be unethical to power an RCT on suicide rates [Rothman and Michels, 1994]. None of the clinical trials on SSRIs in a paediatric setting have recorded a completed suicide, and the setting of the trials might not be comparable to the general population [Hammad et al., 2006, Stone et al., 2009].

The results from observational studies are also divided: some indicate that SSRIs protect from suicidal behaviour [Gibbons et al., 2007], others find no effect [Schneeweiss et al., 2010, Jick et al., 2004], or an increase [Olfson et al., 2006]. However, these studies

suffer from methodological flaws: small samples, high attrition rates and, most importantly, confounding by severity. Given their toxicity in overdose, a prescriber would be unlikely to prescribe a TCA in preference to a SSRI to a patient who was considered to be at risk of suicidal behaviour [Didham et al., 2005]. The evidence from clinical trials and observational studies is summarised in Appendix B on page 191.

Following the CSM advice, fewer children and adolescents in the UK were prescribed antidepressants in primary care [Murray et al., 2005, Bergen et al., 2009]. There was a 48% reduction in the initiation of CSM-contraindicated antidepressants in children between 2002 and 2004. However, the use of fluoxetine and non-SSRI antidepressants in children had not significantly risen during the same period. A similar pattern was found in a study in Australia, where antidepressant use, and SSRI use in particular, in children and adolescents decreased between 2002 and 2005. In stark contrast, the use of SSRIs and all antidepressants increased significantly in adults during the same period. Safety concerns regarding antidepressants, selective serotonin reuptake inhibitors (SSRIs) in particular, have been around since these drugs were initially developed[3]. Suicidal behaviour is common in adolescents: 8% report intentional self-harm [Moran et al., 2012]. Moreover, a third of young people who experience a depressive episode will make a suicide attempt at some stage, and 3-4% of those who experience depression will die from suicide [Harrington et al., 1994]. It remains unclear whether it is the underlying disease or the drugs which cause the apparent link.

B.1 Evidence from randomised clinical trials

Few randomized controlled trials testing SSRIs in children and adolescents have been performed. Their interpretation with regards to suicide-related behaviour has been fraught with problems. As mentioned in the last chapter (reference to page number), the FDA have analysed clinical trial data using a surrogate representing suicide-related behaviour. The term they use for this behaviour, suicidality, was coined by the FDA for this purpose. However, it is unclear what this term exactly entails [Klein, 2005].

[3] Although some argue that concerns arose as early as 1963, when the poet Sylvia Plath committed suicide a few days after starting an antidepressant (a mono-amine oxidase inhibitor). [Cooper, 2003]

The term was originally conceived to cover the suicidal thinking and behaviour that was observed in paediatric clinical trials, as no completed suicides were observed. However, it was unclear whether suicide itself (whether attempted or completed) was included in the term, and how the general public, who would read the term in the black box warning, would interpret the term. As shown in Table B.1, although the FDA themselves needed to clarify the meaning of the word to not include suicide[4], they left it with the press to convey the meaning of the word suicidality to the general public [fda, 2004].

Table B.1: Transcript (pages 213 - 216) from the Joint Meeting of the CDER Psychopharmacologic Drugs Advisory Committee and the FDA Pediatric Advisory Committee held on 14 September 2004. Emphasis added

Dr. Irwin (committee member): Is there a word suicidality? Dr. Goodman (committee chairman): Every time I write it in Word, it gets red underlined. Dr. Irwin: It seems to me, I mean to me, I am not certain anyone really knows what it is that we are saying and what you are voting on, or, to me, I would like to know what suicidality is. Dr. Goodman: I don't think it is in an Oxford Dictionary either. Ms. Griffith (patient representative): It is not in Webster's. Dr. Irwin: In a sense, it confounds things by, you know, the front page of the paper today, I think may lead to kind of a misrepresentation. Dr. Pollock (committee member): Can't we just use the explicit language?
continued on next page

[4]As referenced by Dr Irwin in the transcript, newspapers had misinterpreted the term as meaning that clinical trials had found children who committed suicide while on antidepressants. The confusion surrounding the term suicidality still exists, as exemplified by the Wikipedia page for Suicidality which redirects to the page for Suicide.

Dr. Goodman: That is, in part, what I would favor, is that if we use it, I think we need to at least parenthetically define what we mean when we are answering the question.

Dr. Temple (FDA associate director for medical policy): Yes, that is what we do. I think that is what we actually did in labeling. Whether we should coin a new word is debatable, obviously, but it means suicidal behaviour plus suicidal ideation. That is what we use it to mean as those items.

Dr. Goodman: Would it be fair for us to slightly modify the question, or do we have to take it as it is, because what I would say, if we could use the definition that corresponds to Outcome 3, I would feel most comfortable, because that corresponds to the reclassification and the way you approach the dataset. So, suicidality, suicide attempt, preparatory action/or suicidal ideation.

Dr. Katz (FDA Supv. Medical Officer and Director of Division of Neuropharmacological Drug Products): Yes, you can certain amend the question. We called it suicidal behavior and ideation, but it is clearly what is embodied in Codes 1, 2, and 6.

Dr Goodman: I think we have a clarification on that and hopefully, the public will understand what we mean, too, and that, I think **we will leave it to the press to do their job in trying to best define what we mean and dont mean by that term**, specifically, that we are not talking about actual completed suicide if we are restricting our deliberations to the clinical trials, because there werent any instances.

More controversy surrounding clinical trials for antidepressants in children arose after a trial comparing GlaxoSmithKline's (GSK) paroxetine with imipramine [Keller et al., 2001], also known as study 329, was published in 2001. The study followed 275 adolescents with major depression for 8 weeks while they took paroxetine, imipramine or a placebo. The main outcomes of the study were the endpoint response and change from baseline on the Hamilton Rating Scale for Depression (HAM-D). The study concluded that paroxetine was effective for treating major depression in adolescents and was generally well tolerated.

However, soon after its publication, letters to the editor appeared in the Journal of the American Academy of Child & Adolescent Psychiatry expressing concerns regarding the conclusions of the study. The authors of these letters were particularly concerned with the article's representation of the serious adverse effects that occurred with paroxetine: although 11 adolescents reported serious adverse effects (compared to five for imipramine and two for placebo), only one case (severe headache) was considered to be related to paroxetine [Correll and Pleak, 2002, Parsons, 2002, Weintrob, 2002]. The criteria for determining causation of serious events were not stated. The other 10 reported serious adverse effects, which included five reports of agitated/suicidal behaviour, were attributed to the underlying depression.

When the FDA later reanalysed the data from study 329 in their review of SSRIs in children, they found ten children (out of a total of 93) on paroxetine had experience a potentially suicidal reaction. Although not reported in the original study, the difference in number of adverse events (though small) was statistically significant (p=0.01) [Jureidini et al., 2004]. Nevertheless, Keller et al. concluded that "paroxetine was generally well tolerated in this adolescent population, and most adverse effects were not serious," although seven patients were admitted to hospital during treatment with paroxetine.

Moreover, the study showed evidence of distorted and unbalanced reporting [Jureidini and Tonkin, 2003]. The authors defined what they would classify as a treatment response (a fall in HAM-D below 8 or by 50%) in the methods section of the paper, but this has changed in the results section leading to a p-value of 0.02, rather than 0.11 with the original definition of response. Secondly, while the authors state two primary outcomes in their methods section (a 'response' on the HAM-D, and total score), they only report on one outcome in the results section (the distorted 'response' variable) and mention there was no difference between paroxetine and placebo in the second primary outcome in the discussion section. Drs Jureidini and Tonkin, authors of this letter to the editor, even go as far as to suggest that as the research was funded by GSK, this might have influenced the reporting of this drug "in the most favourable light".

It has since transpired that the study was ghost-written by medical contractor Scientific Therapeutics Information, Inc. for GSK, and that many of the co-authors on the original paper were not involved in the actual study. GSK used Study 329 as an evid-

ence base to market its antidepressant paroxetine as an effective treatment for in children. However, in 2012 it settled a lawsuit for consumer fraud for a record $3 billion (1.9 billion) [Outterson, 2012]. In the case of paroxetine, prosecutors claimed GSK employed several tactics aimed at promoting the use of the drug in children, including helping to publish a medical journal article that misreported data from a clinical trial Thomas and Schmidt [2012], West and Ortiz [2011]. During the trial, documents relating to study 329 revealed that the published article differed significantly from the original study protocol: the primary outcomes were changed, and eight "efficacy measures" that had not been pre-specified were introduced. When analysed using the original protocol, there were no differences between paroxetine and placebo on either of the primary outcomes. The US attorney general handling the case concluded that GSK caused the article to misrepresent and minimise paroxetine's risk to children and adolescents [West and Ortiz, 2011]. To date, the article has not been retracted.

In addition to study 329, GSK conducted two other double-blind placebo-controlled studies of paroxetine for paediatric and adolescent depression: study 377, which ran from April 1995 to May 1998, and study 701, which ran from March 2000 to January 2001. Both studies are unpublished and failed to show a difference in efficacy between paroxetine and placebo on any pre-specified primary or secondary endpoint [West and Ortiz, 2011]. Despite the failure of its three clinical trials and the absence of FDA approval, GSK actively promoted paroxetine to treat adolescent and childhood depression from 1999 to at least 2003.

Clinical trials on other SSRIs suffered from similar bias. A study by Drs Jureidini and Tonkin [Jureidini et al., 2004], who expressed their concern about GSK's study 329, examined the methodology of paediatric SSRI trials in more detail. Out of the seven published trials they identified, six used a placebo control and were included in their review. Funding was disclosed to be from pharmaceutical companies in three of these studies (GSK, Eli Lilly and Pfizer) [Emslie et al., 2002, Keller et al., 2001, Wagner et al., 2003], one study was attributed to the National Institute of mental Health (though FDA data showed it to be sponsored by Eli Lilly) [Emslie et al., 1997], and two older trials did not disclose funding [Mandoki et al., 1997, Simeon et al., 1990].

The studies reported 42 different outcome measures, but only 14 showed a statistical

advantage for an antidepressant over placebo. None of the 10 measures relying on patient or parent reported outcomes showed a statistically significant advantage for an antidepressant. None of the studies presented data on rates of (attempted) self-harm, presentations to emergency or mental health services. Of the six placebo-controlled studies, only two found statistically significant advantages in antidepressants over placebo on primary outcomes. However, in one of these studies, the reported primary outcome differed from the pre-specified outcome in the study protocol[Emslie et al., 1997] (for study 329, the authors used the non-significant protocol-specified primary outcomes; they were not able to calculate these for the study [Emslie et al., 1997]).

As in study 329, the trial by Wagner and colleagues [Wagner et al., 2003] failed to report a statistically significant increase in serious adverse events in patients on an SSRI. In their study on sertraline, 17/189 patients treated with sertraline withdrew because of adverse events, compared to 5/184 in the placebo group (p=0.01). Despite these results they concluded that "sertraline is an effective, safe, and well tolerated short-term treatment for children and adolescents". The rates for serious adverse events (9% in the Wagner study, 12% in the Keller study [Keller et al., 2001]) are likely to be underestimates of the true rates [Herxheimer and Mintzes, 2004, Ioannidis and Lau, 2001].

All trials suffered from high withdrawal rates, ranging from 17% to 32% for patients treated with SSRIs, and from 17% to 46% for patients treated with placebo. These rates are particularly high when the short study periods (6-10 weeks) are taken into account. Moreover, as most studies used an intention to treat, last observation carried forward approach in their analysis, these high withdrawal rates could have introduced bias[5].

In addition, most trials used categorical outcomes (yes/no depression, or response vs. non-response), which are likely to inflate small differences between groups [Kirsch, 2003]. Moreover, unblinding due to the high prevalence of side effects in SSRI users

[5]The last observation carried forward approach is based on the assumption that the condition of patients who have dropped out would have remained unchanged for the remainder of the study, had they continued in it. If patients in one arm, for instance the placebo arm, were more likely to drop out, their last observations (that are likely to still show increased scores on depression questionnaires) will be used in the final analysis, and could skew the results towards showing an advantage in the other group, in our case the SSRI group.

may have also inflated the effects of the antidepressants studied[6]. Finally, the study by Wagner and colleagues [Wagner et al., 2003] is described as two clinical trials, although both use identical methods and are treated as a single trial in the analysis in order to have adequate statistical power to detect small differences between treatments. Neither trial individually showed a statistically significant advantage for sertraline over placebo in terms of the primary endpoint, although combined the effect (2.7 points on a 113 point scale) is statistically significant.

Despite important flaws in the methodology and reporting of these randomized controlled trials, an increased risk of suicidal behaviour for adolescents and young adults is found consistently [Hammad et al., 2006]. A recent Cochrane review found evidence of an increased risk (RR: 1.58; 95% CI 1.02-2.45) of suicide-related outcomes for children and adolescents on antidepressants compared with placebo (based on 17 trials; N=3229) [Hetrick et al., 2012]. However, the reviewers deemed the evidence for this association to be of low quality.

Overall, the results from these trials should be interpreted with caution as they were not primarily designed to measure suicidal behaviour and it would be unethical to do so. Moreover, none of these trials on SSRIs recruited from general population setting: compared to those included in clinical trials, clinical patients tend to have more co-morbidities and be more severely ill. Also, patients with (a history of) suicidal behaviour are often excluded from entering trials. As a possible result from this, no trials have reported a completed suicide [Hammad et al., 2006]. Furthermore, most trials had methodological flaws such as high attrition rates, issues regarding measurement instruments and clinical

[6] A Cochrane review that compared antidepressant trials that used active placebos (placebos that cause side effects) versus inert placebos, found that the latter reported higher efficacy of antidepressants [Moncrieff et al., 2004]. Trial patients who experience side effects will be strengthened in their belief that they are assigned to the treatment group, and will thus experience a stronger placebo effect. The placebo effect in paediatric antidepressant trials is important, as the differences between patients on treatment compared to those on placebo tend to small (statistically, but not clinically significant). For instance, Emslie and colleagues found that fluoxetine led to a 22-point decrease on the CDRS-R, while placebo led to a 15-point decrease [Emslie et al., 2002].

usefulness of outcomes, often variously defined across trials. Finally, the usual length for clinical trials is 8 to 12 weeks, while clinical treatment is recommended for at least six months by the National Institute for Health and Clinical Excellence (NICE) guidelines.

B.2 Evidence from observational studies

Large scale post-licensure medical product safety surveillance is important for detecting adverse events potentially not identified in pre-licensure studies, which often lack power for rare outcomes, enrol relatively restricted populations, and provide little information about longer-term adverse effects [Nelson et al., 2011].

Observational studies in young people have found mixed results. An ecological study examining US and Dutch data found that while SSRI prescriptions decreased in both countries following the warnings regarding paediatric SSRI use, suicide rates for children and adolescents increased [Gibbons et al., 2007]. However, the trends in SSRI prescriptions and suicide rates started changing at different time points, making an association less probable [Jureidini, 2007].

Although different regulators have warned against the use of different antidepressants and antidepressant groups, observational research has found no significant variations in event rates of suicidal behaviour in children taking various antidepressants [Schneeweiss et al., 2010]. The study by Schneeweiss et al. used propensity scores [Rubin, 1997] to be able to compare similar patients and partially taking confounding by indication into account. Their finding of no meaningful differences between fluoxetine, citalopram, fluvoxamine, paroxetine, sertraline or TCAs supports the FDA's decision that all antidepressants should be treated equally in a warning. However, as they did have a control group, they were unable to examine whether rates for suicidal behaviour were increased by antidepressants.

A matched case-control study using GPRD UK primary care data on 159,810 antidepressant users also found that the risk of suicidal behaviour was similar among users of amitriptyline, fluoxetine, and paroxetine compared with the risk of dosulepin, which was used as a reference antidepressant [Jick et al., 2004]. However, the study did find that the risk of suicidal behaviour was increased in the first month after prescriptions star-

ted, especially in the first nine days. The data for this study stems from 1993 to 1999. Although antidepressants were prescribed regularly to adults during this time period, prescriptions for children were still relatively rare (ref to results from chapter 4). Moreover, dosulepin is no longer used as an antidepressant today, resulting in the comparison being less informative.

Another matched case-control study, using US Medicaid[7] data, tried to assess risk of suicidal behaviour for both children and adults [Olfson et al., 2006]. Although suicide attempts and suicide deaths were not associated with antidepressants in adults (ORs 1.10 and 0.90, respectively), there was a significant association for suicide attempts (OR 1.52; 95% CI: 1.12-2.07) and completed suicides (OR 15.62 95% CI: 1.65 -) for children aged 6 18 years. This estimate might be biased by confounding by severity. Given the risk of death in overdose, the lack of efficacy in children, and the side effects associated with them, a prescriber would be less likely to prescribe TCAs in preference to SSRIs for a person at risk of suicidal behaviour [Didham et al., 2005].

The finding of age-dependent effects of antidepressants is supported by animal studies, which have shown that both fluoxetine and paroxetine exert age-dependent effects in rats. In adolescent, as opposed to adult rats, exposure to these drugs resulted in an increase in depression-like behaviour [Homberg et al., 2011, West et al., 2010].

B.3 Evidence for the efficacy of antidepressants

A Cochrane review assessed the available evidence for the efficacy of second generation antidepressants in children and adolescents [Hetrick et al., 2012]. The review included 19 trials, 14 of which provided useable data on efficacy. The results from these trials are summarised in Figure B.3. The trials included in this meta-analysis reported the mean difference in depression scores from baseline as measured on the Children's Depression Rating Scale, Revised (CDRS-R), ranging from a minimum score of 17 (not depressed) to 113 (severely depressed). Although the pooled effect favours antidepressants over placebo, the mean difference is very small at -3.51 points (95% CI: -4.55 to -2.47).

In addition to a small effect size, none of the included studies were judged to be at

[7]Medicaid is the US health program for certain people and families with low incomes and resources.

low risk of bias. Selective reporting was a particular problem in the included trials, with 18 of the included trials at high risk of this type of bias. As such, the review concluded that the evidence that antidepressants can decrease depressive symptom scores is of low quality.

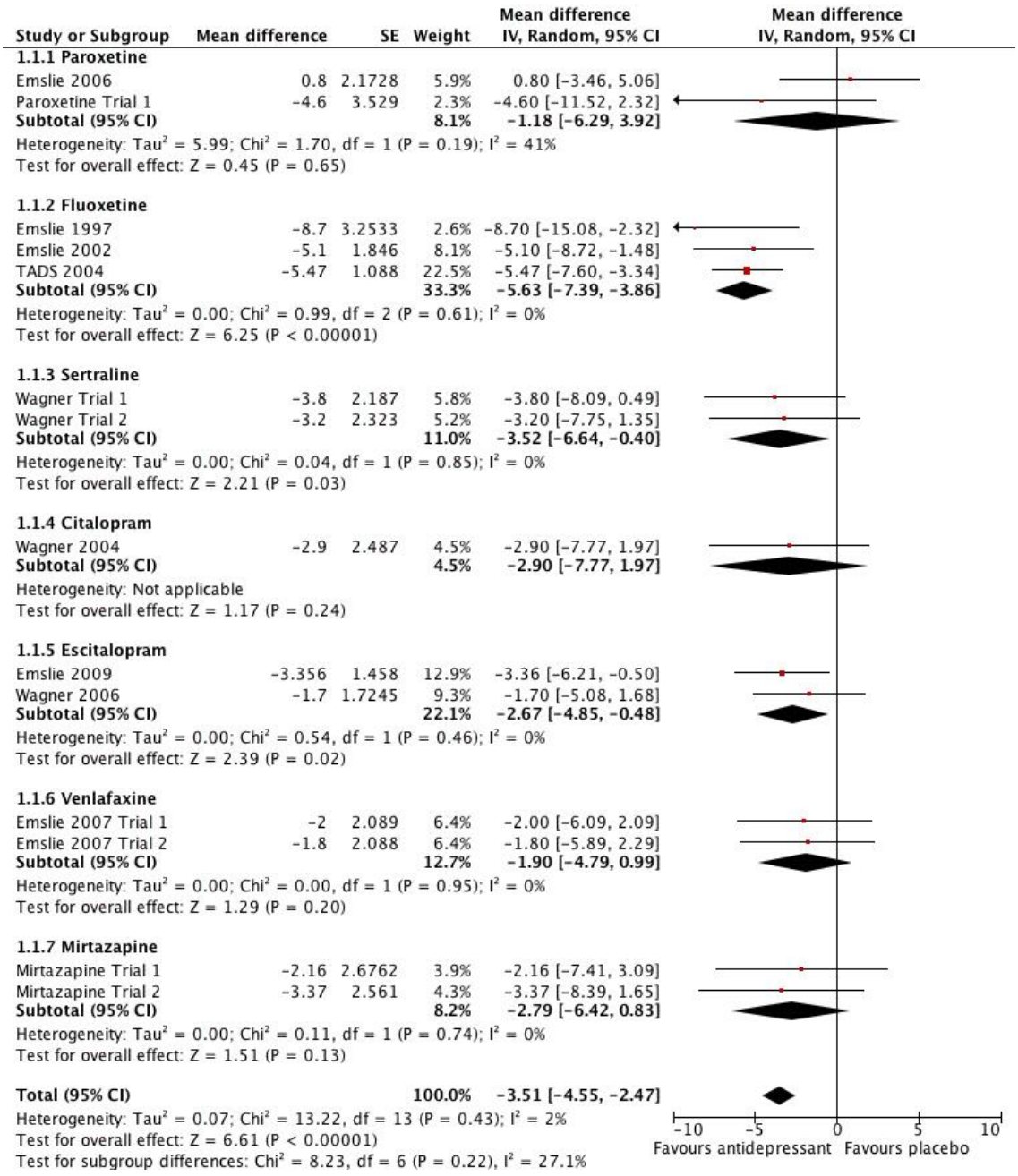


Figure B.3: Forest plot comparing second generation antidepressants versus placebo. Outcome: depression symptoms severity (CDRS-R).

Appendix C

Stata do-files and resulting code lists

C.1 Stata do-file for creating depression code list

```
**************************************
****DEPRESSION code list update****
**************************************
*AUTHOR: LINDA WIJLAARS
*CREATED: JANUARY 2011
*THIN-VERSION: 1005
*UPDATED OLD CODELIST (THIN 0806?)


*VERSION 2.0
*UPDATED FOR THIN1011 (DECEMBER 2011) / STATA12.0


set more off
local path "C:\data\THIN10_1005\Codes/"
local path2 "C:\data\THIN1011\"


/*SEARCH FOR WORDS RELATING TO DEPRESSION
```

```
 IN FULL READCODE LIST*/
use "`path2'Readcodes1101", clear
duplicates drop medcode, force
gen lcase=lower(description)
gen depress=0
foreach word in "depression" "depressed" "depressive" ///
"affective disorder" "affective illness" "dysthymia" {
replace depress=depress|strpos(lcase, "`word'")
}
drop lcase

/*EYEBALL THE RESULTS FOR COMMON STEMS IN THE READCODE*/
sort depress medcode
foreach word in "1B17.12" /// C/O - feeling unhappy
"1BP..00" /// Loss of interest
"1BP0.00" /// Loss of interest in previously
    enjoyable activity
"1BT..11" /// Low mood
"1BT..12" /// Sad mood
"1BU..00" /// Loss of hope for the future
"1BQ..00" /// Loss of capacity for enjoyment
"Eu33200" /// [X]Recurr depress disorder
    cur epi severe without psyc sympt
"Eu32211" /// [X]Endogenous depression
     without psychotic symptoms
"Eu3y011" /// [X]Mixed affective episode
{
replace depress=depress|strpos(medcode, "`word'")
```

```
}
/*DROP CODES THAT ARE NOT RELATED TO DEPRESSION*/
keep if depress

/*CREATE NEW INDICATOR VARIALBE FOR CODES THAT
SHOULD BE EXCLUDED (EG THOSE RELATING TO FAMILY HISTORY
OR QUESTIONNAIRES)*/
gen lcase=lower(description)
gen out=0
foreach word in ///
"scale" "fh" "member" "h/o" "resolved" "score" ///
"screen" "question" "management" "advice" "review" ///
"letter" "monitoring" "except" "administration" ///
"senile" "remission" "beck" "history" "bipolar" ///
"manic-depressive" "manic-depression" "psychosis"{
replace out=out|strpos(lcase, "`word'")
}
drop lcase

/*CHECK CODES PICKED UP IN LAST STEP
AND DELETE THEM FROM LIST*/
sort out depress medcode
replace out=0 if medcode=="E112300" | medcode=="E113300"
keep if out!=1

/*REMOVE CODES NOT RELATING TO DEPRESSION
(EG ECG DEPRESSION/SKULL DEPRESSION)*/
foreach word in "32E4.00" /// ECG: S-T depression
```

```
"6G00.00" /// Postnatal depression counselling
"7J02200" /// Elevation of depressed fracture of cranium
"8HHq.00" /// Referall for guided self-help for depression
"9HA1.00" /// Removed from depression register
"D41y300" /// Bone marrow depression
"E004300" /// Arteriosclerotic dementia with depression
"E02y300" /// Drug-induced depressive state
"E11..12" /// Depressive psychoses
"Eu20400" /// [X]Post-schizophrenic depression
"Eu25.00" /// [X]Schizoaffective disorders
"Eu25000" /// [X]Schizoaffective disorder, manic type
"Eu25100" /// [X]Schizoaffective disorder, depressive type
"Eu25200" /// [X]Schizoaffective disorder, mixed type
"Eu25y00" /// [X]Other schizoaffective disorders
"Eu25z00" /// [X]Schizoaffective disorder, unspecified
"PE03.00" /// Depressions in skull
"Q018.00" /// Fetus or neonate affected by
    maternal postnatal depression
"Q482000" /// Newborn cerebral depression
"R007z13" /// [D]Postoperative depression
"S03z.11" /// Depressed skull fracture NOS
"ZRrI.00" /// Wakefield self-assessment depression inventory
{
replace depress=depress & !strpos(medcode, "`word'")
}

/*REMOVE OBSELETE CODES*/
keep if depress
```

```
drop depress out


label define depcat 1 "Diagnosis" 2 "Symptom" 3 "Antidepressant"

label values depcat depcat


replace DepCat=4 if medcode=="1BT..12" | medcode=="1JJ..00"

drop if DepCat==.

drop DepCat

save "'path`Depression_THIN1011.dta", replace
```

C.2 Depression code list

Read code	Description	Category
1B17.00	Depressed	Diagnosis
1BT..00	Depressed mood	Diagnosis
2257.00	O/E - depressed	Diagnosis
62T1.00	Puerperal depression	Diagnosis
8BK0.00	Depression management programme	Diagnosis
9HA0.00	On depression register	Diagnosis
9k40.00	Depression - enhanced service completed	Diagnosis
9kQ..00	On full dose long term treatment depression - enh serv admin	Diagnosis
9kQ..11	On full dose long term treatment for depression	Diagnosis
E112.00	Single major depressive episode	Diagnosis
E112.11	Agitated depression	Diagnosis
E112.12	Endogenous depression first episode	Diagnosis
E112.13	Endogenous depression first episode	Diagnosis
E112.14	Endogenous depression	Diagnosis
E112000	Single major depressive episode, unspecified	Diagnosis
E112100	Single major depressive episode, mild	Diagnosis
E112200	Single major depressive episode, moderate	Diagnosis
E112300	Single major depressive episode, severe, without psychosis	Diagnosis
E112500	Single major depressive episode, partial or unspec remission	Diagnosis
E112z00	Single major depressive episode NOS	Diagnosis
E113.00	Recurrent major depressive episode	Diagnosis
E113.11	Endogenous depression - recurrent	Diagnosis
E113000	Recurrent major depressive episodes, unspecified	Diagnosis
E113100	Recurrent major depressive episodes, mild	Diagnosis
E113200	Recurrent major depressive episodes, moderate	Diagnosis

continued on next page

Read code	Description	Category
E113300	Recurrent major depressive episodes, severe, no psychosis	Diagnosis
E113500	Recurrent major depressive episodes,partial/unspec remission	Diagnosis
E113700	Recurrent depression	Diagnosis
E113z00	Recurrent major depressive episode NOS	Diagnosis
E118.00	Seasonal affective disorder	Diagnosis
E11y200	Atypical depressive disorder	Diagnosis
E11z200	Masked depression	Diagnosis
E135.00	Agitated depression	Diagnosis
E200300	Anxiety with depression	Diagnosis
E204.00	Neurotic depression reactive type	Diagnosis
E204.11	Postnatal depression	Diagnosis
E290.00	Brief depressive reaction	Diagnosis
E290z00	Brief depressive reaction NOS	Diagnosis
E291.00	Prolonged depressive reaction	Diagnosis
E2B..00	Depressive disorder NEC	Diagnosis
E2B0.00	Postviral depression	Diagnosis
E2B1.00	Chronic depression	Diagnosis
Eu32.00	[X]Depressive episode	Diagnosis
Eu32.11	[X]Single episode of depressive reaction	Diagnosis
Eu32.12	[X]Single episode of psychogenic depression	Diagnosis
Eu32.13	[X]Single episode of reactive depression	Diagnosis
Eu32000	[X]Mild depressive episode	Diagnosis
Eu32100	[X]Moderate depressive episode	Diagnosis
Eu32200	[X]Severe depressive episode without psychotic symptoms	Diagnosis
Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms	Diagnosis
Eu32212	[X]Single episode major depression w'out psychotic symptoms	Diagnosis

continued on next page

Read code	Description	Category
Eu32213	[X]Single episode vital depression w'out psychotic symptoms	Diagnosis
Eu32400	[X]Mild depression	Diagnosis
Eu32500	[X]Major depression, mild	Diagnosis
Eu32600	[X]Major depression, moderately severe	Diagnosis
Eu32700	[X]Major depression, severe without psychotic symptoms	Diagnosis
Eu32y00	[X]Other depressive episodes	Diagnosis
Eu32y11	[X]Atypical depression	Diagnosis
Eu32y12	[X]Single episode of masked depression NOS	Diagnosis
Eu32z00	[X]Depressive episode, unspecified	Diagnosis
Eu32z11	[X]Depression NOS	Diagnosis
Eu32z12	[X]Depressive disorder NOS	Diagnosis
Eu32z13	[X]Prolonged single episode of reactive depression	Diagnosis
Eu32z14	[X] Reactive depression NOS	Diagnosis
Eu33.00	[X]Recurrent depressive disorder	Diagnosis
Eu33.11	[X]Recurrent episodes of depressive reaction	Diagnosis
Eu33.12	[X]Recurrent episodes of psychogenic depression	Diagnosis
Eu33.13	[X]Recurrent episodes of reactive depression	Diagnosis
Eu33.14	[X]Seasonal depressive disorder	Diagnosis
Eu33.15	[X]SAD - Seasonal affective disorder	Diagnosis
Eu33000	[X]Recurrent depressive disorder, current episode mild	Diagnosis
Eu33100	[X]Recurrent depressive disorder, current episode moderate	Diagnosis
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt	Diagnosis
Eu33211	[X]Endogenous depression without psychotic symptoms	Diagnosis
Eu33212	[X]Major depression, recurrent without psychotic symptoms	Diagnosis
Eu33214	[X]Vital depression, recurrent without psychotic symptoms	Diagnosis
Eu33y00	[X]Other recurrent depressive disorders	Diagnosis

continued on next page

Read code	Description	Category
Eu33z00	[X]Recurrent depressive disorder, unspecified	Diagnosis
Eu33z11	[X]Monopolar depression NOS	Diagnosis
Eu34.00	[X]Persistent mood affective disorders	Diagnosis
Eu34100	[X]Dysthymia	Diagnosis
Eu34111	[X]Depressive neurosis	Diagnosis
Eu34113	[X]Neurotic depression	Diagnosis
Eu34114	[X]Persistant anxiety depression	Diagnosis
Eu34y00	[X]Other persistent mood affective disorders	Diagnosis
Eu34z00	[X]Persistent mood affective disorder, unspecified	Diagnosis
Eu3y111	[X]Recurrent brief depressive episodes	Diagnosis
Eu41200	[X]Mixed anxiety and depressive disorder	Diagnosis
Eu41211	[X]Mild anxiety depression	Diagnosis
Eu53011	[X]Postnatal depression NOS	Diagnosis
Eu53012	[X]Postpartum depression NOS	Diagnosis
R007z13	[D]Postoperative depression	Diagnosis
13JK.00	Business worries	Symptom
13JK.14	Work worries	Symptom
13JM.14	Work worries	Symptom
1B1..00	General nervous symptoms	Symptom
1B12.00	'Nerves' - nervousness	Symptom
1B12.11	'Nerves'	Symptom
1B12.12	Tension - nervous	Symptom
1B13.00	Anxiousness	Symptom
1B13.11	Anxiousness - symptom	Symptom
1B17.11	C/O - feeling depressed	Symptom
1B17.12	C/O - feeling unhappy	Symptom

continued on next page

Read code	Description	Category
1B1U.00	Symptoms of depression	Symptom
1B1U.11	Depressive symptoms	Symptom
1BK..00	Worried	Symptom
1BP..00	Loss of interest	Symptom
1BP0.00	Loss of interest in previously enjoyable activity	Symptom
1BQ..00	Loss of capacity for enjoyment	Symptom
1BT..11	Low mood	Symptom
1BU..00	Loss of hope for the future	Symptom
E201.00	Hysteria	Symptom
E201000	Hysteria unspecified	Symptom
E201z00	Hysteria NOS	Symptom
Eu41112	[X]Anxiety reaction	Symptom
R2y2.00	[D]Nervousness	Symptom
R2y2.11	[D]Nerves	Symptom
R2y2.12	[D]Nervous tension	Symptom

C.3 Stata do-file for creating antidepressant code list

```
**************************************
****ANTIDEPRESSANT code list update****
**************************************
*AUTHOR: LINDA WIJLAARS
*CREATED: FEBRUARY 2011
*THIN-VERSION: 1005
*UPDATED OLD CODELIST (THIN 0806?)

*VERSION 2.0
*UPDATED FOR THIN1011 (DECEMBER 2011) / STATA12.0

set more off
local path "C:\data\THIN1011\"
local path2 "C:\data\THIN10_1005\Codes\"

/*SELECT DRUGCODES THAT APPEAR IN BNF CHAPTER 4.3 (ANTIDEPRESSANTS)*/
use "`path'Drugcodes1101", clear
keep if substr(bnfcode1,1,5)=="04.03" |substr(bnfcode2,1,5)=="04.03" ///
 | substr(bnfcode3,1,5)=="04.03"

/*HOUSEKEEPING */
duplicates drop
rename multilexeid drugcode
tostring drugcode, replace

/*MAKE 'STRENGTH' INTO A NUMERICAL VARIABLE*/
```

```
destring strength, replace

/*MERGE 'NEW' CODELIST WITH 'OLD' CODELIST*/
merge m:1 drugcode using "`path2'all_antidepressants_2010_string"

replace merge=4 if merge==.
label define _merge 4 "Code added December 2011", modify

/*GENERATE INDICATOR VARIABLE FOR TYPE AND LABEL*/
*gen type=0
replace type=1 if bnfcode1=="04.03.01.00" | bnfcode2=="04.03.01.00" ///
 | bnfcode3=="04.03.01.00"
replace type=2 if bnfcode1=="04.03.02.00" | bnfcode2=="04.03.02.00" ///
 | bnfcode3=="04.03.02.00"
replace type=3 if bnfcode1=="04.03.03.00" | bnfcode2=="04.03.03.00" ///
 | bnfcode3=="04.03.03.00"
replace type=4 if bnfcode1=="04.03.04.00" | bnfcode2=="04.03.04.00" ///
 | bnfcode3=="04.03.04.00"

*label define typemap 1 "Tricyclic antidepressant" ///
2 "Monoamine-oxidase inhibitor" 3 "SSRI" 4 "Other"
*label values type typemap

/*CHECK WHETHER ALL CODES CORRESPOND TO A DRUG TYPE*/
tab type, missing
*no missings

sort _merge genericname
```

```
drop _merge

*GENERATE DRUGNAME VARIABLE FOR 'NEW' DRUGS*
generate b=strpos(genericname, " ")
generate drug_name2=substr(genericname,1,b-1)
replace drug_name2=genericname if b==0
drop b

*drug_name is a numeric variable with labels attached for each drug
*the added drugs also need to be assigned a value corresponding
to the earlier created labels + 2 new labels for new drugs*

drop drug_name2

*save new file*
compress
save "C:\data\THIN10_1005\Codes\all_antidepressants_2011.dta", replace
```

C.4 Antidepressant code list

This is a sample of antidepressant codes, the full contains 800 drug codes. Here, I have included only one code for each drug. Each drug has multiple codes in the full list, representing different manufacturers, doses, and formulations.

multilexid	BNF chapter 1	BNF chapter 2	ATC code	Type	Drug name
99861989	04.03.01.00	00.00.00.00	N06A A09	TCA	AMITRIPTYLINE
97814988	04.03.01.00	00.00.00.00	N06A A04	TCA	CLOMIPRAMINE
94145992	04.03.01.00	00.00.00.00	N06A A16	TCA	DOSULEPIN
84904998	04.03.01.00	00.00.00.00		TCA	DOXEPIN
95695997	04.03.01.00	00.00.00.00	N06A A10	TCA	NORTRIPTYLINE
98077990	04.03.01.00	00.00.00.00	N06A A07	TCA	LOFEPRAMINE
95927998	04.03.01.00	00.00.00.00	N06A A21	TCA	MAPROTILINE
99492989	04.03.01.00	00.00.00.00	N06A X03	TCA	MIANSERIN
92271990	04.03.01.00	00.00.00.00	N06A X05	TCA	TRAZODONE
98136996	04.03.01.00	00.00.00.00	N06A A06	TCA	TRIMIPRAMINE
94683990	04.03.01.00	00.00.00.00	N06A A02	TCA	IMIPRAMINE
94008998	04.03.01.00	00.00.00.00	N06A A17	TCA	AMOXAPINE
98134998	04.03.01.00	00.00.00.00	N06A A15	TCA	BUTRIPTYLINE
98146998	04.03.01.00	00.00.00.00	N06A A01	TCA	DESIPRAMINE
96637992	04.03.01.00	00.00.00.00		TCA	DIBENZEPIN
96109997	04.03.01.00	00.00.00.00	N06A A13	TCA	IPRINDOLE
97807992	04.03.01.00	00.00.00.00		TCA	NOMIFENSINE
97827992	04.03.01.00	00.00.00.00		TCA	OPIPRAMOL

TCA = tricyclic antidepressant

MAOI = mono-amine oxidase inhibitor

SSRI = selective serotonin reuptake inhibitor

continued on next page

multilexid	BNF chapter 1	BNF chapter 2	ATC code	Type	Drug name
95372998	04.03.01.00	00.00.00.00	N06A A11	TCA	PROTRIPTYLINE
95624998	04.03.01.00	00.00.00.00	N06A X09	TCA	VILOXAZINE
98327992	04.03.01.00	00.00.00.00		TCA	ZIMELDINE
83620998	04.03.01.00	00.00.00.00	N06C A01	TCA	PERPHENAZINE
93759998	04.03.02.00	00.00.00.00	N06A G02	MAOI	MOCLOBEMIDE
99377998	04.03.02.00	00.00.00.00	N06A F03	MAOI	PHENELZINE
96107998	04.03.02.00	00.00.00.00	N06A F05	MAOI	IPRONIAZID
97169990	04.03.02.00	00.00.00.00	N06A F01	MAOI	ISOCARBOXAZID
95143998	04.03.02.00	00.00.00.00	N06C	MAOI	TRANYLCYPROMINE
87662998	04.03.03.00	00.00.00.00	N06A B10	SSRI	ESCITALOPRAM
94895990	04.03.03.00	00.00.00.00	N06A B04	SSRI	CITALOPRAM
96281990	04.03.03.00	00.00.00.00	N06A B03	SSRI	FLUOXETINE
96493998	04.03.03.00	00.00.00.00	N06A B08	SSRI	FLUVOXAMINE
92734990	04.03.03.00	00.00.00.00	N06A B05	SSRI	PAROXETINE
93747990	04.03.03.00	00.00.00.00	N06A B06	SSRI	SERTRALINE
82038998	04.03.03.00	00.00.00.00		SSRI	DAPOXETINE
99634998	04.03.04.00	04.02.01.00	N05A F01	Other	FLUPENTIXOL
86982998	04.03.04.00	00.00.00.00	N06A X11	Other	MIRTAZAPINE
91362996	04.03.04.00	00.00.00.00	N06A X06	Other	NEFAZODONE
88836998	04.03.04.00	00.00.00.00	N06A X18	Other	REBOXETINE
98257998	04.03.04.00	00.00.00.00	N06A X02	Other	TRYPTOPHAN
82540998	04.03.04.00	00.00.00.00	N06A X16	Other	VENLAFAXINE
86998998	04.03.04.00	00.00.00.00	N06A X21	Other	DULOXETINE

TCA = tricyclic antidepressant

MAOI = mono-amine oxidase inhibitor

SSRI = selective serotonin reuptake inhibitor

continued on next page

multilexid	BNF chapter 1	BNF chapter 2	ATC code	Type	Drug name
94663992	04.03.04.00	00.00.00.00		Other	TRYPTOPHARYPTOPHA
82861998	04.03.04.00	00.00.00.00	N06A X22	Other	AGOMELATINE

TCA = tricyclic antidepressant

MAOI = mono-amine oxidase inhibitor

SSRI = selective serotonin reuptake inhibitor

C.5 Sleep disorder code list

Read code	Description	Category
1B1B.00	Cannot sleep - insomnia	Insomnia
1B1B.11	C/O - insomnia	Insomnia
1B1B000	Initial insomnia	Insomnia
1B1B100	Middle insomnia	Insomnia
1B1B200	Late insomnia	Insomnia
1BX0.00	Delayed onset of sleep	Insomnia
E274.12	Insomnia due to nonorganic sleep disorder	Insomnia
E274100	Transient insomnia	Insomnia
E274111	Insomnia NOS	Insomnia
E274200	Persistent insomnia	Insomnia
E274B00	Repeated rapid eye movement sleep interruptions	Insomnia
E274C00	Other sleep stage or arousal dysfunction	Insomnia
E274D00	Repetitive intrusions of sleep	Insomnia
E274D11	Restless sleep	Insomnia
Eu51000	[X]Nonorganic insomnia	Insomnia
Fy00.00	Disorders of initiating and maintaining sleep	Insomnia
R005.00	[D]Sleep disturbances	Insomnia
R005.11	[D]Insomnia - symptom	Insomnia
R005100	[D]Insomnia with sleep apnoea	Insomnia
R005200	[D]Insomnia NOS	Insomnia
R005800	[D]Sleep dysfunction with sleep stage disturbance	Insomnia
R005900	[D]Sleep dysfunction with arousal disturbance	Insomnia
R005z00	[D]Sleep dysfunction NOS	Insomnia
Z1M1.00	Disturbing sleep	Insomnia
1B1B.12	C/O - somnolence	Exessive daytime sleepiness

continued on next page

Read code	Description	Category
1BX1.00	Excessive sleep	Exessive daytime sleepiness
E274.11	Hypersomnia of non-organic origin	Exessive daytime sleepiness
E274300	Transient hypersomnia	Exessive daytime sleepiness
E274311	Hypersomnia NOS	Exessive daytime sleepiness
E274400	Persistent hypersomnia	Exessive daytime sleepiness
E274A00	Sleep drunkenness	Exessive daytime sleepiness
Eu51100	[X]Nonorganic hypersomnia	Exessive daytime sleepiness
F27..00	Cataplexy and narcolepsy	Exessive daytime sleepiness
F271.00	Narcolepsy	Exessive daytime sleepiness
F27z.00	Cataplexy or narcolepsy NOS	Exessive daytime sleepiness
Fy01.00	Disorders of excessive somnolence	Exessive daytime sleepiness
R000000	[D]Drowsiness	Exessive daytime sleepiness
R000100	[D]Somnolence	Exessive daytime sleepiness
R005300	[D]Hypersomnia with sleep apnoea	Exessive daytime sleepiness
R005400	[D]Hypersomnia NOS	Exessive daytime sleepiness
E274600	Shifting sleep-work schedule	Sleep rhythm problem
E274F00	Inversion of sleep rhythm	Sleep rhythm problem
Eu51200	[X]Nonorganic disorder of the sleep-wake schedule	Sleep rhythm problem
Eu51211	[X]Psychogenic inversion of circadian rhythm	Sleep rhythm problem
Eu51212	[X]Psychogenic inversion of nyctohemeral rhythm	Sleep rhythm problem
Eu51213	[X]Psychogenic inversion of sleep rhythm	Sleep rhythm problem
Fy02.00	Disorders of the sleep-wake schedule	Sleep rhythm problem
R005.12	[D]Sleep rhythm problems	Sleep rhythm problem
R005500	[D]Sleep rhythm inversion	Sleep rhythm problem
R005600	[D]Sleep rhythm irregular	Sleep rhythm problem
R005700	[D]Sleep-wake rhythm non-24-hour cycle	Sleep rhythm problem

continued on next page

Read code	Description	Category
1B1D.00	C/O nightmares	Sleep-disruptive behaviors
1B1D.11	Nightmares - symptom	Sleep-disruptive behaviors
1BN1.00	Wanders at night	Sleep-disruptive behaviors
1BN2.00	Wanders during the day and at night	Sleep-disruptive behaviors
E26y000	Bruxism (teeth grinding)	Sleep-disruptive behaviors
E274700	Somnambulism - sleep walking	Sleep-disruptive behaviors
E274800	Night terrors	Sleep-disruptive behaviors
E274900	Nightmares	Sleep-disruptive behaviors
Eu51300	[X]Sleepwalking	Sleep-disruptive behaviors
Eu51400	[X]Sleep terrors	Sleep-disruptive behaviors
Eu51500	[X]Nightmares	Sleep-disruptive behaviors
Eu51511	[X]Dream anxiety disorder	Sleep-disruptive behaviors
F13z200	Restless legs syndrome	Sleep-disruptive behaviors
8G99.00	Sleep restriction therapy	Other / NOS
8G9B.00	Sleep hygiene behaviour education	Other / NOS
8HTn.00	Referral to sleep clinic	Other / NOS
8Q0..00	Sleep management	Other / NOS
9Nk0.00	Seen in sleep clinic	Other / NOS
E274.00	Non-organic sleep disorders	Other / NOS
E274000	Unspecified non-organic sleep disorder	Other / NOS
E274y00	Other non-organic sleep disorder	Other / NOS
E274z00	Non-organic sleep disorder NOS	Other / NOS
Eu51.00	[X]Nonorganic sleep disorders	Other / NOS
Eu51y00	[X]Other nonorganic sleep disorders	Other / NOS
Eu51z00	[X]Nonorganic sleep disorder, unspecified	Other / NOS
Eu51z11	[X]Emotional sleep disorder NOS	Other / NOS

continued on next page

Read code	Description	Category
Fy0..00	Sleep disorders	Other / NOS
Fyu5800	[X]Other sleep disorders	Other / NOS
R005000	[D]Sleep disturbance, unspecified	Other / NOS

Appendix D

Mediation analysis

D.1 Classic mediation analysis

In most epidemiological studies, confounders for the exposure-outcome association are measured and adjusted for. However, for mediation analysis it is also important to consider mediator-outcome confounders. If these confounders are not controlled for then results from the classic approach can be highly biased [Hernández-Díaz et al., 2006, Pearl, 2001].

An example of when classic mediation analysis leads to biased results is the so called 'birth weight paradox' [Hernández-Díaz et al., 2006]. Smoking during pregnancy is associated with an increased risk of low birth weight (LBW) infants, and low birth weight in turn, is associated with increased infant mortality. Smoking during pregnancy is also associated with an increase in the risk of infant mortality. However, when birth weight is included in the analysis as a mediator, the effect of smoking on infant mortality is reversed. Studies have found that among groups of LBW infants, maternal smoking during pregnancy is actually a protective factor: the relative rate of mortality if reduced by 20% for LBW infants of smoking mothers.

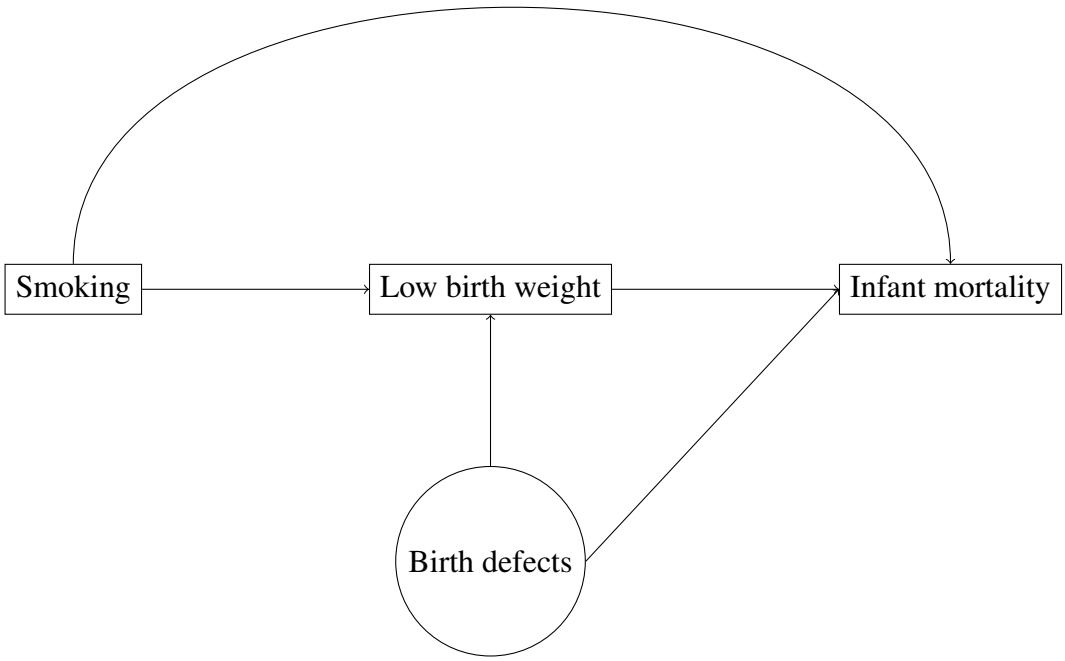


Figure D.1: The birth weight paradox

However, this apparent risk reduction is due to mediator-outcome confounding by covariates such as birth defects (Figure D.1). LBW infants born to smokers may have a lower risk of mortality than other LBW infants whose LBW is due to causes associated with high mortality such as birth defects. Only when mediator-outcome confounding by birth defects is taking into account (or when birth weight is not included as a mediator) a correct estimate can be provided.

The importance of controlling for mediator-outcome confounding when examining direct and indirect effects was also pointed out early on in the psychology literature on mediation in a paper by Judd and Kenny from 1981 [Judd and Kenny, 1981]. However, a paper on the same subject published five years later by Baron and Kenny [Baron and Kenny, 1986] became the go-to paper for researchers interested in mediation analysis. The second paper has been cited almost 40,000 times according to Google Scholar

(compared to just over 1,000 for the first paper) and unfortunately does not mention that mediator-outcome confounding is a limitation to the classic mediation approach. As a result, many papers using this approach do not consider this type of confounding and are thus at risk of bias [VanderWeele and Vansteelandt, 2010].

The second limitation to the classic approach is that it doesn't allow for exposure-mediator interaction. Usually, exposure-mediator interaction terms are not considered for the regression models in mediation analysis. If interaction is present, it could severely bias the results.

Moreover, even if the interaction term is included in the regression analysis, part of the problem remains. As the exposure is linked to two coefficients in a regression model including an interaction term (both the coefficient linked to the exposure, and the coefficient for the exposure-mediator interaction) it is not possible to quantify the mediation. Thus, in the case of exposure-mediator interaction, the classic approach will give biased results.

D.2 Results: classic mediation analysis

In order to explore whether the limitations of the classic method for mediation analysis would affect the outcome of my proposed analysis, I've have performed this analysis as well (Table D.1). The coefficient estimates for the exposure (presented in their exponentiated form as Incidence Rate Ratios (IRRs) to make them more readily interpretable) are very similar between the two models. The IRR for children in families where one parent experiences depression is 1.39 (95% CI: 0.90-2.14) in the model without the potential mediator, and 1.40 (95% CI: 0.89-2.19) in the model with the potential mediator. Simil-

arly, the IRRs for children in families where both parents experience early depression are comparable (IRR = 1.93, 95% CI: 0.49-7.62 and IRR = 1.78, 95% CI: 0.56-6.96) in the models with and without the potential mediator.

Variable	Model 1		Model 2	
	IRR (95% CI)	*P* value	IRR (95% CI)	*P* value
Early parental depression				
No EPD	Reference		Reference	
One parent EPD	1.39 (0.90 - 2.14)	0.13	1.40 (0.89 - 2.19)	0.15
Comorbid EPD	1.93 (0.49 - 7.62)	0.35	1.78 (0.56 - 6.96)	0.41
Recurrent parental depression				
No recurrent depression	-	-	Reference	
1-4 episodes	-	-	1.44 (1.11 - 1.87)	0.006
5-9 episodes	-	-	2.01 (1.36 - 2.97)	<0.001
10+ episoded	-	-	0.88 (0.38 - 2.05)	0.77
Townsend score				
1 (most affluent)	Reference		Reference	
2	0.82 (0.58 - 1.15)	0.25	0.83 (0.59 - 1.17)	0.30
3	0.87 (0.60 - 1.24)	0.46	0.87 (0.61 - 1.23)	0.43
4	1.13 (0.79 - 1.61)	0.51	1.10 (0.77 - 1.57)	0.59
5 (most deprived)	1.39 (0.93 - 2.09)	0.11	1.32 (0.88 - 2.00)	0.18
Maternal age at birth	0.99 (0.95 - 1.02)	0.50	0.99 (0.96 - 1.03)	0.72
Paternal age at birth	1.02 (0.99 - 1.05)	0.14	1.02 (0.99 - 1.05)	0.14
Birth year	0.71 (0.66 - 0.76)	<0.001	0.71 (0.66 - 0.76)	<0.001
Child maltreatment	2.75 (1.77 - 4.27)	<0.001	2.63 (1.70 - 4.06)	<0.001
Illicit drug use	3.86 (0.34 - 44.32)	0.28	3.93 (0.40 - 38.15)	0.24
Alcohol abuse	1.22 (0.61 - 2.46)	0.57	1.17 (0.58 - 2.39)	0.66
Maternal comorbidity	1.00 (0.94 - 1.07)	0.92	0.99 (0.93 - 1.06)	0.86
Paternal comorbidity	1.12 (1.03 - 1.22)	0.01	1.11 (1.02 - 1.21)	0.02
Female child	2.50 (1.94 - 3.23)	<0.001	2.54 (1.97 - 3.28)	<0.001
Model 1: without recurrent parental depression; Model 2: with recurrent parental depression				

Table D.1: Negative binomial regression analysis showing risk ratios for adolescent depression in models with and without recurrent parental depression

Following the classic approach's reasoning, these results would indicate that recurrent parental depression is not a mediator in the association between early parental depression and adolescent depression as the estimates of the coefficients have not substantially changed.

D.3 Counterfactual mediation analysis

I performed a counterfactual mediation analysis in Stata that allows for exposure-mediator interaction to explore why the results from the classic approach differed from those of the SEM modelling. This counterfactual approach has been developed by VanderWeele and Vansteelandt [VanderWeele and Vansteelandt, 2009] and has been implemented in SAS and SPSS [Valeri and VanderWeele, 2013], as well as in Stata [Emsley and Liu, 2013].

Counterfactuals can be used in statistics to model outcomes that we are interested in, but did not observe. For instance, imagine a simple clinical trial where participants are randomised to either receive an active treatment, or a placebo. For each patient, we can only observe one outcome: either associated with receiving the treatment or the placebo. The first patient in the trial might have received the active treatment, and was cured. What we want to know though, is what the outcome would have been if this patient had not received the treatment: the counterfactual outcome. Is the outcome due to patient-related factors, or due to the treatment? While it is impossible to directly observe a counterfactual outcome, it is possible to estimate it on a population level. Using the information of many patients with different characteristics, exposure and outcome levels, counterfactual outcomes can be estimated.

In counterfactual mediation analysis, counterfactuals are estimated for both the exposure and the mediator. Two models are fitted to the data, one to model the outcome, and another to separately model the mediator. This approach allows for mediator-outcome confounding and can quantify exposure-mediator interaction, the two important limitations of the classic mediation approach.

The results of this approach are shown in Table D.2. Interaction between early parental depression and recurrent parental depression is modelled in the exposure-outcome model and is non-significant (coefficient estimate: 0.26, 95% CI: -0.37 - 0.88; P value: 0.42). This appears to indicate that the differences between the results from the classic approach and SEM are not due to exposure-mediator interaction, but that mediator-outcome confounding has biased the classic approach's results.

Using counterfactual mediation analysis, it is also possible to estimate direct and indirect effects. Two types of direct effect are estimated: the controlled and natural direct effect. The controlled direct effect is the direct effect when the level of the mediator is set to the same predetermined level for each individual, independent of the level of the exposure. For instance, in my analysis, I have the mediator level to no parental recurrent depression for all individuals. The model then estimates what the outcome for each individual would be for each level of early parental depression, if their parents would not have experienced any episodes of depression during their childhood.

The natural direct effect is slightly different. Rather than setting the level of the mediator at the same level for each individual, it models the mediator at the level it would have naturally been (hence the name) for each counterfactual level of exposure. The estimates for the controlled and natural direct effects are similar (0.55 and 0.64, re-

	1 depressed parent		Comorbid depression	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
Exposure-outcome model				
Early parental depression (EPD)	-0.60 (-1.60 - 0.40)	0.24	-0.60 (-1.60 - 0.40)	0.24
Recurrent depression	0.41 (0.22 - 0.60)	<0.001	0.41 (0.22 - 0.60)	<0.001
EPD × recurrent depression	0.26 (-0.37 - 0.88)	0.42	0.26 (-0.37 - 0.88)	0.42
Exposure-mediator model				
EPD	2.38 (2.09 - 2.66)	<0.001	0.41 (0.22 - 0.60)	<0.001
Overall effect estimates				
Controlled direct effect	0.55 (0.20 - 1.49)	0.24	0.30 (0.11 - 0.82)	0.02
Natural direct effect	0.64 (0.33 - 1.24)	0.18	0.41 (0.12 - 1.47)	0.17
Natural indirect effect	1.30 (1.06 - 1.60)	0.01	1.50 (1.01 - 2.23)	0.047
Marginal total effect	0.83 (0.50 - 1.38)	0.47	0.62 (0.23 - 1.63)	0.33

Table D.2: Counterfactual mediation analysis results for early parental depression

spectively) and neither reaches statistical significance. However, the natural indirect is statistically significant (estimate: 1.30, 95% CI: 1.06 - 1.60; P value: 0.01), similar to the SEM results. When assessing the total effect, the indirect and direct effects appear to cancel each other out, resulting in a non-significant total effect.

Appendix E

MPlus SEM code

```
Title:
  Stata2Mplus conversion for full_file.dta

Data:
  File is full_file2.dat ;
Variable:
Names are
     pnd  c_dep_count  c_sex c_townsend
     outcome m_age f_age year maltreatment drug_abuse
     drinker smi neg_life_evnt f_comorbidity m_comorbidity
     abdopain headache tatt psychosomatic sleep anxiety dep_pre
     id time ib10 ib13 par_dep;
usevariables are
     pnd  c_sex c_townsend
     outcome m_age f_age year maltreatment
     drug_abuse drinker f_comorbidity
     m_comorbidity  ib10  ib13;
Missing are all (-9999) ;
```

```
categorical are ib10 ib13;


Model: outcome ON ib13 c_dep ib10 pnd c_sex c_townsend
       m_age f_age year maltreatment drug_abuse
       drinker f_comorbidity m_comorbidity;
       ib13 ON c_dep ib10 pnd c_sex c_townsend m_age f_age
       year maltreatment drug_abuse drinker
       f_comorbidity m_comorbidity;
       c_dep ON ib10 pnd c_sex c_townsend m_age f_age
       year maltreatment drug_abuse drinker
       f_comorbidity m_comorbidity;
       ib10 ON  pnd c_sex c_townsend m_age f_age year
       maltreatment drug_abuse drinker
       f_comorbidity m_comorbidity;


Analysis:
    Type=general;
    estimator=ML;


OUTPUT:
  standardized sampstat ;
```

Appendix F

Publications resulting from PhD work

OPEN ACCESS Freely available online

PLoS one

Trends in Depression and Antidepressant Prescribing in Children and Adolescents: A Cohort Study in The Health Improvement Network (THIN)

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Abstract

Background: In 2003, the Committee on Safety of Medicines (CSM) advised against treatment with selective serotonin reuptake inhibitors (SSRIs) other than fluoxetine in children, due to a possible increased risk of suicidal behaviour. This study examined the effects of this safety warning on general practitioners' depression diagnosing and prescription behaviour in children.

Methods and Findings: We identified a cohort of 1,502,753 children (<18 y; registered with GP for >6 m) in The Health Improvement Network (THIN) UK primary care database. Trends in incidence of depression diagnoses, symptoms and antidepressant prescribing were examined 1995–2009, accounting for deprivation, age and gender. We used segmented regression analysis to assess changes in prescription rates. Overall, 45,723 (3%) children had ≥1 depression-related entry in their clinical records. SSRIs were prescribed to 16,925 (1%) of children. SSRI prescription rates decreased from 3.2 (95%CI:3.0,3.3) per 1,000 person-years at risk (PYAR) in 2002 to 1.7 (95%CI:1.7,1.8) per 1,000 PYAR in 2005, but have since risen to 2.7 (95%CI:2.6,2.8) per 1,000 PYAR in 2009. Prescription rates for CSM-contraindicated SSRIs citalopram, sertraline and especially paroxetine dropped dramatically after 2002, while rates for fluoxetine and amitriptyline remained stable. After 2005 rates for all antidepressants, except paroxetine and imipramine, started to rise again. Rates for depression diagnoses dropped from 3.0 (95%CI:2.8,3.1) per 1,000 PYAR in 2002 to 2.0 (95%CI:1.9,2.1) per 1,000 PYAR in 2005 and have been stable since. Recording of symptoms saw a steady increase from 1.0 (95%CI:0.8,1.2) per 1,000 PYAR in 1995 to 4.7 (95%CI:4.5,4.8) per 1,000 PYAR in 2009.

Conclusions: The rates of depression diagnoses and SSRI prescriptions showed a significant drop around the time of the CSM advice, which was not present in the recording of symptoms. This could indicate caution on the part of GPs in making depression diagnoses and prescribing antidepressants following the CSM advice.

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Introduction

Antidepressants (ADs) are commonly prescribed to children and adolescents for depression, anxiety, and a variety of other disorder [1]. Selective serotonin reuptake inhibitors (SSRIs), first introduced in the late 1980s, were prescribed to children for depression on the basis of effectiveness data from trials on adult psychiatric disorders coupled with other trial data demonstrating the ineffectiveness of tricyclic antidepressants (TCAs) [2–5]. In the early 2000s, SSRIs became the preferred treatment for depression in children rather than tricyclic antidepressants (TCAs) [6].

However, doubts have been cast on the use of specific SSRIs in children. In October 2002, the BBC aired an episode of the investigative journalism show 'Panorama' which casted doubt on the safety of the SSRI paroxetine. In response to this, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) reanalysed published and unpublished data on paroxetine, and found that the drug failed to demonstrate significant beneficial effects, and was associated with a small increase in suicidal behaviour and ideation [7]. In June 2003, the MHRA hence advised that paroxetine should not be used to treat depression in children younger than 18 years [8]. Following this investigation, the Committee on Safety of Medicines (CSM) reviewed the safety of all antidepressants in children and adolescents and in December 2003 advised against the initiation of all SSRIs, except fluoxetine in children [9]. Fluoxetine is the only drug currently licensed to treat depression in children in the UK as its benefits were deemed greater than its risks [10,11]. The CSM, however, does recommend psychotherapies, such as cognitive-behavioural therapy, as first-line treatment for children and adolescents with depression. The American Food and Drug Authority (FDA) followed suit in October 2004 and issued a black box warning for all antidepressants prescribed to children [12].

Following the CSM advice, fewer children and adolescents in the UK were prescribed antidepressants in primary care [13]. There was a 48% reduction in the initiation of CSM-contraindi-

cated antidepressants in children between 2002 and 2004. However, the use of fluoxetine and non-SSRI antidepressants in children had not significantly risen during the same period. A similar pattern was found in a study in Australia, where antidepressant use, and SSRI use in particular, in children and adolescents decreased between 2002 and 2005 [14]. In stark contrast, the use of SSRIs and all antidepressants increased significantly in adults during the same period.

Time trends in antidepressant prescribing in children have been described for periods leading up to the CSM advice [1,13], but this is the first comprehensive study which covers trends in the recording of depression diagnoses and symptoms, and the prescription of antidepressants in children and adolescents from 1995 to 2009 in a large UK general practice database.

Methods

Ethics statement

The scheme for THIN to obtain and provide anonymous patient data to researchers was approved by the National Health Service South-East Multicenter Research Ethics Committee (MREC) in 2002 and scientific approval for this study was obtained from CMD Medical Research's Scientific Review Committee in March 2011.

Data Source

Approximately 98% of the population in the UK is registered with a general practitioner [15]. The Health Improvement Network (THIN) database is one of the largest national collections of primary care data and is broadly representative of the general practice (GP) population in terms of demographics and consultation behaviour [16]. Participating general practitioners from 497 practices enter clinical information on patients, including demographics data, diagnoses, and prescriptions so as to offer a longitudinal medical record for each patient which is available to researchers as anonymised data [17]. Clinical diagnoses recorded by GPs on THIN have been shown to be accurate compared with other reliable sources [18]. The database provides the Townsend score measure of deprivation, a composite measure of social deprivation in quintiles (owner occupation, overcrowding, car ownership, and unemployment) [19]. It is based on patient postal code and linked to UK census data from 2001 for approximately 150 households in that postal area. We analysed data from 1995 to 2009.

Study population

We identified a cohort of children aged up to 18 years who were registered with a General Practice which was a part of THIN for at least six months between January 1995 and December 2009. Children entered the cohort when they registered with a General Practice, or, the date when their practice joined the THIN scheme and met standards for acceptable levels of data recording [20]. Children remained in the cohort until aged 18 years, transfer out of the practice, date of death or date of last data collection from the practice.

Measurements

Outcome. We examined entries made of diagnoses and symptoms of depression. Depression diagnosis codes ranged from 'dysthymia' and 'mild depression' to 'recurrent severe major depression', but excluded codes that indicated other mental disorder such as psychosis or anxiety. Depression symptoms relate to codes indicating depression but are not certain enough to be classified as a diagnosis, such as 'symptoms of depression' or 'C\O feeling depressed'. We also examined antidepressants BNF codes prescribed by the general practitioner at any dose, except for high dose TCAs (50 mg) that were indicated for nocturnal enuresis [6]. These code lists have been created and used in previous studies and were developed in line with published methods and reviewed by a general practitioner [21,22].

Potential confounders. We included information on age, gender and social deprivation score in our analysis as these are known to be associated with childhood depression and the distribution of these variables may change over the 15 year study period.

Statistical analysis. We described the baseline socio-demographic characteristics of the cohort using frequency tables. We calculated annual incidence rates and 95% confidence intervals (CI) for depression diagnoses, symptoms and antidepressant prescriptions by dividing the annual number of incident cases by the total person-years at risk (PYAR) for each year.

Incidence rate ratios adjusted for gender, age and quintiles of Townsend deprivation score) were estimated using a Poisson regression model. The analyses were adjusted for clustering at practice level.

A Lewis plot [23] was used to explore the association between time since registration and incidence rates as prior diagnoses might be registered at or near the time of registration and these ought not to be included in the incidence rates. The Lewis plots revealed that there was an increased rate of depression diagnoses, symptoms and antidepressant prescribing in the first month after registration, after which the rate of recording dropped to a steady state (results not shown). To correct for this, we started follow = up one month after registration.

In order to assess the effects of the CSM advice on antidepressant prescribing, a segmented regression analysis [24] was performed using the Jointpoint regression program (version 3.5.1) from the Surveillance Research Program of the US National Cancer Institute [25]. Jointpoint is statistical software for the analysis of trends using Jointpoint models [26]. This analysis allows for identifying points where there is a change in the linear slope of the trend. The analysis started with the minimum number of jointpoints (i.e., 0 jointpoints, which is a straight line), and tested whether one or more jointpoints (up to 4) were statistically significant and should be added to the model. The models incorporated estimated variation for each point by using the standard error of the rate estimate. After identifying the existence of a change in the trend, a segmented regression was fitted and the result of the best model was shown graphically. Finally, the estimated annual percentage of change (APC) and its corresponding 95% CI was computed for each of those trends by fitting a regression line to the natural logarithm of the rates, using calendar year as a regression variable [27].

All other analyses were conducted in of Stata, version 11.2 (Stata Corp, College Station, Texas).

Results

In total, 1,502,753 children up to the age of 18 were registered with their GP for at least one year in The Health Improvement Network (THIN) UK primary care database. Of these children, 45,723 (3%) children had at least one entry of a depressive symptom, diagnosis or antidepressant prescription. Of these children, 17,124 (38%) had a diagnosis of depression, 22,587 (49%) had a record of depressive symptoms, and 25,473 (56%) were prescribed antidepressants, 16,925 of which were SSRIs (Figure 1). Most of these antidepressant prescriptions were for

SSRIs: 16,925 (66%), with TCAs representing 7,777 (31%) and other antidepressants 771 (3%) of prescriptions (Table 1). Of the children receiving SSRIs, 4,339 (26%) were not diagnosed with depression or depression symptoms. Similarly, 7,211 (42%) of children diagnosed with depression were not prescribed antidepressants.

Rates for entries of diagnoses of depression increased from 2.2 (95% CI 1.9–2.5) per 1,000 PYAR in 1995 to 3.0 (95%CI:2.8,3.1) per 1,000 PYAR in 2002, then dropped to 2.0 (95%CI:1.9,2.1) per 1,000 PYAR in 2005 and have since been relatively constant at around 2.0 per 1,000 PYAR (Figure 2). Rates for antidepressant prescribing show a similar pattern: they have gone up from 2.8 (95%CI:2.4,3.1) per 1,000 PYAR in 1995 to 4.5 (95%CI:4.3,4.6) per 1,000 PYAR in 2002, then dropped to rates similar to the initial 1995 rates, but have been increasing again since 2005. Recording of symptoms has seen a dramatic rise from 1.0 (95%CI:0.8,1.2) in 1995 to 4.7 (95%CI:4.5,4.8) per 1,000 PYAR in 2009.

TCAs were the most common antidepressant prescribed to children in 1995, but by 1999 SSRIs had overtaken them and have been the preferred drug type ever since (Figure 3). However, since 2003 there has been a sharp decline in SSRI prescriptions, with rates decreasing from 3.2 (95%CI:3.0,3.3) per 1,000 PYAR in 2002 to 1.7 (95%CI:1.7,1.8) per 1,000 PYAR in 2005. Since then, rates have gradually started increasing again. TCA prescription rates have gradually decreased since 1995, but stopped decreasing in 2006. Rates for MAOIs and other antidepressants were negligible (results not shown).

In children aged 3–11 years, girls were less likely than boys to be diagnosed as depressed (IRR = 0.79, 95%CI:0.67,0.92), have depression symptoms recorded (IRR = 0.90, 95%CI:0.84,0.95) or be prescribed antidepressants (IRR = 0.63, 95%CI:0.58,0.69; Table 2). In children aged 12–18, girls were more likely than boys to have been diagnosed as depressed (IRR = 2.87, 95%CI:2.77,2.97), have symptoms recorded (IRR = 2.31, 95%CI:2.23,2.39) or have been prescribed antidepressants (IRR = 2.71, 95%CI:2.63,2.80). When comparing age groups, the incidence of all three outcomes in the younger age group (3–11 years old) is only a fraction of that in the older age group (12–18 years old).

Rates for all depression indicators increased with deprivation: children and adolescents in the most deprived quintile were twice as likely to be diagnosed as depressed (IRR = 2.14, 95%CI:2.03.2.26) or be prescribed antidepressants (IRR = 1.91, 95%CI:1.82,2.00) compared to children and adolescent in the least deprived quintile. For depression symptoms, there was an almost 50% increase of recording in the most deprived compared to the most affluent children and adolescents (IRR = 1.43, 95%CI:1.36,1.50).

Segmented regression analysis

The Jointpoint analysis suggested for SSRIs as a group, there were two time points were prescription rates changed: 2002 and 2005. Up to 2002 prescription rates for SSRIs had been significantly increasing nearly 16% from 1995–2002 (Table 3, Figures 4A & 4B). However, between 2002 and 2005 the rates were stagnant, followed by a significant increase of nearly 11% from 2005 to 2009 (Table 3).

Individual SSRIs followed a similar pattern: fluoxetine, citalopram, paroxetine and sertraline rates all were increasing from 1995 to the early 2000s before showing a temporary decrease, or stall, in prescription rates. Paroxetine was the only SSRI which showed a statistically significant decrease in prescription rates. Rates for citalopram and sertraline started increasing again in 2005, while rates for fluoxetine and paroxetine remained stable (Table 3).

In contrast, rates for TCAs as a group showed a significant decrease between 1995 and 2006, after which there was no significant change. Rates for amitriptyline prescriptions showed a moderate decrease between 1995 and 2006, but started to increase after this point. Imipramine prescription rates showed a steady decline over the entire period.

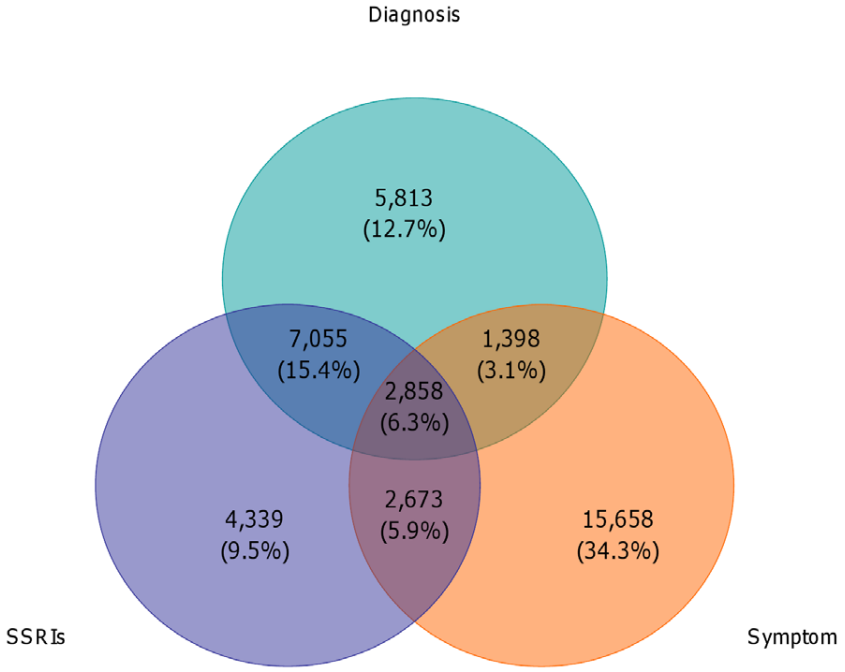

Figure 1. Venn diagram which shows the intersection between depression diagnoses, symptoms and antidepressant prescriptions.
doi:10.1371/journal.pone.0033181.g001

Table 1. Study population characteristics by antidepressant (AD).

Characteristic of first-time new users	Individuals by AD drug group				
	SSRI (n = 16925)	TCA (n = 7777)	Other (n = 769)	MAOI (n = 2)	Any AD (n = 25473)
Socio-demographic					
Girls	12142 (71.7)	4680 (60.2)	488 (63.5)	1 (50.0)	17311 (68.0)
Most commonly prescribed drug (# prescriptions)	Fluoxetine (8157)	Amitriptyline (4402)	Mirtazapine (320)	Moclobemide (2)	-
Deprivation quintile					
1 (most affluent)	3252 (19.2)	1631 (21.0)	144 (18.7)	1 (50.0)	5028 (19.7)
2	3063 (18.1)	1451 (18.7)	105 (13.7)	0	4619 (18.1)
3	3456 (20.4)	1646 (21.2)	139 (18.1)	0	5241 (20.6)
4	3732 (22.1)	1706 (21.9)	182 (23.7)	0	5620 (22.1)
5 (most deprived)	3195 (18.9)	1259 (16.2)	191 (24.8)	1 (50.0)	4646 (18.2)
Not recorded	227 (1.3)	84 (1.1)	8 (1.0)	0	319 (1.3)
Age groups					
3–10 years	179 (1.1)	1577 (20.3)	7 (0.9)	0 (0)	1764 (6.9)
11–14 years	1567 (9.3)	1558 (20.0)	53 (6.9)	1 (50.0)	3192 (19.4)
15–18 years	15179 (89.7)	4642 (59.7)	709 (92.2)	1 (50.0)	20652 (80.7)

Values are numbers (column percentages) unless otherwise indicated.
SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; MAOI = mono-amine oxidase inhibitor; other ADs are: mirtazapine, venlafaxine, flupentixol, duloxetine, nefazodone and reboxetine.
doi:10.1371/journal.pone.0033181.t001

Discussion

Key Findings

To our knowledge, this is the first large paediatric database study to compare depression diagnoses, symptoms and antidepressant prescriptions and the effects the CSM advice over a longer time period in the UK. We have found that prescription rates of SSRIs as a group decreased from 3.2 per 1,000 person-years in 2002 to 1.7 per 1,000 person-years in 2005. More specifically, rates for contra-indicated SSRIs, i.e. citalopram,

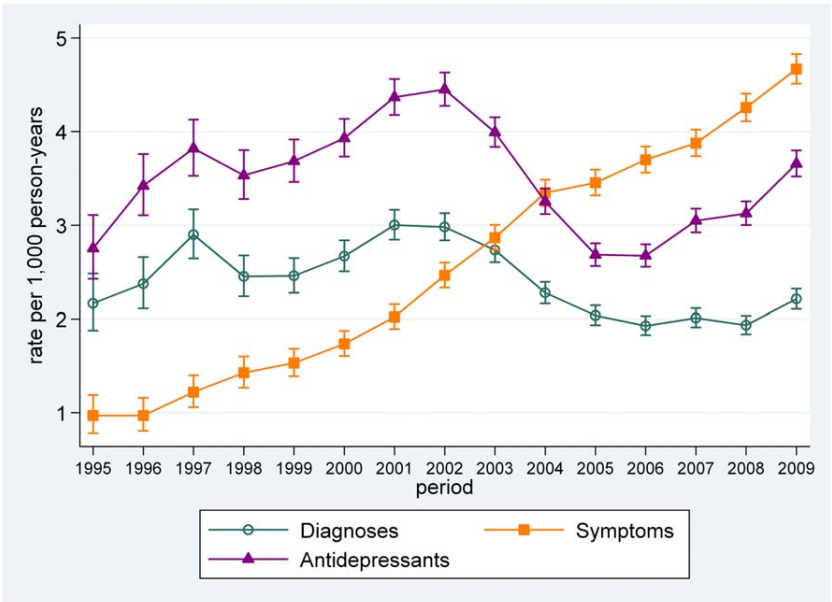

Figure 2. Trends in the incidence of childhood depression, symptoms and antidepressants from 1995 to 2009.
doi:10.1371/journal.pone.0033181.g002

Figure 3. Rates of prescription of Tricyclic Antidepressants (TCA) and Selective Serotonin Reuptake Inhibitors (SSRI) in children.
doi:10.1371/journal.pone.0033181.g003

paroxetine and sertraline, went down during that period, while rates for fluoxetine remained stable and rates for TCAs were not affected. The decline in prescription rates was sharpest for paroxetine. Similar to SSRI prescription rates, rates for depression diagnoses entries decreased from 3.0 per 1,000 person-years in 2002 to 2.0 per 1,000 person years in 2005. Depression symptom recording saw a steady increase over the study period, increasing from 1.0 per 1,000 person-years in 1995 to 4.7 per 1,000 person-years in 2009. Finally, rates for SSRIs as group and citalopram in particular, were increasing after 2005.

The decrease in recording of both depression diagnoses and antidepressant prescriptions after 2002 could indicate caution on the part of GPs in diagnosing depression and prescribing antidepressants following the CSM advice. Moreover, GPs might prefer to record depression symptoms rather than diagnose a child as depressed. The decrease in contra-indicated SSRIs as opposed

Table 2. Incidence rate ratios (IRR) for diagnosis and symptoms of depression and antidepressant prescriptions stratified by gender, age group and deprivation.

	Multivariable[a]: stratified by age group: 3–11		Multivariable[a]: stratified by age group: 12–18		Multivariable[a]: stratified by deprivation: Townsend 1 & 2[c]		Multivariable[a]: stratified by deprivation: Townsend 4 & 5[c]	
	IRR (95% CI)	*P*[b]	IRR (95% CI)	*P*[b]	IRR (95% CI)	*P*[b]	IRR (95% CI)	*P*[b]
Diagnosed depression								
Gender								
Boy	Reference		Reference		Reference		Reference	
Girl	0.79 (0.67–0.92)	0.003	2.87 (2.77–2.97)	<0.001	2.58 (2.44–2.73)	<0.001	2.93 (2.78–3.09)	<0.001
Symptoms of depression								
Gender								
Boy	Reference		Reference		Reference		Reference	
Girl	0.90 (0.84–0.95)	0.001	2.31 (2.23–2.39)	<0.001	1.75 (1.67–1.83)	<0.001	2.12 (2.02–2.22)	<0.001
Antidepressant prescription								
Gender								
Boy	Reference		Reference		Reference		Reference	
Girl	0.63 (0.58–0.69)	<0.001	2.71 (2.63–2.80)	<0.001	2.26 (2.16–2.36)	<0.001	2.57 (2.47–2.69)	<0.001

[a]Adjusted for calendar year, gender, deprivation, age and for clustering by general practitioner practice using robust standard errors.
[b]*P* based on Wald test.
[c]A Townsend score of 1 or 2 represents the most affluent patients, while patients with a Townsend score of 4 or 5 live in the most deprived areas.
doi:10.1371/journal.pone.0033181.t002

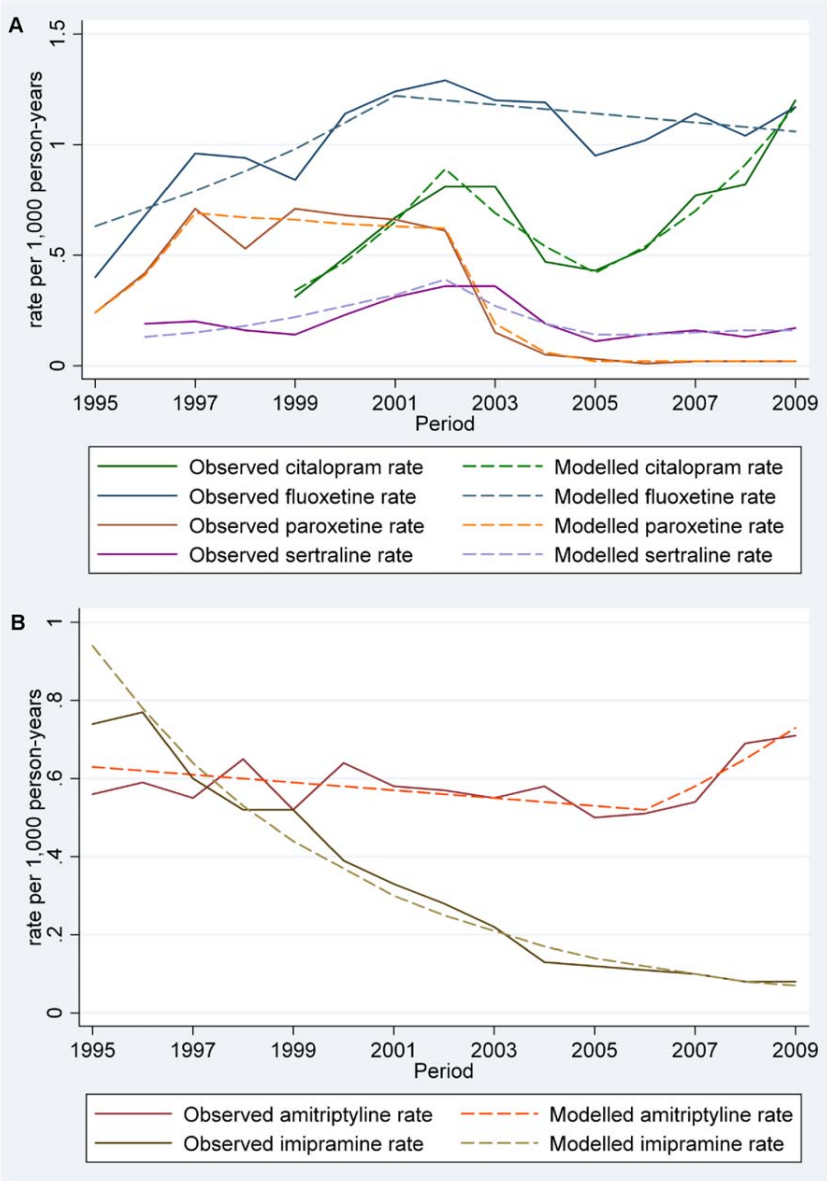

Figure 4. Observed and modelled prescription rates for individual (A) Selective Serotonin Reuptake Inhibitors (SSRIs) and (B) Tricyclic Antidepressants (TCAs).
doi:10.1371/journal.pone.0033181.g004

to fluoxetine strengthens the possibility of a link with the CSM advice.

Although the Jointpoint program points to 2002 as the time point where SSRI rates changed, the observed data shows that rates did not decrease until after 2003, the year when the CSM advice was issued. However, prescription rates could have started decreasing prior to the CSM advice as information regarding the safety and effectiveness of SSRIs was circulating in the specialist community before the advice was issued and could have influenced changes in prescription recommendations. Similarly, the program does not qualify the small dip in fluoxetine rates around 2005 as statistically significant. This dip might be related to the requirement of the US Food and Drug Administration (FDA) to add a black box warning to all antidepressants, including fluoxetine and TCAs, about an increased risk of suicidal behaviour in 2004 [12].

The sharp decline in paroxetine prescription rates could be related to the advice by the MHRA against the prescribing of paroxetine specifically. This advice was issued in June 2003, preceding the overall SSRI advice in December of the same year. It followed a review of randomised controlled trials that showed higher rates of suicidal thought and behaviour (but not completed suicides) in patient who took paroxetine (25 out of 738; 3%), compared to those who took placebo (8 out of 647; 1%; p for difference = 0.01) [8].

The BBC programme that initially started the controversy implied that paroxetine (brand name Seroxat) was addictive, had severe withdrawal symptoms and could increase the risk of suicidal behaviour [28]. This might have led to patients being biased against taking paroxetine as a first line of treatment, and making it difficult to determine whether the sharp decline in paroxetine

Table 3. Annual percentage change (APC) for selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) as groups and individual drugs.

	APC 1 (95% CI)	*Period*	*APC 2 (95% CI)*	*Period*	*APC 3 (95% CI)*	*Period*
SSRIs	15.8* (8.5–23.6)	1995–2002	−19.7 (−36.2–1.0)	2002–2005	10.6* (3.1–18.8)	2005–2009
Fluoxetine	11.6 (−0.4–25.1)	1995–2001	−1.8 (−4.8–1.3)			2001–2009
Citalopram[1]	37.7 (−4.7–98.9)	1999–2002	−22.0 (−51.1–45.4)	2002–2005	29.0* (14.4–45.4)	2005–2009
Paroxetine[2]	67.9 (−27.1–286.9)	1995–1997	−2.2 (−12.2–9.1)	1997–2002	−69.1* (−84.2–39.5)	2002–2005
Sertraline[3]	20.5* (6.1–37.0)	1996–2002	−29.4 (−54.2–9.0)	2002–2005	4.3 (−11.3–22.6)	2005–2009
TCAs	−9.5* (−10.3–8.7)			1995–2006	6.5 (1.0–12.2)	2006–2009
Amitriptyline	−1.8 (−3.8–0.3)			1995–2006	11.9* (2.3–22.3)	2006–2009
Imipramine	−17.1* (−18.6–15.6)					2006–2009

*Annual percentage change (APC) is statistically significant ($p<0.05$) different from 0.
[1]Observations start in 1999 for citalopram as prescription rates were negligible (<10 prescriptions a year) before this year.
[2]Observations stop in 2005 for paroxetine as it is only prescribed sporadically (<5 prescriptions a year) after this time point.
[3]Observations start in 1996 for sertraline as prescription rates were negligible (<10 prescriptions a year) before this year.
doi:10.1371/journal.pone.0033181.t003

prescriptions in primary care was due to a negative public opinion of the drug in response to the issues raised in the programme, or the advice issued by the CSM half a year later.

The increase in SSRI prescription rates after 2005 could indicate that concerns about a possible suicidality risk associated with SSRIs have waned. Several studies found no increased risk of suicidality for SSRIs [29,30], or increases in suicide rates that coincided with decreases in SSRI prescription rates [31]. In the US, 2004 saw the largest single-year increase in suicide rates in adolescents aged 10–19 years [32]. From 1990 to 2003 suicide rates had been decreased by 28%, but in 2004 they had increased with 15% from 6.78 to 7.32 per 100,000 people. This might have led GPs to revaluate prescribing SSRIs to children and adolescents, although doubts continue to exist regarding the safety and effectiveness of SSRIs [33,34].

Comparison to other studies

The antidepressant prescription rates we found are similar in size and trend to those found by a General Practice Research Database study which studied prescription rates from 1992 to 2001 [1]. We also found similar age and gender effects. Our results also confirm findings by Murray et al. who found a decrease in SSRI prescribing in between 2003 and 2004, while prescribing rates for fluoxetine remained stable [13]. However, the study by Murray et al. did not assess data for individual drugs, apart from fluoxetine, whereas our study did take different SSRIs into account.

A study based on Australian data also found a decrease in antidepressant use in children, in particular of SSRIs [14]. They also saw a sharp rise of fluoxetine over time, which we did not find in the UK. This might be explained by sertraline being the most commonly prescribed antidepressant in Australia before the SSRI controversy started, whereas fluoxetine was already the drug of first choice in the UK before the CSM advice.

Main Strengths and Limitations

The main strength of this study is its sample size that enables examination of outcomes separately for girls and boys, and by drug. There is no clear reason to believe the results would differ for the entire population of UK children.

However, there are also limitations. In using data from general practices, few children might have been missed out if their depression was not severe enough to warrant a visit to a GP, or if they were diagnosed outside a general practice setting, e.g. by a child psychiatrist. However, a study on depression in adults found that although incidence rates in the THIN database are lower than depression rates found in epidemiological studies, associations with covariates such as gender and deprivation were similar [35]. Also, non-psychiatric physician's recognition of depression has been found to have a limited sensitivity, but a high specificity [36,37]. Childhood depression rates might have been underestimated in this study, but trends and associations with other variables are likely to be representative of the general population. Moreover, as we were specifically interested in the effects of the CSM advice in primary care settings, this limitation will have only a minimal effect on our results.

While data on prescriptions is available in the THIN database, there is no information on dispensing and treatment compliance. Thus the antidepressant prescription rates we found might not reflect antidepressant use. However, we aimed to study prescription rates in primary care, so this does not affect our estimates.

Conclusions

After 2002, general practitioners decreased their prescribing of contra-indicated SSRIs, particularly paroxetine. Rates for fluoxetine, the only SSRI not to be contra-indicated, remained stable. Depression diagnoses mirrored prescription rates and decreased between 2002 and 2005, suggesting caution on the side of GPs. The timing and direction of these trends imply that GPs followed the CSM advice, although it cannot be ruled out that these trends resulted from the negative media attention SSRIs received around the same time. After 2005, rates for all antidepressants, except paroxetine, started recovering. This is in line with results from observational studies that found no increased risk of suicidal behaviour with SSRIs.

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Author Contributions

Conceived and designed the experiments: LPW IN IP. Analyzed the data: LPW. Wrote the paper: LPW IN IP.

References

1. Murray ML, de Vries CS, Wong IC (2004) A drug utilisation study of antidepressants in children and adolescents using the General Practice Research Database. Arch Dis Child 89: 1098–1102.
2. Stark P, Hardison CD (1985) A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder. J Clin Psychiatry 46: 53–58.
3. Hazell P, O'Connell D, Heathcote D, Henry DA (2002) Tricyclic drug for depression in children and adolescents. Cochrane Database Syst Rev10.1002/14651858.CD002317.
4. Keller MB, Ryan ND, Strober M, Klein RG, Kutcher SP, et al. (2001) Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. J Am Acad Child Adolesc Psychiatry 40: 762–772.
5. Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, et al. (2002) Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry 41: 1205–1215.
6. Paediatric Formulary Committee (2010) BNF for Children 2010–2011. London: BMJ Publishing Group, Pharmaceutical Press, and RCPCH Publications. 240 p.
7. Committee on Safety of Medicines (2003) Paroxetine (Seroxat) - variation assessment report - proposal to contraindicate in adolescents and children under 18 years with major depressive disorder.
8. Waechter F (2003) Paroxetine must not be given to patients under 18. BMJ 326: 1282.
9. Healy D (2003) Lines of evidence on the risks of suicide with selective serotonin reuptake inhibitors. Psychother Psychosom 72: 71–79.
10. National Institute for Health and Clinical Excellence (2005) CG28 Depression in children and young people: NICE guideline.
11. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, et al. (2004) Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. Lancet 363: 1341–1345.
12. FDA website Suicidality in Children and Adolescents Being Treated With Antidepressant Medications. Available: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161679.htm. Accessed 2012 Feb 3.
13. Murray ML, Thompson M, Santosh PJ, Wong IC (2005) Effects of the Committee on Safety of Medicines advice on antidepressant prescribing to children and adolescents in the UK. Drug Saf 28: 1151–1157.
14. Dean AJ, Hendy A, McGuire T (2007) Antidepressants in children and adolescents - changes in utilisation after safety warnings. Pharmacoepidemiology and drug safety 16: 1048–1053.
15. Lis Y, Mann RD (1995) The VAMP Research multi-purpose database in the U.K. J Clin Epidemiol 48: 431–443.
16. Bourke A, Dattani H, Robinson M (2004) Feasibility study and methodology to create a quality-evaluated database of primary care data. Inform Prim Care 12: 171–177.
17. Booth N (1994) What are the Read Codes? Health Libr Rev 11: 177–182.
18. Khan NF, Harrison SE, Rose PW (2010) Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract 60: e128–e136.
19. Townsend P, Phillimore P, Beattie A (1988) The construction of a measure of deprivation. In: Health and Deprivation: Inequality and the North. London: Routledge. pp 34–38.
20. Maguire A, Blak BT, Thompson M (2009) The importance of defining periods of complete mortality reporting for research using automated data from primary care. Pharmacoepidemiol Drug Saf 18: 76–83.
21. Davé S, Petersen I (2009) Creating medical and drug code lists to identify cases in primary care databases. Pharmacoepidemiology and drug safety 18: 704–707.
22. Davé S, Petersen I, Sherr L, Nazareth I (2010) Incidence of Maternal and Paternal Depression in Primary Care: A Cohort Study Using a Primary Care Database. Arch Pediatr Adolesc Med 164: 1038–1044.
23. Lewis JD, Bilker WB, Weinstein RB, Strom BL (2005) The relationship between time since registration and measured incidence rates in the General Practice Research Database. Pharmacoepidemiol Drug Saf 14: 443–451.
24. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D (2002) Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 27: 299–309.
25. National Cancer Institute (2011) Jointpoint regression program, version 3.5.1.
26. Kim HJ, Fay MP, Feuer EJ, Midthune DN (2000) Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 19: 335–351.
27. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK (2009) Estimating average annual per cent change in trend analysis. Stat Med 28: 3670–3682.
28. Cowen PJ (2002) TV: Panorama: "The Secrets of Seroxat". BMJ.
29. Jick H, Kaye JA, Jick SS (2004) Antidepressants and the risk of suicidal behaviors. JAMA 292: 338–343.
30. Didham RC, McConnell DW, Blair HJ, Reith DM (2005) Suicide and self-harm following prescription of SSRIs and other antidepressants: confounding by indication. Br J Clin Pharmacol 60: 519–525.
31. Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, et al. (2007) Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 164: 1356–1363.
32. Lubell KM, Kegler SR, Crosby AE, Karch D. Suicide (2007) Trends Among Youths and Young Adults Aged 10–24 Years, United States, 1990–2004. MMWR 56(35): 905–908.
33. Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, et al. (2007) Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 297(15): 1683–1696.
34. Hammad TA, Laughren T, Racoosin J (2006) Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 63(3): 332–339.
35. Rait G, Walters K, Griffin M, Buszewicz M, Petersen I, et al. (2009) Recent trends in the incidence of recorded depression in primary care. Br J Psychiatry 195: 520–524.
36. Cepoiu M, McCusker J, Cole MG, Sewitch M, Belzile E, et al. (2008) Recognition of depression by non-psychiatric physicians–a systematic literature review and meta-analysis. J Gen Intern Med 23: 25–36.
37. Kamphuis MH, Stegenga BT, Zuithoff NP, King M, Nazareth I, et al. (2011) Recognition of depression in primary care: does it affect outcome? The PREDICT-NL study. Fam Pract.

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Suicide-related events in young people following prescription of SSRIs and other antidepressants: a self-controlled case series analysis

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ABSTRACT

Objectives: We aimed to examine the temporal association between selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressant (TCA) prescriptions and suicide-related events in children and adolescents.

Design: Self-controlled case series.

Setting: Electronic health records were used from 479 general practices in The Health Improvement Network (THIN) UK primary care database from 1995 to 2009.

Participants: 81 young people aged 10–18 years with a record of completed suicide, 1496 who attempted suicide, 1178 with suicidal ideation and 2361 with intentional self-harm.

Main outcome measures: Incidence Rate Ratios (IRRs) for completed and attempted suicide, suicidal ideation and intentional self-harm.

Results: For non-fatal suicide-related behaviour, IRRs were similar for the time the person was prescribed either SSRIs or TCAs: IRRs increased during pre-exposure, peaked on prescription day, were stable up to the fourth prescription-week, and decreased after the prescriptions were stopped. For both types of antidepressants, IRRs were lower or similar to pre-exposure levels during the period of prescription. For SSRIs, there was an increase in the IRR for completed suicide on the day of prescription (N=5; IRR=42.5, 95% CI 4.5 to 403.4), and during the fourth week of SSRI prescription (N=2; IRR=11.3, 95% CI 1.1 to 115.6).

Conclusions: We found that a very small number of young people were prescribed antidepressants and that there was an absence of a sustained increase in rates of suicide-related events in this group. There were no systematic differences between the association of TCAs and SSRIs and the incidence risk ratios for attempted suicide, suicidal ideation or intentional self-harm and, apart from the day of prescription, rates did not exceed pre-exposure levels. The pattern of IRR for suicide for SSRIs was similar to that found in non-fatal suicide-related events. Our results warrant a re-evaluation of the current prescription of SSRIs in young people. We recommend the creation of a pragmatic registry for active pharmacovigilance.

ARTICLE SUMMARY

Strengths and limitations of this study

- Only a limited number of young people had a prescription for an antidepressant in the year before their suicide-related event, making it difficult to interpret the findings of this study.
- The self-controlled case series method inherently controls for time-independent variables such as genetics, location and socio-economic status.
- Changes in depression severity are poorly recorded over time, which is a limitation.

INTRODUCTION

Between 1% and 6% of adolescents in the community suffer from major depressive disorder (MDD).[1] In addition, suicide is the third leading cause of death in 15-year-olds to –19-year-olds at 6.9/100 000 population, and the fourth in 10-year-olds to 14-year-olds at 0.9/100 000 population.[2] This calls for safe and effective depression treatments in this age group. As tricyclic antidepressants (TCAs) lack efficacy for depression treatment in this age group and have a poor side-effect profile,[3] selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed pharmacological treatment for children and adolescents.[4]

However, there has been concern that SSRIs might be associated with an increased risk of suicide-related events in paediatric patients. Results from clinical trials led the Expert Working Group of the Committee on Safety of Medicines (CSM) to advise against initiation of treatment with selective serotonin inhibitors (SSRIs) for childhood depression in the UK in December 2003.[5] Fluoxetine, the only drug which is licensed to treat depression in young people in the UK, was exempted from this advice following a review that concluded that there was a

favourable balance of benefits and risk.[6] The US Food and Drug Administration (FDA) issued similar advice in 2004.[7]

There is inconsistent evidence of an increased rate of suicide-related events and intentional self-harm associated with SSRIs.[8] Data from randomised controlled trials in adolescents and young adults report an increased risk of suicide-related events.[9] Part of this difference appears to depend on the methodology used. If suicide-related events were ascertained using the method of 'adverse events', there was a small but significant increase in suicidal ideation. However, if the studies used rating scales to assess suicide-related events, most studies showed an improvement in suicide-related events.

The results from these trials should be interpreted with caution, as they were not primarily designed to measure suicide-related events and it would be unethical to do so using placebo as a control.[10 11] Moreover, none of these trials on SSRIs recruited from a general population setting and completed suicides have occurred in any studies.[9]

Observational studies in young people have found mixed results: some indicate that SSRIs protect from suicide-related events[12]; others find no effect[13 14] or an increase in risk of suicide-related events.[15 16] These studies, however, have methodological limitations including small numbers, high attrition rates and, most importantly, confounding by severity.

We have previously shown that rates for SSRI prescriptions in children and adolescents increased between 2005 and 2009.[4] Neither TCAs nor SSRIs are considered appropriate first-line treatment by the National Institute for Clinical Excellence (NICE) for depression in children and adolescents. Given the risk of death in overdose, the lack of efficacy in children and the side effects associated with them, a prescriber would be less likely to prescribe TCAs in preference to SSRIs for a person at risk of suicide-related events.[17]

It is only when children and adolescents do not respond to psychological treatment that treatment with SSRIs should be considered.[6] It is therefore important to reassess the risks of existing clinical data to inform future practice. We aimed to assess the temporal association between the risk of completed suicide, attempted suicide, suicidal thoughts, intentional self-harm and antidepressant prescription in adolescents, comparing SSRIs and TCAs and correcting for age and gender, using a large UK primary care database.

METHODS

Data source

We used data from The Health Improvement Network (THIN) primary care database, including information from UK primary care data prospectively recorded between 1 January 1995 and 31 December 2009. THIN includes anonymised general practice records on more than 9 million patients from 479 practices in the UK and is one of the largest primary care databases available internationally. It is broadly representative of the UK general practice population in terms of demographics and consultation behaviour.[18] Data on diagnoses, interventions, symptoms and referrals to secondary care are electronically recorded as Read codes, a hierarchical coding system used in UK primary care.[19] All prescriptions are also electronically recorded. Clinical diagnoses recorded using Read codes have recently been shown to be accurate compared with other reliable sources.[20]

Study population

This study included a cohort of young people and adolescents, aged 10–18 years, who had a record of a suicide-related event. Patients were included if they were registered with a practice for at least 6 months between January 1995 and December 2009. Patients were followed up from the latest date they registered at the general practitioner (GP), 1 January 1995, or their 10th birthday, until (1) 31 December 2009, (2) their 19th birthday, (3) the date of death or (4) the date they left the practice.

Measurements

Outcome

We identified completed suicides using relevant Read codes that were confirmed by a date of death within 2 weeks of the suicide event date. We searched a cause of death, if available. The list of codes was an updated version of a published suicide code list.[21] To make sure that we did not miss any suicides, we extracted medical records on all young people who died between the ages of 10 and 18 and examined the free text if there was no clear cause of death (eg, childhood cancer or a traffic accident) for possible suicides. We excluded cases where there was doubt whether the death was due to suicide (ie, 12 deaths which received an open verdict by the coroner). Of these potential suicides, one patient had records of TCA prescriptions, whereas four had records of SSRI prescriptions in the last year. A suicide attempt, suicidal ideation and self-harm were identified using a Read code list that was developed in line with the published methods and reviewed by a GP (IN).[22]

Exposure

We used British National Formulary (BNF) codes representing antidepressants.[23] We classified antidepressants as TCAs, SSRIs and other antidepressants according to BNF. We excluded TCAs that were prescribed for nocturnal enuresis or neuropathic pain. Comparing prescription data in THIN to dispensing data from NHS Prescription Services showed that the mean practice redemption rate (the percentage of recorded prescriptions which were dispensed) was as high as 96.7% for antidepressants.[24]

We then identified the separate episodes of antidepressant prescription for each individual. To

constitute a new episode of antidepressant prescriptions, there had to be a preceding gap of at least 3 months of no prescriptions. We choose 3 months as a prescription supply of antidepressants is typically 1 month or less, and therefore a gap of at least 3 months between prescriptions would quite likely represent a new episode of antidepressant prescriptions (although not necessarily a new episode of depression). If a person switched from one drug to another within 3 months, this would not constitute a new episode.

Covariates

We extracted information on gender, age and social deprivation score (Townsend quintiles). Patients who were prescribed TCAs for nocturnal enuresis (as confirmed by Read codes) were excluded. Finally, we considered consultation behaviour as a confounder. Patients who consult infrequently with their GP, for example, only when their prescription has run out, might not have correctly timed records of all their events. To correct for this, we conducted a sensitivity analysis where we only included patients who consulted at least once a week during the month after their first antidepressant prescription.

Statistical analysis

The self-controlled case series (SCCS) method

We calculated incidence rate ratios (IRRs—calculated by dividing the incidence rate in the exposed period by the incidence rate in the control period) for completed suicide and suicide-related events using the self-controlled case series (SCCS) method.[25] The SCCS method was developed to investigate associations between acute outcomes and transient exposures, using only data on cases. Since each case served as his/her own control, the case–series method inherently accounts for confounding factors that do not change over the observation period (such as variables related to genetics, socioeconomic status and gender). Using a Poisson model, IRRs can be calculated for any number of predefined risk periods associated with the exposure, using the time outside of these risk periods (the time when a subject is unexposed) as a reference. A major advantage of SCCS is that it can have high efficiency relative to the retrospective cohort method from which it is derived. As suicide-related events are rare, even in depressed persons, the SCCS method is particularly suited for assessing its association with antidepressants, as it requires a much smaller number of persons to be included. Moreover, in using a self-controlled design, we circumvent the problem of selecting appropriate controls that cohort or case-control designs encounter. In the case of suicide-related events and antidepressants, this has proven crucial as patients who are diagnosed as depressed but do not receive antidepressants might differ from patients who are receiving antidepressants in severity of depression, a major confounder in the association studied.

The SCCS method is limited in that it only works for non-recurrent events when the event risk is small over the observation period, which is the case for completed suicide. Also, it requires variability in the age at the time of the event: if all events were to happen at exactly the same age (which is not the case in our study), then the method would fail. Finally, the method only produces estimates of relative incidence, rather than absolute incidence.

Suicide attempts, suicidal ideation and self-harm

For the analyses on suicide attempts, suicidal ideation and self-harm, we used an adapted version of the standard SCCS method, allowing for repeated exposures and events and correcting by 1 year age groups.[25 26] By including a pre-exposure period, we corrected our estimates for event-dependent exposure. If the probability of exposure to antidepressants is changed from baseline after an event, it follows that the probability of the occurrence of an event is also changed in the immediate pre-exposure period. Including a pre-exposure period removes this time from the baseline and corrects the estimates accordingly.

Participants who went on to commit suicide were excluded from these analyses. Using the SCCS method, the IRR for the three outcomes was estimated during 14 different risk periods (figure 1): baseline (or unexposed to antidepressants); four 1-month pre-exposure periods, the last of which is the reference; the day of prescription; four 1-week early exposure periods; a period of variable length to cover the remainder of the period of exposure to the antidepressant for that episode; and three 1-month periods of washout after the end of the antidepressant episode. We included separate 1-week periods at the start of the prescription as it is known that antidepressants (especially SSRIs) take this amount of time to have an effect.[27] We also compared the effects of individual antidepressants on the IRR of the three suicide-related event outcomes.

Suicide

We used an adapted method (SCCS for censored post-event exposures) to assess the effects of antidepressants on childhood suicide as the original approach cannot deal with deaths.[28] This method takes account of the early cessation of the observation period due to deaths and accordingly corrects the IRR estimates. We corrected for age by creating four age groups: 10–12, 13–14, 15–16 and 17–18-year-olds. We estimated IRRs for the same risk periods as for the other outcomes, without the four pre-exposure risk periods, and used the baseline (time unexposed to antidepressants) as a reference.

All analyses were conducted with the use of Stata software, V.12.1 (Stata Corp, College Station, Texas). The scheme for THIN to obtain and provide anonymous patient data to researchers was approved by the National Health Service South-East Multicenter Research Ethics Committee (MREC) in 2002 and scientific approval for this study was obtained from CMD Medical Research's Scientific Review Committee in May 2011.

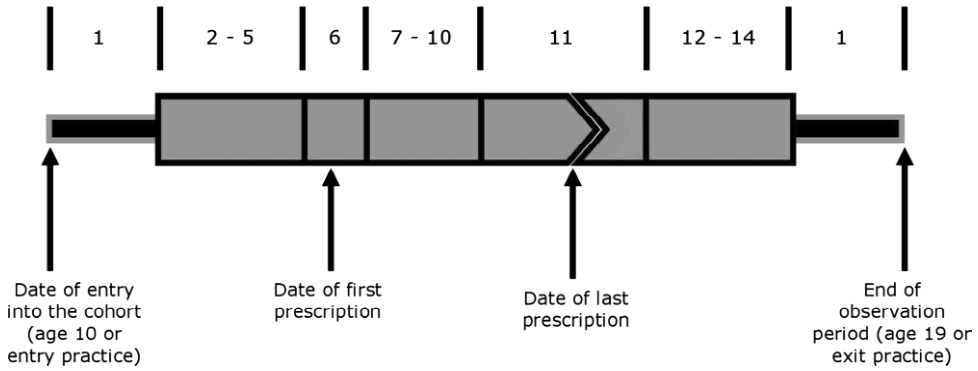

Figure 1 Risk periods included in self-controlled case series analysis for attempted suicide, suicidal ideation and self-harm and suicide. 1=baseline; 2–5=1 month pre-exposure periods; 6=prescription day; 7–10=four 1 week exposure periods; 11=remainder of antidepressant exposure; 12–14=three 1-month washout periods.

RESULTS

There was a total follow-up time of 4 190 410 person-years of 10-year-olds to 18-year-olds in THIN. In total, 81 young people were identified with a record of a completed suicide, 1496 young people with a record of attempted suicide, 1178 young people with a record of suicidal ideation, and 2361 with a record of intentional self-harm. Of the young people with completed suicides, 30% were women, compared to 60%, 73% and 74% of young people with a record of attempted suicide, suicidal ideation or self-harm, respectively (table 1). There was no significant difference in age of first event between the different outcomes. The data were complete for all variables except Townsend scores, which were missing for 92 (2%) persons. Owing to the small numbers, we were not able to analyse antidepressants other than SSRIs or TCAs.

Attempted suicide, suicidal ideation and self-harm

For attempted suicide, suicidal ideation and self-harm, there were similar patterns between young people who were prescribed SSRIs and TCAs (table 2 and figure 2A–C): there was an upward trend in IRR during pre-exposure; a peak on the day of prescription; a stable or slightly increased rate ratio during the first weeks of prescription; and during the washout period, the levels decreased again. The increase on prescription day was highest for young people with a record of suicidal ideation (SSRIs: IRR=33.4, 95% CI 23.6 to 47.4; TCAs: IRR=14.0, 95% CI 6.8 to 28.8). There were no significant differences between IRRs for any of the event types for any risk periods. Patterns were similar between individual SSRIs (fluoxetine, citalopram, sertraline and paroxetine, results in the appendix).

The IRR for each type of event has a strong relation with age. When compared to 15-year-olds to 16-year-olds, 17-year-olds to 18-year-olds are twice as likely to attempt suicide (IRR=1.90, 95% CI 1.6 to 2.3 and IRR=2.1, 95% CI 1.7 to 2.5 for SSRIs and TCAs, respectively), but those between 10 and 12 years old are less likely to attempt suicide (IRR=0.3, 95% CI 0.2 to 0.4 and IRR=0.2, 95% CI 0.1 to 0.2 for SSRIs and TCAs, respectively). Patterns were similar for the other outcomes.

Table 1 Demographics by category of suicidal or self-harming behaviour

	Completed suicide 81	Attempted suicide 1496	Suicidal ideation 1178	Self-harm 2361	General population 952 892
Girls (%)	24 (29.6)	1089 (72.8)	708 (60.1)	1752 (74.2)	461 610 (48.4)
Number of taking ADs (%)	19 (23.1)	527 (36.6)	578 (52.8)	128 (5.7)	27 632 (2.9)
Number of depressed (%)	21 (25.9)	728 (48.7)	819 (69.5)	173 (7.3)	41 101 (4.3)
Number of Townsend score (%)					
1 (most affluent)	20 (24.7)	266 (17.8)	193 (16.4)	442 (18.7)	227 178 (23.8)
2	5 (6.2)	240 (16.0)	202 (17.2)	405 (17.2)	198 686 (20.9)
3	13 (16.1)	286 (19.1)	236 (20.0)	452 (19.1)	184 934 (19.4)
4	25 (30.9)	364 (24.3)	283 (24.0)	571 (24.2)	169 792 (17.8)
5 (most deprived)	16 (19.8)	316 (21.1)	241 (20.5)	446 (18.9)	120 116 (12.6)
Median age in years at (first) event (5–95%)	16.8 (12.0–18.8)	16.5 (12.9–18.7)	16.7 (12.0–18.7)	15.9 (12.6–18.7)	–
Median time in study in years (5–95%)	3.5 (0.2–8.4)	5.5 (1.4–9.0)	5.9 (1.5–9.0)	5.9 (1.5–9.0)	–

Table 2 Incidence rate ratios (IRRs) for different types of suicidal or self-harming behaviour by risk period and antidepressant type: selective serotonin reuptake inhibitors (SSRIs) and tricyclic anti-depressants (TCAs)

	SSRIs			TCAs		
	Suicide attempt *423 events**	Suicidal ideation *458 events**	Self-harm *654 events**	Suicide attempt *79 events**	Suicidal ideation *81 events**	Self-harm *118 events**
Risk period	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**	**IRR (95% CI)**
Unexposed	0.09 (0.07 to 0.13)	0.07 (0.05 to 0.10)	0.12 (0.09 to 0.17)	0.20 (0.09 to 0.46)	0.09 (0.05 to 0.18)	0.15 (0.08 to 0.30)
Pre-exposure 1 (–4 months)	0.19 (0.10 to 0.38)	0.29 (0.15 to 0.54)	0.37 (0.22 to 0.61)	0.61 (0.18 to 2.10)	0.15 (0.03 to 0.68)	0.29 (0.08 to 1.03)
Pre-exposure 2 (–3 months)	0.31 (0.17 to 0.53)	0.45 (0.26 to 0.77)	0.59 (0.38 to 0.90)	0.29 (0.06 to 1.39)	0.30 (0.10 to 0.90)	0.09 (0.01 to 0.71)
Pre-exposure 3 (–2 months)	0.62 (0.40 to 0.96)	0.76 (0.48 to 1.19)	0.65 (0.43 to 0.98)	0.14 (0.02 to 1.16)	0.21 (0.06 to 0.74)	0.46 (0.16 to 1.33)
Pre-exposure 4 (–1 month)	Reference	Reference	Reference	Reference	Reference	Reference
Prescription day	4.17 (2.44 to 7.12)	33.41 (23.56 to 47.39)	11.48 (7.93 to 16.62)	8.82 (2.79 to 27.82)	14.00 (6.81 to 28.75)	3.47 (0.97 to 12.45)
Week 1	0.79 (0.40 to 1.55)	0.38 (0.13 to 1.05)	0.69 (0.35 to 1.35)	1.18 (0.24 to 5.68)	0.59 (0.13 to 2.59)	0.77 (0.17 to 3.50)
Week 2	0.74 (0.39 to 1.42)	0.57 (0.26 to 1.27)	0.96 (0.55 to 1.68)	1.02 (0.21 to 4.91)	0.25 (0.03 to 1.91)	0.33 (0.04 to 2.57)
Week 3	1.07 (0.61 to 1.86)	1.56 (0.91 to 2.68)	1.33 (0.82 to 2.19)	0.53 (0.06 to 4.29)	1.03 (0.34 to 3.13)	1.01 (0.28 to 3.61)
Week 4	0.52 (0.24 to 1.15)	0.98 (0.51 to 1.91)	1.23 (0.73 to 2.07)	0.57 (0.07 to 4.67)	0.84 (0.24 to 2.94)	0.37 (0.05 to 2.90)
Rest of AD episode	0.53 (0.36 to 0.78)	0.72 (0.49 to 1.08)	0.64 (0.45 to 0.90)	0.38 (0.11 to 1.33)	0.52 (0.20 to 1.35)	0.48 (0.18 to 1.25)
Washout 1 (+1 month)	0.42 (0.25 to 0.69)	0.40 (0.23 to 0.70)	0.28 (0.16 to 0.48)	0.66 (0.21 to 2.09)	0.43 (0.16 to 1.11)	0.09 (0.01 to 0.69)
Washout 2 (+2 months)	0.17 (0.09 to 0.35)	0.12 (0.06 to 0.29)	0.32 (0.19 to 0.55)	0.28 (0.06 to 1.33)	0.27 (0.09 to 0.83)	0.43 (0.15 to 1.25)
Washout 3 (+3 months)	0.15 (0.09 to 0.25)	0.20 (0.12 to 0.33)	0.19 (0.12 to 0.31)	0.41 (0.16 to 1.03)	0.13 (0.06 to 0.27)	0.35 (0.17 to 0.73)

*Number of events in young people taking antidepressants. AD, antidepressant.

There were no statistically-significant differences between boys and girls for either SSRIs or TCAs (results not shown). A small group of 25 patients had a prescription for an antidepressant and a primary diagnosis other than depression (obsessive compulsive disorder (OCD) or anxiety). Owing to the small size of this group, we did not perform a subgroup analysis. Finally, restricting the analyses to regular consulters (those who consulted at least five times during the first 4 weeks of prescription) did not alter the effect estimates. Of the young people with a record of attempted suicide or intentional self-harm, 33% were regular consulters, compared to 49% of young people with a record of suicidal ideation.

Suicide

Using an expected suicide rate of 3.28 (95% CI 3.12 to 3.43) per 100 000 person-years in the UK population of 10-year-olds to 18-year-olds,[29] we would expect 137 (95% CI 131 to 144) completed suicides in our study population. However, 41% of suicides registered by the Office of National Statistics were of undetermined intent, leaving 59% or 81 (95% CI 77 to 85) expected suicides that received a verdict by a coroner. This estimate corresponds to the number of 81 completed suicides we identified between 1995 and 2009 within the THIN database. Of the 81 young people with a completed suicide, 21 (26%) had a prior record of a depression diagnosis or depression symptoms. Nineteen young people (23%) were taking antidepressants in the year before their suicide, and 11 (14%) were still taking them at the time of or shortly before their suicide. There was also a high proportion of young people with (a history of) behaviour disorders 16 (20%), a history of self-harm 8 (10%), a psychiatric referral 19 (23%), a hyperkinetic disorder 5 (6%) or an eating disorder 3 (4%).

There were no completed suicides within the risk periods for antidepressants other than SSRIs (table 3). Eleven (14%) completed suicides were within the risk periods. Similar to the results from the data on suicide-related events, IRR was highest on the day of prescription (IRR=42.5, 95% CI 4.5 to 403.4). There were no events in the first 2 weeks of the SSRI episode, but there was an increased rate ratio in week 3 (IRR=8.0, 95% CI 0.8 to 76.7, based on a single case) and a statistically significant increase in week 4 (IRR=11.3, 95% CI 1.1 to 115.6, though based on two cases). After the fourth week of the SSRI episode, IRR decreased and returned to baseline levels during washout. There were no significant differences between age groups.

DISCUSSION

Overall, there are no systematic differences between TCAs and SSRIs in IRRs for attempted suicide, suicidal ideation or intentional self-harm, and apart from an increase common to both TCAs and SSRIs on the day of prescription, rates were not statistically significantly different from pre-exposure levels. The pattern of IRRs for

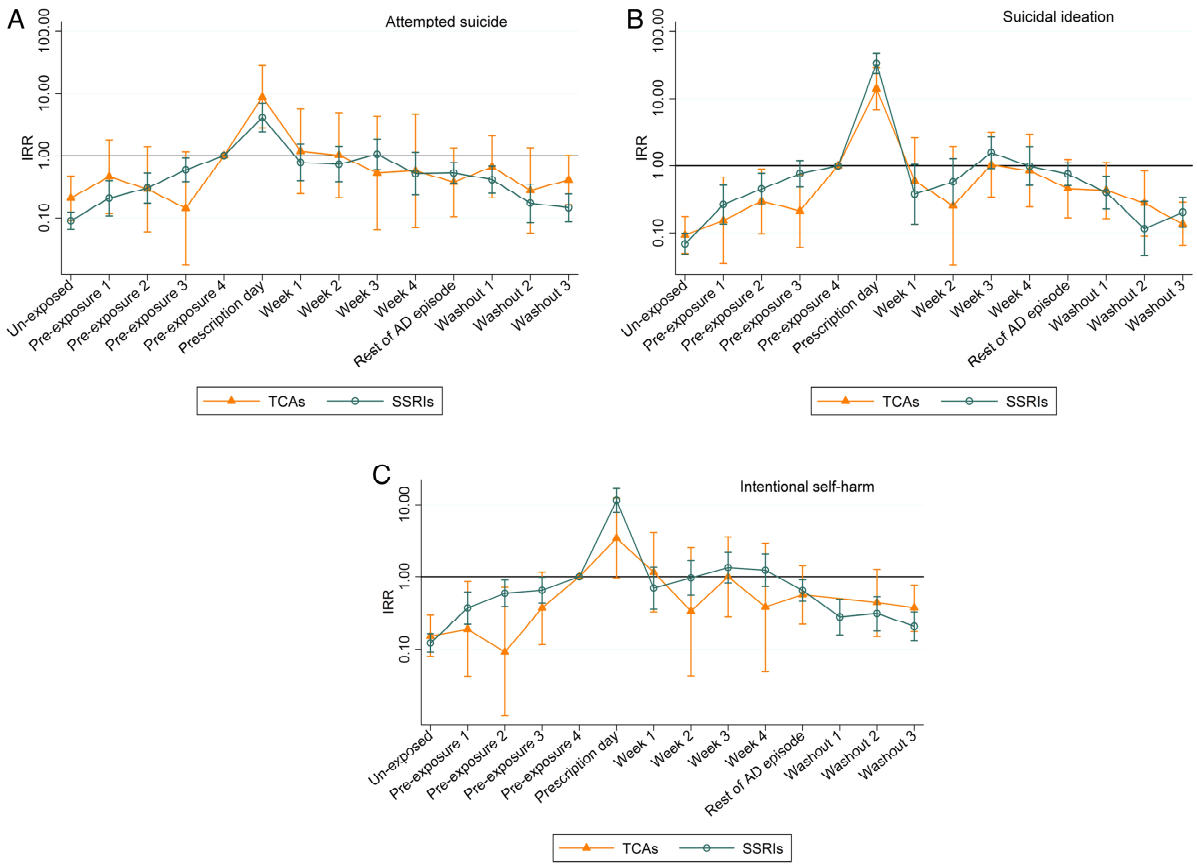

Figure 2 Incidence rate ratios for (A) attempted suicide, (B) suicidal ideation and (C) self-harm for tricyclic antidepressants and selective serotonin inhibitors. The month before a prescription was issued (pre-exposure 4) was used as the reference.

completed suicides for the 11 people prescribed SSRIs was similar to that found in attempted suicide, suicidal ideation and self-harm. However, concerns regarding antidepressants need to be weighed against the risk of untreated depression.

Table 3 Incidence rate ratios (IRRs) for completed suicide by risk period and age

Risk period	Censoring model IRR (95% CI)	Number of deaths*
Prescription day	42.52 (4.48 to 403.43)	5
Week 1	No events	0
Week 2		
Week 3	8.00 (0.84 to 76.71)	1
Week 4	11.25 (1.09 to 115.58)	2
Rest of AD episode	5.42 (0.57 to 51.94)	1
Washout 1	2.27 (0.24 to 21.76)	1
Washout2	2.08 (0.22 to 19.69)	1
Age groups		Number of total deaths†
10 to 12	0.61 (0.21 to 1.77)	8
13 to 14	1.14 (0.45 to 2.90)	15
15 to 16	Reference	21
17 to 18	0.41 (0.12 to 1.39)	37

*Number of suicides during risk periods (only includes youths who were taking antidepressants at the time of suicide, or those who had recently stopped).
†Number of suicides by age category.

Pre-exposure IRRs for attempted suicide, suicidal ideation and self-harm appeared to be marginally higher, though not statistically significant, for SSRIs compared to TCAs. This could be because young people who are deemed to be more at risk of suicide-related events could preferentially be prescribed SSRIs over TCAs, given TCAs' toxicity in overdose.[17]

The high IRRs on the day of antidepressant prescription for all three non-fatal outcomes could be an artefact of GP-recording behaviour. Rather than the antidepressant causing the suicide-related events, the event is an indication for the GP to prescribe the drug and to record depression in the electronic records on the same day. As antidepressants should only be prescribed by child and adolescent psychiatrics (2005 NICE guidelines[6]), this artefact could also arise when GPs continue a prescription started in secondary care and record the initial indication when first prescribing this drug.

Up to the fourth week of prescription, the IRRs for attempted suicide, suicidal ideation and self-harm remained around the levels experienced during the pre-exposure period. Considering that suicide-related events are common in young depressed people, some suicidal and self-harm events would be expected irrespective of whether SSRIs are prescribed or not.[30] The rate of

suicide-related events decreased when the prescriptions were stopped. Given the nature of the data, it is difficult to know whether the SSRIs were causing suicide-related events and these events improved when the SSRIs were discontinued, or if the SSRIs were discontinued when the young person's depression (and as a consequence the risk of suicide-related events) improved.

There are three possible explanations for the slightly increased IRRs during the first month of prescription. One is that the SSRIs fail to relieve the risk of suicide-related events associated with depression because of a lag in the antidepressant effect, an incomplete response, or a treatment-resistant depression. It is known that SSRIs take a couple of weeks to reach their full antidepressant effects and hence reduce the risk of suicide-related events.[27]

A second possibility is that the SSRIs generate a novel set of suicidal emotions or behaviours. Early improvements in clinical depression can lead to a person acting on existing suicidal feelings. This activation syndrome has been described for TCAs and SSRIs, and is widely recognised by psychiatrists as well as the FDA.[31 32] While patients might be demotivated and demoralised at the height of their depression, when they start treatment they become more active during the first weeks of taking the drug. During this time, the antidepressant effect of the medication will not have reached its full effect, resulting in persistent depression but simultaneous increased activity. This could lead to a greater risk of suicide-related events until the full effects of antidepressants are realised a few weeks later.[31]

Several studies and systematic reviews have shown an age effect in the risk of suicide-related events with the use of SSRIs. In adults and the elderly, the risk is neutral or SSRIs show a protective effect, while in adolescents and young adults there appears to be an increased risk of suicide-related events.[9 15 33]

Although we did not find a statistically significantly sustained increase in suicide-related events with either SSRIs or TCAs, negative outcomes did not appear to be decreased either—although our study was not designed to assess this. This is in line with the Cochrane reviews on both drug groups: the review on TCAs concludes that these drugs are not useful in treating depression in prepubertal children, and that there is only marginal evidence to support the use of TCAs in adolescents, although the magnitude of the effect is likely to be moderate at best.[3] Similarly, it is unclear what the effect is of SSRIs on suicide completion. Although evidence from clinical trials implies an increased risk of suicide-related outcomes (but not completed suicide), the evidence for this association is of low quality.[34]

Comparison to other studies

Our results build on the findings of Schneeweis *et al*[13] They found no statistically significant differences in the relative risk of attempted and completed suicide between different types of antidepressants (fluoxetine, citalopram, fluvoxamine, paroxetine, sertraline and TCAs) when examining 266 attempted and three completed suicides. Moreover, an ecological study found no change in rates of completed suicides or hospital admissions for self-harm following the CSM advice,[35] suggesting that there is no, or only a weak, relationship with antidepressant prescriptions. Our findings are also similar to those of Simon *et al*[36] who used computerised health plan records and reported the highest rates for attempted suicide in the month before prescription, rather than after start of the prescription. Finally, a meta-analysis[37] found that, of 27 paediatric randomised controlled trials on antidepressants prescribed for MDD, OCD and non-OCD anxiety disorders, the risk of suicidal ideation or attempt among patients on placebo was greater in trials assessing MDD. Although this difference in baseline risk for suicide-related events was not statistically-significant, it could indicate that a part of the association between antidepressants and suicide-related events can be explained by the underlying disease, rather than the drug. Importantly, the authors concluded that relative to placebo, the benefits (though only modest in MDD) outweigh the risks from suicidal ideation/suicide attempts. Owing to the small numbers of patients with primary diagnoses of OCD and anxiety disorders, we could not repeat the meta-analysis's subgroup comparison.

Main strength and limitations

The main strength of this study is its sample size that enables the examination of outcomes separately by completed and attempted suicide, suicidal ideation and self-harm, as well as by individual antidepressants. However, even in using a database as large as THIN, we could identify only a small number of completed suicides, leading to limited power in that analysis. Similarly, power was limited for analysing individual antidepressants, which are presented in the appendix. Nevertheless, the use of the SCCS method allows us to control for time-independent confounders, making our estimations more robust.

A limitation to our study is that the THIN database only provides data on antidepressant prescriptions. We do not know whether the prescriptions were dispensed, or whether the patients adhered to the prescription. However, though it is known that adherence levels are around 50% for young people taking SSRIs, and even lower for TCAs,[38] our data do represent a real-life situation. Moreover, by assessing episodes of antidepressant prescription, we take account of multiple prescriptions per patient, which increases the likelihood of adherence, as we expect patients who are not taking their medication will not return for a new prescription.

Moreover, it is known that suicide-related events are often missed in clinical assessment.[39] However, it is quite likely that the most severe forms (attempted suicides and severe suicidal ideation) are most likely to be recorded by clinicians. Also, in using a self-controlled

design, we decrease the chance of misclassifying controls. There is some suggestion that antidepressants might specifically increase suicide-related events in patients who did not experience these events prior to starting antidepressant treatment. Owing to the variation in the clinicians' assessment and recording of (the absence of) suicide-related events, we could not examine this hypothesis using this database. Furthermore, the relatively low number of young people who had a prescription for an antidepressant at the time of their suicide-related event limits the interpretation of our results. However, Windfuhr *et al*[29] also found that mental health service contact was low in juveniles who committed suicide: only 14% contacted services in the year before they died. Finally, we were not able to account for changes in depression severity over time as this is poorly recorded.

CONCLUSION

Our study shows that there are similar IRR patterns for attempted suicide, suicidal ideation and self-harm for SSRIs and TCAs. Also, the pattern for completed suicides associated with SSRI prescriptions is similar, though there are no records of completed suicides within our predefined risk periods for TCAs. Although the CSM's warning was a sensible cautionary recommendation at the time, it appears that the current line of evidence suggests a reverse causality: it is the underlying depression that leads to suicide-related events and the prescription of antidepressants, although a causal effect of SSRIs or no effect at all cannot be ruled out. Moreover, even if antidepressant drugs would temporarily increase the risk of suicide-related events in young persons, the risk posed by untreated depression is far greater. In conclusion, our results indicate that the association of suicide-related events associated with antidepressants occurs primarily around the day of prescription, suggesting depression severity and GP-recording behaviour as the culprit rather than antidepressants, and thus warrants a re-evaluation of the current guidelines regarding the prescription of SSRIs in primary care.

RECOMMENDATION

Our results are not definitive, and due to the rare nature of the outcome and the intricacies of the problem studied, it is difficult to think of a single study or study design that will be able to provide a satisfying answer to the problem at hand. It is possible that the creation of a pragmatic registry, similar to that proposed by van Staa *et al*[40] in their pragmatic randomised trial, will allow for active pharmacovigilance. Such a system would, at low cost and with no additional burden on clinician, health service or patient time, facilitate long-term, anonymous, unobtrusive follow-up for major clinical outcomes. As such, clinicians would be prompted to monitor and record (the absence of) suicide-related events and ideation more regularly and closely, using similar outcome measurements as those used in clinical trials, as well as (changes in) depression severity.

Acknowledgements The authors would like to thank the general practitioners who contributed data to THIN.

Contributors All authors were responsible for study conception and design. LPW was responsible for data analysis. LPW drafted the manuscript. All authors participated in the interpretation of data, critical revision and final approval of the manuscript.

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Competing interests LPMMW had financial support in the form of a studentship from the National Institute of Health Research School for Primary Care Research for the submitted work.

Ethics approval National Health Service South-East Multicenter Research Ethics Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Examples of statistical code used for the self-controlled case series method (including the adapted method for dealing with censored data) are available from the Open University website. Statistical code is available from the corresponding author.

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REFERENCES

1. Kessler RC, Avenevoli S, Ries, *et al*. Mood disorders in children and adolescents: an epidemiologic perspective. *Bioll Psychiatry* 2001;49:1002–14.
2. Heron M. Deaths: leading causes for 2007. *Natl Vital Stat Rep* 2011;59:1–95.
3. Hazell P, O'Connell D, Heathcote D, *et al*. Tricyclic drug for depression in children and adolescents. *Cochrane Database Syst Rev* 2010;(4):CD002317.
4. Wijlaars LP, Nazareth I, Petersen I. Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in the health improvement network (THIN). *PLoS ONE* 2012;7:e33181.
5. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. *BMJ* 2005;330:385.
6. National Institute for Health and Clinical Excellence. *CG28 depression in children and young people: NICE guideline*. London: National Institute for Health and Clinical Excellence, 2005.
7. FDA. *Suicidality in children and adolescents being treated with antidepressant medications*. US Food and Drug Administration. 2004. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161679.htm (accessed 29 June 2011).
8. Whittington CJ, Kendall T, Fonagy P, *et al*. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004;363:1341–5.
9. Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. *Arch Gen Psychiatry* 2006;63:332–9.
10. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med* 1994;331:394–8.
11. Grosso A, Douglas I, MacAllister R, *et al*. Use of the self-controlled case series method in drug safety assessment. *Expert Opin Drug Saf* 2011;10:337–40.

12. Gibbons RD, Brown CH, Hur K, *et al*. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry* 2007;164:1356–63.
13. Schneeweiss S, Patrick AR, Solomon DH, *et al*. Comparative safety of antidepressant agents for children and adolescents regarding suicidal acts. *Pediatrics* 2010;125:876–88.
14. Jick H, Kaye JA, Jick SS. Antidepressants and the risk of suicidal behaviors. *JAMA* 2004;292:338–43.
15. Olfson M, Marcus SC, Shaffer D. Anti-depressant drug therapy and suicide in severely depressed children and adults—a case-control study. *Arch Gen Psychiatry* 2006;63:865–72.
16. Gibbons RD, Brown CH, Hur K, *et al*. Suicidal thoughts and behavior with antidepressant treatment: reanalysis of the randomised placebo-controlled studies of fluoxetine and venlafaxine. *Arch Gen Psychiatry* 2012;69:580-7.
17. Didham RC, McConnell DW, Blair HJ, *et al*. Suicide and self-harm following prescription of SSRIs and other antidepressants: confounding by indication. *Br J Clin Pharmacol* 2005;60:519–25.
18. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. *Inform Prim Care* 2004;12:171–7.
19. Booth N. What are the read codes? *Health Libr Rev* 1994;11:177–82.
20. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the general practice research database: a systematic review. *Br J Gen Pract* 2010;60:e128–36.
21. Arana A, Wentworth CE, yuso-Mateos JL, *et al*. Suicide-related events in patients treated with antiepileptic drugs. *N Engl J Med* 2010;363:542–51.
22. Davé S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiol Drug Saf* 2009;18:704–7.
23. British National Formulary. 60th edn. London: BMJ Group, RPS Publishing, 2010.
24. The NHS Information Centre PaPCS. Prescription compliance: a review of the proportion of prescriptions dispensed. 7-9-2011.
25. Whitaker HJ, Farrington CP, Spiessens B, *et al*. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006;25:1768–97.
26. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. *Stat Methods Med Res* 2009;18:7–26.
27. Taylor MJ, Freemantle N, Geddes JR, *et al*. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. *Arch Gen Psychiatry* 2006;63:1217–23.
28. Farrington CP, Whitaker HJ, Hocine MN. Case series analysis for censored, perturbed, or curtailed post-event exposures. *Biostatistics* 2009;10:3–16.
29. Windfuhr K, While D, Hunt I, *et al*. Suicide in juveniles and adolescents in the United Kingdom. *J Child Psychol Psychiatry* 2008;49:1155–65.
30. Bridge JA, Goldstein TR, Brent DA. Adolescent suicide and suicidal behavior. *J Child Psychol Psychiatry* 2006;47:372–94.
31. Sinclair LI, Christmas DM, Hood SD, *et al*. Antidepressant-induced jitteriness/anxiety syndrome: systematic review. *Br J Psychiatry* 2009;194:483–90.
32. Culpepper L, Davidson JR, Dietrich AJ, *et al*. Suicidality as a possible side effect of antidepressant treatment. *J Clin Psychiatry* 2004;65:742–9.
33. Barbui C, Esposito E, Cipriani A. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. *CMAJ* 2009;180:291–7.
34. Hetrick SE, McKenzie JE, Cox GR, *et al*. Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database Syst Rev* 2012;11:CD004851.
35. Wheeler BW, Gunnell D, Metcalfe C, *et al*. The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study. *BMJ* 2008;336:542–5.
36. Simon GE, Savarino J, Operskalski B, *et al*. Suicide risk during antidepressant treatment. *Am J Psychiatry* 2006;163:41–7.
37. Bridge JA, Iyengar S, Salary CB, *et al*. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA* 2007;297:1683–96.
38. Barbui C, Hotopf M, Freemantle N, *et al*. Selective serotonin reuptake inhibitors versus tricyclic and heterocyclic antidepressants: comparison of drug adherence. *Cochrane Database Syst Rev* 2000;(4):CD002791.
39. Fitzpatrick C, Abayomi NN, Kehoe A, *et al*. Do we miss depressive disorders and suicidal behaviours in clinical practice? *Clin Child Psychol Psychiatry* 2012;17:449–58.
40. van Staa T, Goldacre B, Gulliford M, *et al*. Pragmatic randomised trials using routine electronic health records: putting them to the test. *BMJ* 2012;344:e55.

Appendix G

Scientific approval

SRC Feedback

Researcher Name: Dr Irene Petersen
Organisation: UCL
SRC Reference Number: 11-005A
Date: 10/05/2011
Study title: Trends in the incidence of childhood depression in the United Kingdom
Committee opinion: Amendment approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

I am happy to approve this amendment to the original proposal. I have no fundamental concerns and I am happy to approve the revision.

I have made two further suggestions which the applicants may find useful. However these are not compulsory revisions, only suggestions.

IDENTIFICATION OF OUTCOME EVENTS (SUICIDES)

My understanding is that there is some difficulty in ascertaining whether deaths are suicides in electronic primary care records. (1) There may be problems in identification of some diagnoses in electronic primary care records. (2) However there are methods for identification of suicides in electronic primary care records and it would be useful for the authors to refer to these methods. (3)

PRELIMINARY ANALYSIS

There may be a problem of confounding associated with prescription. It is likely that more severely depressed children are more likely to be prescribed antidepressants (or antidepressants unlicensed for use in adolescents) and are also more likely to commit suicide.

The authors might like to consider a matched case control study as an initial investigation of the relationship between antidepressant drug prescription and suicide. Cases are children with a diagnosis of suicide identified using a previously described methodology (ref 3) and who have been prescribed an antidepressant in the 6 months prior to diagnosis. Controls are age and sex matched who have also been prescribed an antidepressant in the 6 months prior to diagnosis. Odds ratios can be determined by conditional logistic regression analysis. These will give an indication whether there is a difference in frequency of exposure to a specific type of antidepressants prior to suicide.

This is a more rapid analysis than a retrospective cohort study and may help decide if there is prima facie evidence of an association between. Including only persons prescribed an antidepressant removes some of the confounding associated with prescription.

Ref:

1) Hall G. Validation of death and suicide recording on the THIN UK primary care database Pharmacoepidemiology and Drug Safety 2009 Feb;18(2):120-131
2) Khan NF et al Validity of diagnostic coding within GPRD: a systematic review BJGP 2010 Mar;60(572):e128-36.
3) Arana A et al An algorithm for the diagnosis of suicide in the THIN database Pharmacoepidemiology and Drug Safety 2010 18:S1-347

We are pleased to inform that you can proceed with the study as amendment is now approved.

Once the study has been completed and published, you must let CSD Medical Research know in order for your reference number to be closed.

CSD Medical Research will let the relevant Ethics committee know this study has been approved by the SRC and will inform them of study completion (when known) on your behalf.

I wish you and your team all the best with the study progression.

Kind Regards,

Mustafa Dungarwalla
Research Associate

SRC Feedback

Researcher Name: Linda Wijlaars
Organisation: UCL
SRC Reference Number: 12-032
Date: 20/08/2012
Study title: Trends in sleep disorders and sleeping drug treatment in children and the association with depression
Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

The protocol appears to be of a reasonably good standard. The proposed methods are valid and the objectives may be feasibly addressed using THIN data.
The overall response therefore is to approve the protocol. The comments given in the advice section are to help the researcher to fine-tune their methods.

Advice (General advice for the researchers as information only)
Overall, the protocol is well written, expressing clearly the aims, methods and potential limitations. The first two objectives may be readily addressed using THIN data; the third objective may also be addressed using THIN data, although consider how to handle the potential limitations highlighted in the comments below. The methods are appropriate for addressing the study questions. Some specific comments/ suggestions: 1. The background section highlights well the lack of previous research in this area. However, could you provide more detail in the background of the need/motivation for the research and perceived value of the research in terms of the potential public health/ clinical benefit? 2. The third objective could be more precisely expressed 3. Clarify why the population comprises children aged 3 to 18 years, while the children enter the cohort from age 5 years. 4. When defining start and end dates for follow-up, consider use of data quality control dates (e.g. AMR date). 5. Townsend score is included in the analyses. Consider pre-specifying how to handle patients with missing Townsend score. Will practices with no Townsend data be excluded? 6. Sleeping problems due to physical illness e.g asthma/ sickle cell will be excluded. How will these cases be identified? Are there specific codes for sleeping problems due to asthma or will all patients with asthma be excluded? 7. Consider whether there may be other possible confounders than Townsend score. If these factors are not available in THIN, how might not adjusting for the confounders affect the results? 8. Sleeping disorders and depression may recur. How will repeated episodes be handled in the analyses? Will patients who have prior episodes at baseline be excluded? 9. Clarify how the proportional hazards assumption will be tested. 10. Have preliminary analyses been carried out to estimate the size (number of children) in the cohort? How many children are likely to have sleep disorders in THIN? 11. Could individual likelihood to consult lead to bias in the association between sleep disorders and depression (children/ parents may differ in their likelihood to consult their GP in general - those who consult more may be more likely to consult for both depression and sleep disorders than those who don't which could lead to overestimation of an association). 12. For the oldest children, is up to one year long enough to allow people to get depression after their sleep disorders? 13. Might the cohort be limited by the number of variables you are choosing to match on? It may be better to control for some of these variables in the analysis instead. 14. It may be difficult to determine the temporal relationship between sleep disorders and depression. The researchers may need to derive rules to distinguish between the exposure and

outcome occuring contemperaneously and when they are truly occuring before or after each other.
15. The list of physical disorders which may give rise to secondary sleep conditions needs to be carefully developed
16. The researchers list some important limitations to the work which will always need to be considered during analysis, write-up and dissemination. The prescription of antihistamines for indications other than sleep is particularly important. Is it worth developing codelists for the most common alternative diagnoses for which antihistamines are prescribed?
17. The researchers list some important limitations to the work which will always need to be considered during analysis, write-up and dissemination. The prescription of antihistamines for indications other than sleep is particularly important. Is it worth developing codelists for the most common alternative diagnoses for which antihistamines are prescribed?

We are pleased to inform that you can proceed with the study as this is now approved.

Once the study has been completed and published, you must let CSD Medical Research know in order for your reference number to be closed.

CSD Medical Research will let the relevant Ethics committee know this study has been approved by the SRC and will inform them of study completion (when known) on your behalf.

I wish you and your team all the best with the study progression.

Kind Regards,

Mustafa Dungarwalla
Research Associate

SRC Feedback

Researcher Name: Linda PMM Wijlaars
Organisation: UCL
SRC Reference Number: 13-041
Date: 15th July 2013
Study title: A longitudinal study on the association between parental depression in the first postpartum year and adolescent depression
Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

While we approve the protocol, I hope the attached comments will prove useful to the investigators

Advice (General advice for the researchers as information only – for advice only)
A) Triads that move out may differ from those who remain, despite the statement at the top of page 7. I am not certain about the literature on "movers" but suspect they may be more deprived and possibly more subject to depression (their depression may lead to relationship breakdown leading to re-housing, and after a move, a family may become at greater risk of depression - the former phenomenon is likely to be more of an issue for this project)
B) Parental divorce may impact more strongly on adolescent depression than parental depression. Yet because of divorce, fewer episodes of depression may come to light (especially among fathers who are more likely to move out) - is parental divorce thus a collider rather than a confounder?
C) Inclusion criteria in penultimate para on page 2 mentions children born from 1994-2011, but page 5 says all children with 15 years of follow-up (so presumably children born before 1997 ?). Will this still provide sufficient sample size?
D) Rev 2:- (i)I'd imagine that the composite "internalizing behavior" as a mediator of depression is a particularly challening diagnosis to confirm, and there potentially could be exposure misclassification. Has any preliminary work been conducted to assess the charactecteristics of this classification in terms of predicting depression in adolescents? (ii)Is there the possibility for confounder misclassification regarding child abuse, drug abuse,a nd alcohol abuse? How would this affect the IPW analysis suggested? Could additional sensitivity analyses assess this effect? (iii)Is will follow-up time be adequate to assess the outcome of interest for the birth cohort? Have any preliminary sample size calculations [NB from chair: I think comment (iii) is like my own comment C) above.]
Re point A above: do a descriptive comparison of triads who move versus those who stay. This is among families whose child should have reached adolescence by the end point of data collection (?? born earlier than 1997) Re point B: I am confident the range of statistical models proposed by the authors can address the concern outlined above, even if my hunch is correct - I would only ask the investigators to consider the point. I am very impressed by the innovative use of statistical methods such as marginal structural models. I was only curious about the IPW (lower half of page 4): is it really desirable that a rare confounder should receive high weight in an analysis? Rev 1:- This is a very interesting study and the team obviously have a good understanding of the

strengths and weaknesses of the data, as well as the clinical problem.
I thought there might be other explanations for any positive findings in the pathway analysis if so-called internalising behaviours proved important. These conditions might be markers for other things. In addition, these internalising conditions will be more frequently recorded in some patients than others, perhaps including those with depression.
I was worried that life events would not be well recorded
[NB from chair: the comment on "internalising behaviours" may have overlap with Reviewer 1's comment D)(i) above]

Rev 2:-
In general, this is a well-constructed research proposal, designed by a research team that is familiar with THIN and has done some similar research in this database previously. I have some minor concerns listed above not as "fundamental issues" that should inhibit the approval of this proposal per se, but perhaps would be best used as questions to think about in conducting the study. Additional sensitivity analyses may be useful to explore the effects of confounder and mediator misclassification on the relationship between the exposure and outcome.

We are pleased to inform that you can proceed with the study as this is now approved. CSD Medical Research will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform CSD Medical Research in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

Mustafa Dungarwalla
Research Associate

Bibliography

Transcript of the joint meeting of the CDER psychopharmacologic drugs advisory committee and the FDA pediatric advisory committee - 13 september 2004, 2004. URL http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs.

P. D. Allison. *Missing data*. Number 136. Sage, 2001.

American Psychiatric Association. Mood disorders. In *Diagnostic and Statistical Manual of Mental Disorders*, volume Fourth Edition, Text Revision, pages 349–428. Washington, DC, 2000. URL http://books.google.co.uk/books?id=3SQrtpnHb9MC&lpg=PP1&pg=PA356#v=twopage&q&f=true.

I. M. Anderson. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. *Journal of affective disorders*, 58(1):19–36, 2000.

J. Anderson, S. Williams, R. McGee, and P. Silva. DSM-III disorders in preadolescent children. prevalence in a large sample from the general population. *Arch Gen Psychiatry*, 44(0003-990X (Print)):69–76, Jan. 1987. URL PM:2432848.

A. Angold. Effects of age and pubertal status on depression in a large clinical sample. *Development and psychopathology*, 4(1):5, 1992. ISSN 0954-5794.

A. Angold, E. Costello, and C. Worthman. Puberty and depression: the roles of age, pubertal status and pubertal timing. *Psychol Med*, 28(0033-2917 (Print)):51–61, Jan. 1998. URL PM:9483683.

P. Anttila, A. Sourander, L. Metsähonkala, M. Aromaa, H. Helenius, and M. Sillanpää. Psychiatric symptoms in children with primary headache. *Journal of the American Academy of Child & Adolescent Psychiatry*, 43(4):412–419, 2004.

R. Bagby, A. Ryder, D. Schuller, and M. Marshall. The hamilton depression rating scale: has the gold standard become a lead weight? *Am J Psychiatry*, 161(0002-953X (Print)):2163–2177, Dec. 2004. doi: 10.1176/appi.ajp.161.12.2163. URL PM:15569884.

C. Baglioni, G. Battagliese, B. Feige, K. Spiegelhalder, C. Nissen, U. Voderholzer, C. Lombardo, and D. Riemann. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. *Journal of affective disorders*, 135 (1):10–19, 2011.

C. Ballard and R. Davies. Postnatal depression in fathers. *International review of psychiatry*, 8:65–71, 1996.

C. Ballard, R. Davis, P. Cullen, R. Mohan, and C. Dean. Prevalence of postnatal psychiatric morbidity in mothers and fathers. *The British Journal of Psychiatry*, 164(6): 782–788, 1994.

D. Barker, P. Gluckman, K. Godfrey, J. Harding, J. Owens, and J. Robinson. Fetal nutrition and cardiovascular disease in adult life. *Lancet*, 341(0140-6736 (Print)):938–941, Apr. 1993. URL PM:8096277.

R. M. Baron and D. A. Kenny. The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. 51(6):11731182, 1986. URL https://umdrive.memphis.edu/grelyea/public/PUBH%207152-Stat%20Methods%20II/Chapter%2010/Mediation/Baron_%26_Kenny_1986.pdf.

P. Bateson, D. Barker, T. Clutton-Brock, D. Deb, B. D'Udine, R. A. Foley, P. Gluckman, K. Godfrey, T. Kirkwood, M. M. Lahr, J. McNamara, N. B. Metcalfe, P. Monaghan, H. G. Spencer, and S. E. Sultan. Developmental plasticity and human health. 430 (6998):419–421, July 2004. ISSN 0028-0836. doi: 10.1038/nature02725. URL http://dx.doi.org/10.1038/nature02725.

W. Beardslee, D. Brent, and V. e. a. Weersing. Prevention of depression in at-risk adolescents: Longer-term effects. *JAMA Psychiatry*, pages –, 2013. doi: 10.1001/jamapsychiatry.2013.295. URL +http://dx.doi.org/10.1001/jamapsychiatry.2013.295.

A. Beck, C. Ward, M. Mendelson, J. Mock, and J. Erbaugh. An inventory for measuring depression. *Arch Gen.Psychiatry*, 4(0003-990X (Print)):561–571, June 1961. URL PM:13688369.

A. T. Beck, R. A. Steer, and G. K. Brown. Manual for the beck depression inventory-II. *San Antonio, TX: Psychological Corporation*, 1:82, 1996.

A. T. Beck, D. Guth, R. A. Steer, and R. Ball. Screening for major depression disorders in medical inpatients with the beck depression inventory for primary care. *Behaviour research and therapy*, 35(8):785–791, 1997. ISSN 0005-7967.

M. A. Bellis, H. Lowey, N. Leckenby, K. Hughes, and D. Harrison. Adverse childhood experiences: retrospective study to determine their impact on adult health behaviours and health outcomes in a uk population. *Journal of public health*, 2013.

L. M. Bendz and A. C. Scates. Melatonin treatment for insomnia in pediatric patients with attention-deficit/hyperactivity disorder. *The Annals of pharmacotherapy*, 44(1): 185–191, 2010.

H. Bergen, K. Hawton, E. Murphy, J. Cooper, N. Kapur, C. Stalker, and K. Waters. Trends in prescribing and self-poisoning in relation to uk regulatory authority warnings against use of ssri antidepressants in under-18-year-olds. *British journal of clinical pharmacology*, 68(4):618–629, 2009.

M. Bergstrøm. Depressive symptoms in new first-time fathers: Associations with age, sociodemographic characteristics, and antenatal psychological well-being. 40(1):32–38, Mar. 2013. ISSN 1523-536X. URL `http://dx.doi.org/10.1111/birt.12026`.

E. Bielawska-Batorowicz and K. Kossakowska-Petrycka. Depressive mood in men after the birth of their offspring in relation to a partner's depression, social support, fathers' personality and prenatal expectations. *Journal of Reproductive and Infant Psychology*, 24(1):21–29, 2006.

B. Birmaher, D. Brent, W. Bernet, O. Bukstein, H. Walter, R. Benson, A. Chrisman, T. Farchione, L. Greenhill, J. Hamilton, H. Keable, J. Kinlan, U. Schoettle, S. Stock, K. Ptakowski, and J. Medicus. Practice parameter for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad.Child Adolesc Psychiatry*, 46(0890-8567 (Print)):1503–1526, Nov. 2007. URL PM:18049300.

B. R. Birmaher. Childhood and adolescent depression: A review of the past 10 years. part i. *Journal of the American Academy of Child & Adolescent Psychiatry*, 35(11):1427–1439, Nov. 1996. ISSN 0890-8567. doi: 10.1097/00004583-199611000-00011. URL http://www.sciencedirect.com/science/article/pii/S0890856709664030.

S.-J. Blakemore and K. L. Mills. Is adolescence a sensitive period for sociocultural processing? *Psychology*, 65:2014, 2013.

N. Booth. What are the read codes? *Health Libr.Rev*, 11(0265-6647 (Print)):177–182, Sept. 1994. URL PM:10139676.

E. U. Brady and P. C. Kendall. Comorbidity of anxiety and depression in children and adolescents. *Psychological Bulletin*, 111(2):244, 1992.

P. Brennan, C. Hammen, M. Andersen, W. Bor, J. Najman, and G. Williams. Chronicity, severity, and timing of maternal depressive symptoms: relationships with child outcomes at age 5. *Dev Psychol*, 36(0012-1649 (Print)):759–766, Nov. 2000. URL PM:11081699.

P. A. Brennan, C. Hammen, A. R. Katz, and R. M. Le Brocque. Maternal depression,

paternal psychopathology, and adolescent diagnostic outcomes. *Journal of consulting and clinical psychology*, 70(5):1075, 2002.

N. Breslau, R. Lipton, W. Stewart, L. Schultz, and K. Welch. Comorbidity of migraine and depression investigating potential etiology and prognosis. *Neurology*, 60(8):1308–1312, 2003.

J. Bridge, S. Iyengar, C. Salary, R. Barbe, B. Birmaher, H. Pincus, L. Ren, and D. Brent. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*, 297(1538-3598 (Electronic)):1683–1696, Apr. 2007. URL `PM:17440145`.

R. Burton and H. Jackson. *The Anatomy of Melancholy*. London, 1827.

B. M. Byrne. *Structural equation modeling with Mplus: Basic concepts, applications, and programming*. Routledge Academic New York, 2011.

A. L. Calear and H. Christensen. Systematic review of school-based prevention and early intervention programs for depression. *Journal of Adolescence*, 33(3):429–438, 2010.

J. V. Campo, C. Di Lorenzo, L. Chiappetta, J. Bridge, D. K. Colborn, J. C. Gartner, P. Gaffney, S. Kocoshis, and D. Brent. Adult outcomes of pediatric recurrent abdominal pain: do they just grow out of it? *Pediatrics*, 108(1):e1–e1, 2001.

J. V. Campo, J. Bridge, M. Ehmann, S. Altman, A. Lucas, B. Birmaher, C. Di Lorenzo, S. Iyengar, and D. A. Brent. Recurrent abdominal pain, anxiety, and depression in primary care. *Pediatrics*, 113(4):817–824, 2004.

A. Caspi, K. Sugden, T. E. Moffitt, A. Taylor, I. W. Craig, H. Harrington, J. McClay, J. Mill, J. Martin, A. Braithwaite, and R. Poulton. Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science*, 301(5631):386–389, July 2003. doi: 10.1126/science.1083968. URL `http://www.sciencemag.org/cgi/content/abstract/sci;301/5631/386`.

M. Cepoiu, J. McCusker, M. Cole, M. Sewitch, E. Belzile, and A. Ciampi. Recognition of depression by non-psychiatric physicians–a systematic literature review and meta-analysis. *J.Gen.Intern.Med.*, 23(1525-1497 (Electronic)):25–36, Jan. 2008. URL `PM:17968628`.

J. Chisholm. The read clinical classification. *BMJ*, 300(0959-8138 (Print)):1092, Apr. 1990. URL `PM:2344534`.

H. Clarke, J. Flint, A. S. Attwood, and M. R. Munaf. Association of the 5- HTTLPR genotype and unipolar depression: a meta-analysis. *Psychol Med*, 40(11):1767–1778, Nov. 2010. ISSN 1469-8978. doi: 10.1017/S0033291710000516. PMID: 20380781.

L. Clegg, B. Hankey, R. Tiwari, E. Feuer, and B. Edwards. Estimating average annual per cent change in trend analysis. *Stat.Med.*, 28(1097-0258 (Electronic)):3670–3682, Dec. 2009. URL `PM:19856324`.

P. Cohen and J. Brook. Family factors related to the persistence of psychopathology in childhood and adolescence. *Psychiatry*, 50(0033-2747 (Print)):332–345, Nov. 1987. URL `PM:3423159`.

S. Collishaw, B. Maughan, R. Goodman, and A. Pickles. Time trends in adolescent

mental health. *J Child Psychol Psychiatry*, 45(0021-9630 (Print)):1350–1362, Nov. 2004. URL PM:15482496.

I. Colman, M. Wadsworth, T. Croudace, and P. Jones. Forty-year psychiatric outcomes following assessment for internalizing disorder in adolescence. *Am J Psychiatry*, 164 (0002-953X (Print)):126–133, Jan. 2007. doi: 10.1176/appi.ajp.164.1.126. URL PM:17202554.

Committee on Safety of Medicines. Paroxetine (seroxat) - variation assessment report - proposal to contraindicate in adolescents and children under 18 years with major depressive disorder. Technical report, June 2003. URL http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON014153.

B. Cooper. Sylvia plath and the depression continuum. *J R.Soc.Med*, 96(0141-0768 (Print)):296–301, June 2003. URL PM:12782699.

P. J. Cooper and L. Murray. Fortnightly review: Postnatal depression. *BMJ: British Medical Journal*, 316(7148):1884, 1998.

C. U. Correll and R. R. Pleak. Paroxetine in the treatment of adolescent major depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41(11):1269, Nov. 2002. ISSN 0890-8567. doi: 10.1097/00004583-200211000-00001. URL http://www.sciencedirect.com/science/article/pii/S0890856709606250.

S. Cortese, S. Faraone, E. Konofal, and M. Lecendreux. Sleep in children with attention-deficit/hyperactivity disorder: meta-analysis of subjective and objective studies. *J Am*

Acad.Child Adolesc.Psychiatry, 48(1527-5418 (Electronic)):894–908, Sept. 2009. doi: 10.1097/CHI.0b013e3181ac09c9. URL PM:19625983.

E. Costello, A. Erkanli, and A. Angold. Is there an epidemic of child or adolescent depression? 47(12):1263–1271, 2006. ISSN 0021-9630. URL ISI:000242791000008.

P. Cowen. TV: panorama: "The secrets of seroxat". *BMJ*, Oct. 2002.

J. Cox and J. Holden. *Perinatal Mental Health: a guide to the Edinburgh Postnatal Depression Scale*. The Royal College of Psychiatrists, London, 2003. ISBN 1-901242-81-1.

J. Cox, J. Holden, and R. Sagovsky. Detection of postnatal depression. development of the 10-item edinburgh postnatal depression scale. 150(6):782–786, 1987. ISSN 0007-1250.

J. Cox, D. Murray, and G. Chapman. A controlled study of the onset, duration and prevalence of postnatal depression. *Br.J Psychiatry*, 163(0007-1250 (Print)):27–31, July 1993. URL PM:8353695.

J. L. Cox, G. Chapman, D. Murray, and P. Jones. Validation of the edinburgh postnatal depression scale (EPDS) in non-postnatal women. *Journal of Affective Disorders*, 39 (3):185–189, July 1996. ISSN 0165-0327. URL http://www.sciencedirect.com/science/article/pii/0165032796000080.

V. Currò, E. De Rosa, S. Maulucci, M. L. Maulucci, M. T. Silvestri, A. Zambrano, and V. Regine. The use of edinburgh postnatal depression scale to identify postnatal depression symptoms at well child visit. *Italian journal of pediatrics*, 35(1):32, 2009.

J. M. Cyranowski, E. Frank, E. Young, and M. Shear. Adolescent onset of the gender difference in lifetime rates of major depression: A theoretical model. *Arch Gen Psychiatry*, 57(1):21–27, Jan. 2000.

S. Davé and I. Petersen. Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiology and drug safety*, 18(8):704–707, 2009. ISSN 1053-8569.

S. Davé, I. Nazareth, L. Sherr, and R. Senior. The association of paternal mood and infant temperament: A pilot study. 23(4):609–621, Nov. 2005. ISSN 2044-835X. doi: 10.1348/026151004X22962.

S. Davé, I. Petersen, L. Sherr, and I. Nazareth. Incidence of maternal and paternal depression in primary care: A cohort study using a primary care database. *Arch.Pediatr.Adolesc.Med.*, 164(1538-3628 (Electronic)):1038–1044, Nov. 2010.

S. Davies. Chief medical officer's annual report 2012: Our children deserve better: Prevention pays. Technical report, Department of Health, 2013.

A. Dean, A. Hendy, and T. McGuire. Antidepressants in children and adolescents - changes in utilisation after safety warnings. *Pharmacoepidemiology and drug safety*, 16(9):1048–1053, 2007. ISSN 1053-8569.

R. Didham, D. McConnell, H. Blair, and D. Reith. Suicide and self-harm following prescription of SSRIs and other antidepressants: confounding by indication. *Br.J.Clin.Pharmacol.*, 60(0306-5251 (Print)):519–525, Nov. 2005.

DiMatteo M, Lepper HS, and Croghan TW. Depression is a risk factor for noncom-

pliance with medical treatment: Meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*, 160(14):2101–2107, July 2000. ISSN 0003-9926. doi: 10.1001/archinte.160.14.2101. URL `http://dx.doi.org/10.1001/archinte.160.14.2101`.

U. A. Doerry and L. Kent. Prescribing practices of community child and adolescent psychiatrists. 27(11):407–410, Nov. 2003.

M. Dudley, K. Roy, N. Kelk, and D. Bernard. Psychological correlates of depression in fathers and mothers in the first postnatal year. *Journal of Reproductive and Infant Psychology*, 19(3):187–202, 2001.

M. Dudley, R. Goldney, and D. Hadzi-Pavlovic. Are adolescents dying by suicide taking SSRI antidepressants? a review of observational studies. *Australas.Psychiatry*, 18 (1440-1665 (Electronic)):242–245, June 2010. URL `PM:20482427`.

R. Emsley and H. Liu. PARAMED: stata module to perform causal mediation analysis using parametric regression models, Apr. 2013.

G. Emslie, J. Heiligenstein, K. Wagner, S. Hoog, D. Ernest, E. Brown, M. Nilsson, and J. Jacobson. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J.Am.Acad.Child Adolesc.Psychiatry*, 41(0890-8567 (Print)):1205–1215, Oct. 2002. URL `PM:12364842`.

G. J. Emslie, A. J. Rush, W. A. Weinberg, R. A. Kowatch, C. W. Hughes, T. Carmody, and J. Rintelmann. A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Archives of General Psychiatry*, 54(11): 1031, 1997.

M. J. England, L. J. Sim, et al. *Depression in parents, parenting, and children: Opportunities to improve identification, treatment, and prevention*. National Academies Press, 2009.

V. Escribà-Agüir and L. Artazcoz. Gender differences in postpartum depression: a longitudinal cohort study. *J Epidemiol Community Health*, 65(4):320–326, Apr. 2011. ISSN , 1470-2738. doi: 10.1136/jech.2008.085894. URL `http://jech.bmj.com/content/65/4/320`. PMID: 20515899.

L. R. Fabrigar, D. T. Wegener, R. C. MacCallum, and E. J. Strahan. Evaluating the use of exploratory factor analysis in psychological research. *Psychological methods*, 4(3): 272, 1999. ISSN 1939-1463.

FDA. Suicidality in children and adolescents being treated with antidepressant medications, Oct. 2004. URL `http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm161679.htm`.

T. R. Flaherty EG. Adverse childhood experiences and child health in early adolescence. *JAMA Pediatr*, 167(7):622–629, July 2013. ISSN 2168-6203. doi: 10.1001/jamapediatrics.2013.22. URL `http://dx.doi.org/10.1001/jamapediatrics.2013.22`.

O. for National Statistics. Babies born in england and wales had a father with an average age of 32.6 in 2011, June 2013. Fathers tend to be older than mothers; average age of mothers was 29.7.

D. E. Ford and D. B. Kamerow. Epidemiologic study of sleep disturbances and psychiatric disorders. *JAMA: the journal of the American Medical Association*, 262(11): 1479–1484, 1989.

G. Garry and G. Paley. An audit of waiting times at a specialist psychotherapy service. 30(5):182–184, May 2006. URL `http://pb.rcpsych.org/content/30/5/182.abstract`.

R. Gibbons, C. Brown, K. Hur, S. Marcus, D. Bhaumik, J. Erkens, R. Herings, and J. Mann. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. *Am J Psychiatry*, 164(0002-953X (Print)):1356–1363, Sept. 2007. URL `PM:17728420`.

V. Glover, T. OConnor, and K. ODonnell. Prenatal stress and the programming of the HPA axis. *Neuroscience & Biobehavioral Reviews*, 35(1):17–22, Sept. 2010. ISSN 0149-7634. doi: 10.1016/j.neubiorev.2009.11.008. URL `http://www.sciencedirect.com/science/article/pii/S0149763409001742`.

D. Goldberg and P. Williams. *General health questionnaire*. GL Assessment, 2006.

D. P. Goldberg and V. Hillier. A scaled version of the general health questionnaire. *Psychological medicine*, 9(01):139–145, 1979. ISSN 1469-8978.

J. Goodman. Paternal postpartum depression, its relationship to maternal postpartum depression, and implications for family health. *J.Adv.Nurs.*, 45(0309-2402 (Print)): 26–35, Jan. 2004. URL `PM:14675298`.

S. H. Goodman and I. H. Gotlib. Transmission of risk to children of depressed parents: Integration and conclusions. 2002.

I. Goodyer. *The depressed child and adolescent*. 2000. ISBN 6610309531.

R. L. Gorsuch. Factor analysis, 2nd. 1983.

S. Grace, A. Evindar, and D. Stewart. The effect of postpartum depression on child cognitive development and behavior: a review and critical analysis of the literature. *Arch.Womens Ment.Health*, 6(1434-1816 (Print)):263–274, Nov. 2003. URL PM:14628179.

A. M. Gregory and T. G. O'Connor. Sleep problems in childhood: a longitudinal study of developmental change and association with behavioral problems. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41(8):964–971, 2002.

A. M. Gregory, A. Caspi, T. C. Eley, T. E. Moffitt, T. G. OConnor, and R. Poulton. Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. *Journal of Abnormal Child Psychology*, 33(2):157–163, 2005.

P. Gringras, C. Gamble, A. Jones, L. Wiggs, P. Williamson, A. Sutcliffe, P. Montgomery, W. Whitehouse, I. Choonara, T. Allport, et al. Melatonin for sleep problems in children with neurodevelopmental disorders: randomised double masked placebo controlled trial. *BMJ: British Medical Journal*, 345, 2012.

D. Gunnell, J. Saperia, and D. Ashby. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled,

randomised controlled trials submitted to the MHRA's safety review. *BMJ*, 330(1468-5833 (Electronic)):385, Feb. 2005. URL PM:15718537.

G. Hajak, W. Müller, H.-U. Wittchen, D. Pittrow, and W. Kirch. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction*, 98(10):1371–1378, 2003.

G. Hall. Pharmacoepidemiology using a uk database of primary care records. *Pharmacoepidemiology and Drug Safety*, 1(1):33–37, 1992.

M. Hamilton. A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry*, 23(1):56, 1960.

T. Hammad, T. Laughren, and J. Racoosin. Suicidality in pediatric patients treated with antidepressant drugs. *Arch.Gen.Psychiatry*, 63(0003-990X (Print)):332–339, Mar. 2006. URL PM:16520440.

C. Hammen and P. A. Brennan. Severity, chronicity, and timing of maternal depression and risk for adolescent offspring diagnoses in a community sample. *Archives of general psychiatry*, 60(3):253, 2003.

C. Hammen, J. H. Shih, and P. A. Brennan. Intergenerational transmission of depression: Test of an interpersonal stress model in a community sample. 72(3):511–522, 2004. ISSN 0022-006X. doi: 10.1037/0022-006X.72.3.511. URL http://espace.library.uq.edu.au/view/UQ:8033.

L. Hanington, P. Ramchandani, and A. Stein. Parental depression and child temperament:

assessing child to parent effects in a longitudinal population study. *Infant Behavior and Development*, 33(1):88–95, 2010.

L. Hanington, J. Heron, A. Stein, and P. Ramchandani. Parental depression and child outcomes - is marital conflict the missing link? *Child Care Health Dev.*, (1365-2214 (Electronic)), July 2011. URL PM:21771000.

R. Harrington, D. Bredenkamp, C. Groothues, M. Rutter, H. Fudge, and A. Pickles. Adult outcomes of childhood and adolescent depression. III. links with suicidal behaviours. *J Child Psychol Psychiatry*, 35(0021-9630 (Print)):1309–1319, Oct. 1994. URL PM:7806612.

A. Harris and J. Seckl. Glucocorticoids, prenatal stress and the programming of disease. *Hormones and Behavior*, 59(3):279–289, Mar. 2011. ISSN 0018-506X. doi: 10.1016/j.yhbeh.2010.06.007. URL http://www.sciencedirect.com/science/article/pii/S0018506X10001674.

I. Harvey and G. McGrath. Psychiatric morbidity in spouses of women admitted to a mother and baby unit. *Br.J Psychiatry*, 152(0007-1250 (Print)):506–510, Apr. 1988. URL PM:3167402.

P. Hazell, D. O'Connell, D. Heathcote, and D. Henry. Tricyclic drug for depression in children and adolescents. *Cochrane Database Syst.Rev*, (4), 2010. doi: 10.1002/14651858.CD002317. URL http://www2.cochrane.org/reviews/en/ab002317.html.

Health Service Journal. VAMP comes alive. *Health Service Journal*, Aug. 1999.

D. Healy. Lines of evidence on the risks of suicide with selective serotonin reuptake inhibitors. *Psychother Psychosom.*, 72(0033-3190 (Print)):71–79, Mar. 2003. URL PM:12601224.

S. Hernández-Díaz, E. F. Schisterman, and M. A. Hernán. The birth weight Paradox uncovered? *Am. J. Epidemiol.*, 164(11):1115–1120, Dec. 2006. ISSN 0002-9262, 1476-6256. doi: 10.1093/aje/kwj275. URL http://aje.oxfordjournals.org/content/164/11/1115. PMID: 16931543.

E. Herrett, S. L. Thomas, W. M. Schoonen, L. Smeeth, and A. J. Hall. Validation and validity of diagnoses in the general practice research database: a systematic review. 69(1):414, 2010. ISSN 1365-2125. doi: 10.1111/j.1365-2125.2009.03537.x. URL http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2125.2009.03537.x/abstract.

A. Herxheimer and B. Mintzes. Antidepressants and adverse effects in young patients: uncovering the evidence. *CMAJ.*, 170(0820-3946 (Print)):487–489, Feb. 2004. URL PM:14970096.

S. E. Hetrick, J. E. McKenzie, G. R. Cox, M. B. Simmons, and S. N. Merry. Newer generation antidepressants for depressive disorders in children and adolescents. *Cochrane Database of Systematic Reviews*, 2012. URL http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004851.pub3/pdf.

K. Hogg, E. Price, C. Hanna, and W. Robinson. Prenatal and perinatal environmental influences on the human fetal and placental epigenome. *Clin Pharmacol Ther*, 92(6):

716–726, Dec. 2012. ISSN 0009-9236. URL http://dx.doi.org/10.1038/clpt.2012.141.

J. Homberg, J. Olivier, T. Blom, T. Arentsen, B. C. van, P. Schipper, G. Korte-Bouws, L. G. van, and L. Reneman. Fluoxetine exerts age-dependent effects on behavior and amygdala neuroplasticity in the rat. *PLoS One*, 6(1932-6203 (Electronic)):e16646, 2011. URL PM:21304948.

L. Horsfall, K. Walters, and I. Petersen. Identifying periods of acceptable computer usage in primary care research databases. *Pharmacoepidemiology and drug safety*, 22(1):64–69, 2013.

K. F. Huybrechts, K. Palmsten, H. Mogun, M. Kowal, J. Avorn, S. Setoguchi-Iwata, and S. Hernndez-Daz. National trends in antidepressant medication treatment among publicly insured pregnant women. *General Hospital Psychiatry*, 35 (3):265–271, May 2013. ISSN 0163-8343. doi: 10.1016/j.genhosppsych.2012.12.010. URL http://www.sciencedirect.com/science/article/pii/S0163834313000042.

J. Ioannidis and J. Lau. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA*, 285(0098-7484 (Print)):437–443, Jan. 2001. URL PM:11242428.

O. Ipsiroglu, A. Fatemi, I. Werner, M. Tiefenthaler, M. Urschitz, B. Schwarz, et al. [prevalence of sleep disorders in school children between 11 and 15 years of age]. *Wiener klinische Wochenschrift*, 113(7-8):235, 2001.

J. Jan, B. Michael, M. Bomben, R. Freeman, and W. Rietveld. Melatonin therapy of circadian rhythm sleep disorders in neurodevelopmentally disordered children: A neurological viewpoint. *Melatonin: From Molecules to Therapy.First Edition.Nova Science Publishers, Inc*, pages 581–604, 2006.

H. Jick, J. Kaye, and S. Jick. Antidepressants and the risk of suicidal behaviors. *JAMA*, 292(1538-3598 (Electronic)):338–343, July 2004.

S. Jick, A. Dean, and H. Jick. Antidepressants and suicide. *BMJ*, 310(0959-8138 (Print)): 215–218, Jan. 1995. URL PM:7677826.

E. O. Johnson, H. D. Chilcoat, and N. Breslau. Trouble sleeping and anxiety/depression in childhood. *Psychiatry research*, 94(2):93–102, 2000.

A. Josefsson and G. Sydsjö. A follow-up study of postpartum depressed women: recurrent maternal depressive symptoms and child behavior after four years. *Archives of women's mental health*, 10(4):141–145, 2007.

C. M. Judd and D. A. Kenny. Process analysis estimating mediation in treatment evaluations. *Eval Rev*, 5(5):602–619, Oct. 1981. ISSN 0193-841X, 1552-3926. doi: 10.1177/0193841X8100500502. URL http://erx.sagepub.com/content/5/5/602.

J. Jureidini. The black box warning: decreased prescriptions and increased youth suicide? *Am.J Psychiatry*, 164(0002-953X (Print)):1907–1910, Dec. 2007. doi: 10.1176/appi.ajp.2007.07091463. URL PM:18056248.

J. Jureidini and A. Tonkin. PAROXETINE IN MAJOR DEPRESSION. *Journal of the*

American Academy of Child & Adolescent Psychiatry, 42(5):514, May 2003. ISSN 0890-8567. doi: 10.1097/01.CHI.0000046825.95464.DA. URL http://www.sciencedirect.com/science/article/pii/S0890856709609321.

J. Jureidini, C. Doecke, P. Mansfield, M. Haby, D. Menkes, and A. Tonkin. Efficacy and safety of antidepressants for children and adolescents. *BMJ*, 328, Apr. 2004.

H. F. Kaiser. The varimax criterion for analytic rotation in factor analysis. *Psychometrika*, 23(3):187–200, Sept. 1958. ISSN 0033-3123, 1860-0980.

M. Kamphuis, B. Stegenga, N. Zuithoff, M. King, I. Nazareth, N. de Wit, and M. Geerlings. Recognition of depression in primary care: does it affect outcome? the PREDICT-NL study. *Fam.Pract.*, (1460-2229 (Electronic)), Aug. 2011. URL PM:21859837.

J. Kashani, R. McGee, S. Clarkson, J. Anderson, L. Walton, S. Williams, P. Silva, A. Robins, L. Cytryn, and D. McKnew. Depression in a sample of 9-year-old children, prevalence and associated characteristics. *Arch Gen Psychiatry*, 40(0003-990X (Print)):1217–1223, Nov. 1983. URL PM:6639292.

M. Keller, N. Ryan, M. Strober, R. Klein, S. Kutcher, B. Birmaher, O. Hagino, H. Koplewicz, G. Carlson, G. Clarke, G. Emslie, D. Feinberg, B. Geller, V. Kusumakar, G. Papatheodorou, W. Sack, M. Sweeney, K. Wagner, E. Weller, N. Winters, R. Oakes, and J. McCafferty. Efficacy of paroxetine in the treatment of adolescent major depression: a randomized, controlled trial. *J.Am.Acad.Child Adolesc.Psychiatry*, 40(0890-8567 (Print)):762–772, July 2001. URL PM:11437014.

B. Kerstis, G. Engström, K. Sundquist, M. Widarsson, and A. Rosenblad. The association between perceived relationship discord at childbirth and parental postpartum depressive symptoms: a comparison of mothers and fathers in sweden. *Upsala journal of medical sciences*, 117(4):430–438, 2012.

R. Kessler, P. Berglund, O. Demler, R. Jin, D. Koretz, K. Merikangas, A. Rush, E. Walters, and P. Wang. The epidemiology of major depressive disorder: results from the national comorbidity survey replication (NCS-R). *JAMA*, 289(1538-3598 (Electronic)): 3095–3105, June 2003. doi: 10.1001/jama.289.23.3095. URL PM:12813115.

R. Kessler, P. Berglund, O. Demler, R. Jin, K. Merikangas, and E. Walters. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the national comorbidity survey replication. *Arch Gen.Psychiatry*, 62(0003-990X (Print)):593–602, June 2005. doi: 10.1001/archpsyc.62.6.593. URL PM:15939837.

R. C. Kessler, K. A. McGonagle, M. Swartz, D. G. Blazer, and C. B. Nelson. Sex and depression in the national comorbidity survey i: Lifetime prevalence, chronicity and recurrence. *Journal of Affective Disorders*, 29(23):85–96, Oct. 1993. ISSN 0165-0327. URL http://www.sciencedirect.com/science/article/pii/016503279390026G.

C. W. Kessler RC. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the national comorbidity survey replication. *Arch Gen Psychiatry*, 62(6):617–627, June 2005. ISSN 0003-990X. doi: 10.1001/archpsyc.62.6.617. URL http://dx.doi.org/10.1001/archpsyc.62.6.617.

M. K. Kessler RC. Lifetime and 12-month prevalence of dsm-iii-r psychiatric dis-

orders in the united states: Results from the national comorbidity survey. *Arch Gen Psychiatry*, 51(1):8–9, Jan. 1994. ISSN 0003-990X. doi: 10.1001/archpsyc.1994.03950010008002. URL http://dx.doi.org/10.1001/archpsyc.1994.03950010008002.

Z. Khadjesari, L. Marston, I. Petersen, I. Nazareth, and K. Walters. Alcohol consumption screening of newly-registered patients in primary care: a cross-sectional analysis. *British Journal of General Practice*, 63(615):e706–e712, 2013.

N. Khan, S. Harrison, and P. Rose. Validity of diagnostic coding within the general practice research database: a systematic review. *Br J Gen.Pract*, 60(1478-5242 (Electronic)):e128–e136, Mar. 2010. URL PM:20202356.

H. Kim, M. Fay, E. Feuer, and D. Midthune. Permutation tests for joinpoint regression with applications to cancer rates. *Stat.Med.*, 19(0277-6715 (Print)):335–351, Feb. 2000. URL PM:10649300.

J. Kim-Cohen, A. Caspi, T. Moffitt, H. Harrington, B. Milne, and R. Poulton. Prior juvenile diagnoses in adults with mental disorder: Developmental follow-back of a prospective-longitudinal cohort. *Archives of General Psychiatry*, 60(7):709–717, 2003. doi: 10.1001/archpsyc.60.7.709. URL +http://dx.doi.org/10.1001/archpsyc.60.7.709.

H. King. Once upon a text: Hysteria from hippocrates. In S. Gilman, editor, *Hysteria beyond Freud*, pages 3–90. University of California Press, London, 1993.

I. Kirsch. St john's wort, conventional medication, and placebo: an egregious double standard. *Complementary Therapies in Medicine*, 11(3):193–195, Sept. 2003.

ISSN 0965-2299. doi: 10.1016/S0965-2299(03)00109-2. URL http://www.sciencedirect.com/science/article/pii/S0965229903001092.

D. F. Klein. The flawed basis for fda post-marketing safety decisions: the example of anti-depressants and children. *Neuropsychopharmacology*, 31(4):689–699, 2005.

J. B. Kotch, D. C. Browne, V. Dufort, J. Winsor, and D. Catellier. Predicting child maltreatment in the first 4 years of life from characteristics assessed in the neonatal period. *Child Abuse & Neglect*, 23(4):305–319, 1999.

L. Kriston and A. von Wolff. Not as golden as standards should be: Interpretation of the hamilton rating scale for depression. *Journal of Affective Disorders*, 128(12):175–177, Jan. 2011. ISSN 0165-0327. URL http://www.sciencedirect.com/science/article/pii/S0165032710004921.

K. Kroenke, R. L. Spitzer, and J. B. Williams. The phq-9. *Journal of general internal medicine*, 16(9):606–613, 2001.

B. M. Kuehn. Antidepressant use increases. *JAMA*, 306(20):2207–2207, Nov. 2011. URL http://jama.ama-assn.org/content/306/20/2207.1.short.

R. Kumar and K. Robson. A prospective study of emotional disorders in childbearing women. 144(1):35–47, Jan. 1984. URL http://bjp.rcpsych.org/content/144/1/35.abstract.

S. Kurstjens and D. Wolke. Effects of maternal depression on cognitive development of children over the first 7 years of life. *J.Child Psychol.Psychiatry*, 42(0021-9630 (Print)):623–636, July 2001. URL PM:11464967.

A. Lane, R. Keville, M. Morris, A. Kinsella, M. Turner, and S. Barry. Postnatal depression and elation among mothers and their partners: prevalence and predictors. *The British Journal of Psychiatry*, 171(6):550–555, 1997.

D. F. Levinson. The genetics of depression: a review. *Biological Psychiatry*, 60(2):84–92, 2006. ISSN 0006-3223.

P. Lewinsohn, P. Rohde, and J. Seeley. Major depressive disorder in older adolescents: prevalence, risk factors, and clinical implications. *Clin Psychol Rev*, 18(0272-7358 (Print)):765–794, Nov. 1998. URL PM:9827321.

G. Lewis, F. Rice, G. Harold, S. Collishaw, and A. Thapar. Investigating environmental links between parent depression and child depressive/anxiety symptoms using an assisted conception design. *J Am Acad.Child Adolesc.Psychiatry*, 50(1527-5418 (Electronic)):451–459, May 2011. URL PM:21515194.

J. Lewis, W. Bilker, R. Weinstein, and B. Strom. The relationship between time since registration and measured incidence rates in the general practice research database. *Pharmacoepidemiol.Drug Saf*, 14(1053-8569 (Print)):443–451, July 2005. URL PM:15898131.

J. Lewis, R. Schinnar, W. Bilker, X. Wang, and B. Strom. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiol.Drug Saf*, 16(1053-8569 (Print)):393–401, Apr. 2007. URL PM:17066486.

S. Lovestone and R. Kumar. Postnatal psychiatric illness: the impact on partners. 163

(2):210–216, Aug. 1993. URL http://bjp.rcpsych.org/content/163/2/210.abstract.

T. Luntamo, A. Sourander, D. Gyllenberg, L. Sillanmäki, M. Aromaa, T. Tamminen, K. Kumpulainen, I. Moilanen, and J. Piha. Do headache and abdominal pain in childhood predict suicides and severe suicide attempts? finnish nationwide 1981 birth cohort study. *Child Psychiatry & Human Development*, pages 1–9, 2013.

S. Maccari, P. V. Piazza, M. Kabbaj, A. Barbazanges, H. Simon, and M. L. Moal. Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. *J. Neurosci.*, 15(1):110–116, Jan. 1995. ISSN 0270-6474, 1529-2401. URL http://www.jneurosci.org/content/15/1/110. PMID: 7823121.

H. magazine". Hi magazine uncovers six month waits for nhs counselling. *HI magazine*, Aug. 2011. URL https://www.healthinsurancedaily.com/health-insurance/product-area/occupational-health/article376595.ece?page=1.

A. Maguire, B. Blak, and M. Thompson. The importance of defining periods of complete mortality reporting for research using automated data from primary care. *Pharmacoepidemiol.Drug Saf*, 18(1099-1557 (Electronic)):76–83, Jan. 2009. URL PM:19065600.

S.-L. Man, I. Petersen, M. Thompson, and I. Nazareth. Antiepileptic drugs during pregnancy in primary care: a UK population based study. *PLoS ONE*, 7(12):e52339, 2012. ISSN 1932-6203. PMID: 23272239.

M. W. Mandoki, M. R. Tapia, M. A. Tapia, G. Sumner, and J. L. Parker. Venlafaxine in the treatment of children and adolescents with major depression. *Psychopharmacology bulletin*, 33(1):149, 1997.

J. J. Mann, G. Emslie, R. J. Baldessarini, W. Beardslee, J. A. Fawcett, F. K. Goodwin, A. C. Leon, H. Y. Meltzer, N. D. Ryan, D. Shaffer, et al. Acnp task force report on ssris and suicidal behavior in youth. *Neuropsychopharmacology*, 31(3):473–492, 2005.

C. Manning and A. Gregoire. Effects of parental mental illness on children. *Psychiatry*, 8(1):7–9, 2009.

L. Marc. *Des femmes enceintes des nouvelles accouches et des nourrices [Treatise on the madness of pregnant women, recently delivered women, and nursing women]*. J.B.Baillire et Fils, Paris, 1858.

B. Mars, S. Collishaw, D. Smith, A. Thapar, R. Potter, R. Sellers, G. T. Harold, N. Craddock, F. Rice, and A. Thapar. Offspring of parents with recurrent depression: Which features of parent depression index risk for offspring psychopathology? *Journal of Affective Disorders*, 136(1-2):44–53, Jan. 2012. ISSN 0165-0327. doi: 10.1016/j.jad.2011.09.002. URL `http://www.sciencedirect.com/science/article/pii/S0165032711005283`.

L. A. Martin, H. W. Neighbors, and D. M. Griffith. The experience of symptoms of depression in men vs womenanalysis of the national comorbidity survey replication-symptoms of depression in men vs womensymptoms of depression in men vs women. *JAMA Psychiatry*, 2013.

C. Martins and E. Gaffan. Effects of early maternal depression on patterns of infant-mother attachment: A meta-analytic investigation. 41(6):737–746, Sept. 2000. ISSN 1469-7610. URL http://dx.doi.org/10.1111/1469-7610.00661.

C. A. Mathews and V. I. Reus. Assortative mating in the affective disorders: A systematic review and meta-analysis. *Comprehensive Psychiatry*, 42(4):257–262, July 2001. ISSN 0010-440X. doi: 10.1053/comp.2001.24575. URL http://www.sciencedirect.com/science/article/pii/S0010440X01465679.

S. Matthey, B. Barnett, J. Ungerer, and B. Waters. Paternal and maternal depressed mood during the transition to parenthood. *J.Affect.Disord.*, 60(0165-0327 (Print)):75–85, Nov. 2000. URL PM:10967366.

J. McArdle. Latent variable modeling of differences and changes with longitudinal data. *Annu.Rev Psychol*, 60(0066-4308 (Print)):577–605, 2009.

L. J. Meltzer, J. A. Mindell, J. A. Owens, and K. C. Byars. Use of sleep medications in hospitalized pediatric patients. *Pediatrics*, 119(6):1047–1055, 2007.

L. J. Meltzer, C. Johnson, J. Crosette, M. Ramos, and J. A. Mindell. Prevalence of diagnosed sleep disorders in pediatric primary care practices. *Pediatrics*, 125(6):e1410–e1418, 2010.

A. Mezulis, J. Hyde, and R. Clark. Father involvement moderates the effect of maternal depression during a child's infancy on child behavior problems in kindergarten. *J.Fam.Psychol.*, 18(0893-3200 (Print)):575–588, Dec. 2004. URL PM:15598163.

J. Milgrom, A. W. Gemmill, J. L. Bilszta, B. Hayes, B. Barnett, J. Brooks, J. Ericksen,

D. Ellwood, and A. Buist. Antenatal risk factors for postnatal depression: A large prospective study. *Journal of Affective Disorders*, 2008. ISSN 0165-0327.

J. A. Mindell. Sleep disorders in children. *Health Psychology*, 12(2):151, 1993.

J. Moncrieff, S. Wessely, and R. Hardy. Active placebos versus antidepressants for depression. *Cochrane.Database.Syst.Rev.*, (1469-493X (Electronic)):CD003012, 2004. doi: 10.1002/14651858.CD003012.pub2. URL PM:14974002.

P. Moran, C. Coffey, H. Romaniuk, C. Olsson, R. Borschmann, J. B. Carlin, and G. C. Patton. The natural history of self-harm from adolescence to young adulthood: a population-based cohort study. *The Lancet*, 379(9812):236–243, 2012.

T. I. Mueller, A. C. Leon, M. B. Keller, D. A. Solomon, J. Endicott, W. Coryell, M. Warshaw, and J. D. Maser. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *American Journal of Psychiatry*, 156(7): 1000–1006, 1999.

C. Murray and A. Lopez. Global mortality, disability, and the contribution of risk factors: Global burden of disease study. *Lancet*, 349(0140-6736 (Print)):1436–1442, May 1997. URL PM:9164317.

D. Murray and J. L. Cox. Screening for depression during pregnancy with the edinburgh depression scale (EDDS). *Journal of Reproductive and Infant Psychology*, 8(2):99–107, 1990. ISSN 0264-6838.

L. Murray. The impact of postnatal depression on infant development. *J.Child Psychol.Psychiatry*, 33(0021-9630 (Print)):543–561, Mar. 1992. URL PM:1577898.

L. Murray, C. Kempton, M. Woolgar, and R. Hooper. Depressed mothers' speech to their infants and its relation to infant gender and cognitive development. *J Child Psychol Psychiatry*, 34(0021-9630 (Print)):1083–1101, Oct. 1993. URL PM:8245134.

L. Murray, A. Fiori-Cowley, R. Hooper, and P. Cooper. The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. *Child Dev*, 67(0009-3920 (Print)):2512–2526, Oct. 1996a. URL PM:9022253.

L. Murray, A. Hipwell, R. Hooper, A. Stein, and P. Cooper. The cognitive development of 5-year-old children of postnatally depressed mothers. *J Child Psychol Psychiatry*, 37(0021-9630 (Print)):927–935, Nov. 1996b. URL PM:9119940.

L. Murray, A. Arteche, P. Fearon, S. Halligan, I. Goodyer, and P. Cooper. Maternal postnatal depression and the development of depression in offspring up to 16 years of age. *J Am Acad Child Adolesc Psychiatry*, 50(5):460–470, May 2011. ISSN 1527-5418. doi: 10.1016/j.jaac.2011.02.001. URL http://www.ncbi.nlm.nih.gov/pubmed/21515195. PMID: 21515195.

M. Murray, C. de Vries, and I. Wong. A drug utilisation study of antidepressants in children and adolescents using the general practice research database. *Arch Dis Child*, 89(1468-2044 (Electronic)):1098–1102, Dec. 2004. URL PM:15557040.

M. Murray, M. Thompson, P. Santosh, and I. Wong. Effects of the committee on safety of medicines advice on antidepressant prescribing to children and adolescents in the UK. *Drug Saf*, 28(0114-5916 (Print)):1151–1157, 2005. URL PM:16329717.

T. Muscat, K. Thorpe, and P. Obst. Disconfirmed expectations of infant behaviours and

postnatal depressive symptoms among parents. *Journal of Reproductive and Infant Psychology*, 30(1):51–61, 2012.

National Cancer Institute. Joinpoint regression program, version 3.5.1, July 2011. URL http://surveillance.cancer.gov/joinpoint/.

National Institute for Health and Clinical Excellence. CG28 depression in children and young people: NICE guideline. Technical report, National Institute for Health and Clinical Excellence, London, Sept. 2005.

National Institute for Health and Clinical Excellence. CG28 depression in adults: NICE guideline. Technical report, National Institute for Health and Clinical Excellence, London, Oct. 2009.

J. C. Nelson, A. J. Cook, O. Yu, S. Zhao, L. A. Jackson, and B. M. Psaty. Methods for observational post-licensure medical product safety surveillance. Dec. 2011. URL http://smm.sagepub.com/content/early/2011/12/01/0962280211413452.abstract.

R. Nesse. IS depression an adaptation? *Arch Gen Psychiatry*, 57(1):14–20, Jan. 2000. ISSN 0003-990X. doi: 10.1001/archpsyc.57.1.14. URL http://dx.doi.org/10.1001/archpsyc.57.1.14.

Neuroskeptic. Very severely stupid about depression, Aug. 2010. URL neuroskeptic.blogspot.co.uk/2010/08/very-severely-stupid.html.

A. Nishimura and K. Ohashi. Risk factors of paternal depression in the early postnatal period in japan. *Nursing & health sciences*, 12(2):170–176, 2010.

P. M. Oberlander TF. PRenatal effects of selective serotonin reuptake inhibitor antidepressants, serotonin transporter promoter genotype (slc6a4), and maternal mood on child behavior at 3 years of age. *Arch Pediatr Adolesc Med*, 164(5):444–451, May 2010. ISSN 1072-4710. doi: 10.1001/archpediatrics.2010.51. URL `http://dx.doi.org/10.1001/archpediatrics.2010.51`.

A. Ogdie, S. M. Langan, J. Parkinson, H. Dattani, K. Kostev, and J. M. Gelfand. Medical record databases. In B. Strom, S. E. Kimmel, and S. Hennessy, editors, *Pharmacoepidemiology*, volume 5, pages 224–243. 2012.

M. O'Hara and A. Swain. Rates and risk of postpartum depression - a meta-analysis. *International review of psychiatry*, 8(1):37–54, 1996.

M. M. Ohayon. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep medicine reviews*, 6(2):97–111, 2002.

M. Olfson, S. Marcus, and D. Shaffer. Antidepressant drug therapy and suicide in severely depressed children and adults - a case-control study. *Arch Gen Psychiatry*, 63(8):865–872, 2006. ISSN 0003-990X. URL `ISI:000239573200004`.

J. Olivier, T. Blom, T. Arentsen, and J. Homberg. The age-dependent effects of selective serotonin reuptake inhibitors in humans and rodents: A review. *Prog.Neuropsychopharmacol.Biol.Psychiatry*, 35(1878-4216 (Electronic)): 1400–1408, Aug. 2011a. URL `PM:20883714`.

J. D. A. Olivier, A. Valls, F. v. Heesch, A. Afrasiab-Middelman, J. J. P. M. Roelofs, M. Jonkers, E. J. Peeters, G. A. H. Korte-Bouws, J. P. Dederen, A. J. Kiliaan, G. J. Martens, D. Schubert, and J. R. Homberg. Fluoxetine administration to pregnant rats increases anxiety-related behavior in the offspring. *Psychopharmacology*, 217(3):419–432, Oct. 2011b. ISSN 0033-3158, 1432-2072. doi: 10.1007/s00213-011-2299-z. URL `http://link.springer.com/article/10.1007/s00213-011-2299-z`.

K. Outterson. Punishing health care fraud - is the GSK settlement sufficient? *N Engl J Med*, Sept. 2012. ISSN 0028-4793. doi: 10.1056/NEJMp1209249. URL `http://dx.doi.org/10.1056/NEJMp1209249`.

R. Owen and P. Tyrer. Benzodiazepine dependence. *Drugs*, 25(4):385–398, 1983.

J. Owens, S. Sheldon, R. Ferber, and M. Kryger. Epidemiology of sleep disorders during childhood. *Principles and practices of pediatric sleep medicine*, pages 27–33, 2005.

Paediatric Formulary Committee. *BNF for Children 2010-2011*, volume 2010-2011. BMJ Publishing Group, Pharmaceutical Press, and RCPCH Publications, London, 2010. URL `http://bnfc.org/bnfc/`.

K. Palmsten, S. Hernández-Díaz, K. F. Huybrechts, P. L. Williams, K. B. Michels, E. D. Achtyes, H. Mogun, and S. Setoguchi. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the united states. *BMJ: British Medical Journal*, 347, 2013.

L. A. Papp and J. M. Gorman. Suicidal preoccupation during fluoxetine treatment. *American Journal of Psychiatry*, 147(10):1380–1380, 1990.

Y. Parfitt and S. Ayers. Postnatal mental health and parenting: The importance of parental anger. *Infant Mental Health Journal*, 33(4):400–410, 2012.

C. M. Pariante. Depression, stress and the adrenal axis. 15(8):811812, 2003. ISSN 1365-2826. doi: 10.1046/j.1365-2826.2003.01058.x. URL `http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2826.2003.01058.x/abstract`.

M. Parsons. Paroxetine in adolescent major depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41(4):364, Apr. 2002. ISSN 0890-8567. doi: 10.1097/00004583-200204000-00003. URL `http://www.sciencedirect.com/science/article/pii/S0890856709608583`.

J. Paulson and S. Bazemore. Prenatal and postpartum depression in fathers and its association with maternal depression: a meta-analysis. *JAMA*, 303(1538-3598 (Electronic)): 1961–1969, May 2010. URL `PM:20483973`.

J. Paulson, S. Dauber, and J. Leiferman. Individual and combined effects of postpartum depression in mothers and fathers on parenting behavior. *Pediatrics*, 118(1098-4275 (Electronic)):659–668, Aug. 2006. URL `PM:16882821`.

J. F. Paulson, H. A. Keefe, and J. A. Leiferman. Early parental depression and child language development. *Journal of Child Psychology and Psychiatry*, 50(3):254–262, 2009.

S. Pawlby, D. Hay, D. Sharp, C. Waters, and C. Pariante. Antenatal depression and offspring psychopathology: the influence of childhood maltreatment. *Br J Psychiatry*, 199(1472-1465 (Electronic)):106–112, Aug. 2011.

J. Pearl. Direct and indirect effects. In *Proceedings of the seventeenth conference on uncertainty in artificial intelligence*, page 411420, 2001. URL `http://dl.acm.org/citation.cfm?id=2074073`.

R. M. Pearson, J. Evans, D. Kounali, G. Lewis, J. Heron, P. G. Ramchandani, T. G. OConnor, and A. Stein. Maternal depression during pregnancy and the postnatal periodrisks and possible mechanisms for offspring depression at age 18 yearsdepression during pregnancy and postnatal perioddepression during pregnancy and postnatal period. *JAMA Psychiatry*, 2013.

A. Perera, P. Gupta, R. Samuel, and B. Berg. A survey of anti-depressant prescribing practice and the provision of psychological therapies in a south london CAMHS from 2003-2006. *Child and adolescent mental health*, 12(2):70–72, 2007. ISSN 1475-357X.

I. Petersen, R. Gilbert, S. Evans, A. Ridolfi, and I. Nazareth. Oral antibiotic prescribing during pregnancy in primary care: Uk population-based study. *Journal of antimicrobial chemotherapy*, 65(10):2238–2246, 2010.

I. Petersen, R. E. Gilbert, S. J. W. Evans, S.-L. Man, and I. Nazareth. Pregnancy as a major determinant for discontinuation of antidepressants: an analysis of data from the health improvement network. *J Clin Psychiatry*, 72(7):979–985, July 2011. ISSN 1555-2101. doi: 10.4088/JCP.10m06090blu. PMID: 21457681.

A. Petitclerc, M. Boivin, G. Dionne, M. Zoccolillo, and R. E. Tremblay. Disregard for rules: the early development and predictors of a specific dimension of disruptive behavior disorders. *Journal of Child Psychology and Psychiatry*, 50(12):1477–1484, 2009.

M. Piccinelli and G. Wilkinson. Gender differences in depression: Critical review. 177 (6):486–492, Dec. 2000. URL http://bjp.rcpsych.org/content/177/6/486.abstract.

D. S. Pine, P. Cohen, D. Gurley, J. Brook, and Y. Ma. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Archives of general psychiatry*, 55(1):56, 1998.

S. Rabe-Hesketh and A. Skrondal. Classical latent variable models for medical research. 17(1):532, 2008.

L. S. Radloff. The CES-D scale a self-report depression scale for research in the general population. *Applied psychological measurement*, 1(3):385–401, 1977. ISSN 0146-6216.

G. Rait, K. Walters, M. Griffin, M. Buszewicz, I. Petersen, and I. Nazareth. Recent trends in the incidence of recorded depression in primary care. *Br J Psychiatry*, 195 (1472-1465 (Electronic)):520–524, Dec. 2009. URL PM:19949202.

P. Ramchandani and L. Psychogiou. Paternal psychiatric disorders and children's psychosocial development. *Lancet*, 374(1474-547X (Electronic)):646–653, Aug. 2009. URL PM:19411102.

P. Ramchandani, A. Stein, J. Evans, and T. O'Connor. Paternal depression in the postnatal period and child development: a prospective population study. *Lancet*, 365(1474-547X (Electronic)):2201–2205, June 2005a. URL PM:15978928.

P. Ramchandani, A. Stein, M. Hotopf, and N. Wiles. Early parental and child predict-

ors of recurrent abdominal pain at school age: results of a large population-based study. *J.Am.Acad.Child Adolesc Psychiatry*, 45(0890-8567 (Print)):729–736, June 2006. URL PM:16721323.

P. Ramchandani, T. O'Connor, J. Evans, J. Heron, L. Murray, and A. Stein. The effects of pre- and postnatal depression in fathers: a natural experiment comparing the effects of exposure to depression on offspring. *J.Child Psychol.Psychiatry*, 49(1469-7610 (Electronic)):1069–1078, Oct. 2008a. URL PM:19017023.

P. Ramchandani, A. Stein, T. O'Connor, J. Heron, L. Murray, and J. Evans. Depression in men in the postnatal period and later child psychopathology: a population cohort study. *J.Am.Acad.Child Adolesc Psychiatry*, 47(1527-5418 (Electronic)):390–398, Apr. 2008b. URL PM:18388761.

P. G. Ramchandani, M. Hotopf, B. Sandhu, A. Stein, and ALSPAC Study Team. The epidemiology of recurrent abdominal pain from 2 to 6 years of age: results of a large, population-based study. *Pediatrics*, 116(1):46–50, July 2005b. ISSN 1098-4275. doi: 10.1542/peds.2004-1854. PMID: 15995029.

J. Rampono, S. Proud, L. P. Hackett, J. H. Kristensen, and K. F. Ilett. A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. 7(3):329334, 2004. URL http://journals.cambridge.org/production/action/cjoGetFulltext?fulltextid=241748.

V. Raskin, J. Richman, and C. Gaines. Patterns of depressive symptoms in expectant and new parents. *Am.J.Psychiatry*, 147(0002-953X (Print)):658–660, May 1990.

A. Ravelli, J. van der Meulen, R. Michels, C. Osmond, D. Barker, C. Hales, and O. Bleker. Glucose tolerance in adults after prenatal exposure to famine. *The Lancet*, 351(9097):173–177, Jan. 1998. ISSN 0140-6736. doi: 10.1016/S0140-6736(97)07244-9. URL http://www.sciencedirect.com/science/article/pii/S0140673697072449.

N. S. Rawson, G. L. Pearce, and W. H. Inman. Prescription-event monitoring: methodology and recent progress. *Journal of Clinical Epidemiology*, 43(5):509–522, 1990.

D. Regier, R. Hirschfeld, F. Goodwin, J. Burke, J. Lazar, and L. Judd. The NIMH depression awareness, recognition, and treatment program: structure, aims, and scientific basis. *Am.J Psychiatry*, 145(0002-953X (Print)):1351–1357, Nov. 1988. URL PM:2847566.

B. M. Roane and D. J. Taylor. Adolescent insomnia as a risk factor for early adult depression and substance abuse. *Sleep*, 31(10):1351, 2008.

W. J. Robins LN. The composite international diagnostic interview: An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Arch Gen Psychiatry*, 45(12):1069–1077, Dec. 1988. ISSN 0003-990X. doi: 10.1001/archpsyc.1988.01800360017003. URL http://dx.doi.org/10.1001/archpsyc.1988.01800360017003.

K. Rothman and K. Michels. The continuing unethical use of placebo controls. *N.Engl.J Med*, 331(0028-4793 (Print)):394–398, Aug. 1994. URL PM:8028622.

P. Royston and D. G. Altman. Regression using fractional polynomials of continuous

covariates: Parsimonious parametric modelling. *Journal of the Royal Statistical Society.Series C (Applied Statistics)*, 43(3):429–467, Jan. 1994. ISSN 00359254. URL http://www.jstor.org/stable/2986270. ArticleType: research-article / Full publication date: 1994 / Copyright - 1994 Royal Statistical Society.

D. Rubin. Estimating causal effects from large data sets using propensity scores. *Annals of internal medicine*, 127:757–763, 1997. ISSN 0003-4819.

A. Sadeh, R. Gruber, and A. Raviv. Sleep, neurobehavioral functioning, and behavior problems in school-age children. 73(2):405–417, 2002. ISSN 1467-8624. doi: 10.1111/1467-8624.00414. URL http://dx.doi.org/10.1111/1467-8624.00414.

N. Sartorius, T. B. Üstün, Y. Lecrubier, and H.-U. Wittchen. Depression comorbid with anxiety: Results from the who study on" psychological disorders in primary health care.". *The British journal of psychiatry*, 1996.

K. Sayal, V. Tischler, C. Coope, S. Robotham, M. Ashworth, C. Day, A. Tylee, and E. Simonoff. Parental help-seeking in primary care for child and adolescent mental health concerns: qualitative study. *The British Journal of Psychiatry*, 197(6):476–481, 2010.

S. Schneeweiss, A. Patrick, D. Solomon, C. Dormuth, M. Miller, J. Mehta, J. Lee, and P. Wang. Comparative safety of antidepressant agents for children and adolescents regarding suicidal acts. *Pediatrics*, 125(1098-4275 (Electronic)):876–888, May 2010. URL PM:20385637.

C. J. Schnoes, B. R. Kuhn, E. F. Workman, and C. R. Ellis. Pediatric prescribing practices for clonidine and other pharmacologic agents for children with sleep disturbance. 45 (3):229–238, Apr. 2006. URL http://cpj.sagepub.com/content/45/3/229.abstract.

S. Scott. Parenting quality and childrens mental health. 25(4):301–306, July 2012. ISSN 0951-7367. doi: 10.1097/YCO.0b013e328354a1c5. URL http://ovidsp.tx.ovid.com/sp-3.8.1a/ovidweb.cgi?QS2=434f4e1a73d37e8c54b7bccef7797d0c101827e467f40a13269a465b39e3fec5c

L. Sharp and M. Lipsky. Screening for depression across the lifespan: a review of measures for use in primary care settings. *Am Fam Physician*, 66(6):1001–1009, 2002.

J. G. Simeon, V. F. Dinicola, H. B. Ferguson, and W. Copping. Adolescent depression: a placebo-controlled fluoxetine treatment study and follow-up. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 14(5):791–795, 1990.

J. F. Simonds and H. Parraga. Prevalence of sleep disorders and sleep behaviors in children and adolescents. *Journal of the American Academy of Child Psychiatry*, 21(4): 383–388, 1982.

D. Sinclair and L. Murray. Effects of postnatal depression on children's adjustment to school. teacher's reports. *Br.J Psychiatry*, 172(0007-1250 (Print)):58–63, Jan. 1998. URL PM:9534834.

M. S. Smith, S. P. Martin-Herz, W. M. Womack, and J. L. Marsigan. Comparative study of anxiety, depression, somatization, functional disability, and illness attribution in adolescents with chronic fatigue or migraine. *Pediatrics*, 111(4):e376–e381, 2003.

E. Soliday, K. Cluskey-Fawcett, and M. O'Brien. Postpartum affect and depressive symptoms in mothers and fathers. *Am.J.Orthopsychiatry*, 69(0002-9432 (Print)):30–38, Jan. 1999. URL PM:9990434.

W. J. Spitzer RL. The structured clinical interview for DSM-III-R (SCID): i: history, rationale, and description. *Arch Gen Psychiatry*, 49(8):624–629, Aug. 1992. ISSN 0003-990X. doi: 10.1001/archpsyc.1992.01820080032005. URL http://dx.doi.org/10.1001/archpsyc.1992.01820080032005.

P. Stark and C. Hardison. A review of multicenter controlled studies of fluoxetine vs. imipramine and placebo in outpatients with major depressive disorder. *J.Clin.Psychiatry*, 46(0160-6689 (Print)):53–58, Mar. 1985. URL PM:3882682.

J. A. Sterne, M. A. Hernán, B. Ledergerber, K. Tilling, R. Weber, P. Sendi, M. Rickenbach, J. M. Robins, and M. Egger. Long-term effectiveness of potent antiretroviral therapy in preventing aids and death: a prospective cohort study. *The Lancet*, 366 (9483):378–384, 2005.

M. Stone, T. Laughren, M. Jones, M. Levenson, P. Holland, A. Hughes, T. Hammad, R. Temple, and G. Rochester. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US food and drug administration. *BMJ*, 339(1468-5833 (Electronic)):b2880, 2009. URL PM:19671933.

M. Teicher, C. Glod, and J. Cole. Antidepressant drugs and the emergence of suicidal tendencies. *Drug Saf*, 8(0114-5916 (Print)):186–212, Mar. 1993. URL PM:8452661.

P. The NHS Information Centre and P. C. Services. Prescription compliance: a review of the proportion of prescriptions dispensed. Technical report, Sept. 2011. URL

http://www.ic.nhs.uk/webfiles/publications/007_Primary_Care/Prescribing/Prescribing%20Compliance/Prescribing_Compliance_report_070911.pdf.

C. Thiedke. Sleep disorders and sleep problems in childhood. *Am Fam Physician*, 63(2): 277–285, 2001.

K. Thomas and M. Schmidt. Glaxo agrees to pay $3 billion in fraud settlement. July 2012. URL http://www.nytimes.com/2012/07/03/business/glaxosmithkline-agrees-to-pay-3-billion-in-fraud-settlement.html?_r=2&nl=todaysheadlines&emc=edit_th_20120703.

K. J. Thorpe, T. Dragonas, and J. Golding. The effects of psychosocial factors on the mother's emotional well-being during early parenthood: A cross-cultural study of britain and greece. 10(4):205–217, 1992. ISSN 0264-6838. doi: 10.1080/02646839208403954. URL http://www.tandfonline.com/doi/abs/10.1080/02646839208403954.

C. M. R. UK. CSD medical research UK, 2012. URL http://csdmruk.cegedim.com/our-data/statistics.shtml.

L. Valeri and T. J. VanderWeele. Mediation analysis allowing for exposuremediator interactions and causal interpretation: Theoretical assumptions and implementation with SAS and SPSS macros. 18(2):137, 2013. URL http://psycnet.apa.org/journals/met/18/2/137/.

T. VanderWeele and S. Vansteelandt. Conceptual issues concerning mediation, interven-

tions and composition. 2:457468, 2009. URL http://archive.ugent.be/record/954554.

T. J. VanderWeele and S. Vansteelandt. Odds ratios for mediation analysis for a dichotomous outcome. 172(12):13391348, 2010.

E. E. von, D. Altman, M. Egger, S. Pocock, P. Gotzsche, and J. Vandenbroucke. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*, 370(1474-547X (Electronic)):1453–1457, Oct. 2007. URL PM:18064739.

P. Vostanis, A. Graves, H. Meltzer, R. Goodman, R. Jenkins, and T. Brugha. Relationship between parental psychopathology, parenting strategies and child mental health. *Soc Psychiat Epidemiol*, 41(7):509–514, July 2006. ISSN 0933-7954, 1433-9285. doi: 10.1007/s00127-006-0061-3. URL http://link.springer.com/article/10.1007/s00127-006-0061-3.

F. Waechter. Paroxetine must not be given to patients under 18. 326(7402):1282, June 2003. doi: 10.1136/bmj.326.7402.1282-b. URL http://www.bmj.com/content/326/7402/1282.3.short.

A. Wagner, S. Soumerai, F. Zhang, and D. Ross-Degnan. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm.Ther*, 27 (0269-4727 (Print)):299–309, Aug. 2002. URL PM:12174032.

K. D. Wagner, P. Ambrosini, M. Rynn, C. Wohlberg, R. Yang, M. S. Greenbaum, A. Childress, C. Donnelly, D. Deas, et al. Efficacy of sertraline in the treatment of children

and adolescents with major depressive disorder. *JAMA: the journal of the American Medical Association*, 290(8):1033–1041, 2003.

L. S. Walker and J. W. Greene. Children with recurrent abdominal pain and their parents: more somatic complaints, anxiety, and depression than other patient families? *Journal of Pediatric Psychology*, 14(2):231–243, 1989.

M. Wall and R. Li. Comparison of multiple regression to two latent variable techniques for estimation and prediction. *Stat.Med*, 22(0277-6715 (Print)):3671–3685, Dec. 2003.

T. Walley and A. Mantgani. The UK general practice research database. *Lancet*, 350: 1097–1099, 1997.

R. Warner, L. Appleby, A. Whitton, and B. Faragher. Demographic and obstetric risk factors for postnatal psychiatric morbidity. 168(5):607–611, May 1996. URL `http://bjp.rcpsych.org/content/168/5/607.abstract`.

A. Weintrob. Paroxetine in adolescent major depression. *Journal of the American Academy of Child & Adolescent Psychiatry*, 41(4):363–364, Apr. 2002. ISSN 0890-8567. doi: 10.1097/00004583-200204000-00002. URL `http://www.sciencedirect.com/science/article/pii/S0890856709608571`.

C. West, J. Ritchie, and J. Weiss. Paroxetine-induced increase in activity of locus coeruleus neurons in adolescent rats: implication of a countertherapeutic effect of an antidepressant. *Neuropsychopharmacology*, 35(1740-634X (Electronic)):1653–1663, July 2010. URL `PM:20357759`.

T. West and C. Ortiz. US complaint against GSK. Technical report,

Nov. 2011. URL http://www.justice.gov/opa/documents/gsk/us-complaint.pdf.

C. Whittington, T. Kendall, P. Fonagy, D. Cottrell, A. Cotgrove, and E. Boddington. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet*, 363(1474-547X (Electronic)):1341–1345, Apr. 2004. URL PM:15110490.

WHO. Depression, 2011. URL http://www.who.int/mental_health/management/depression/definition/en/.

S. Wilson, D. Nutt, C. Alford, S. Argyropoulos, D. Baldwin, A. Bateson, T. Britton, C. Crowe, D. Dijk, C. Espie, P. Gringras, G. Hajak, C. Idzikowski, A. Krystal, J. Nash, H. Selsick, A. Sharpley, and A. Wade. British association for psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders. 24(11):1577–1601, Nov. 2010.

D. Wong, J. Horng, F. Bymaster, K. Hauser, and B. Molloy. A selective inhibitor of serotonin uptake: Lilly 110140, 3-(p-trifluoromethylphenoxy)-n-methyl-3-phenylpropylamine. *Life Sci*, 15(0024-3205 (Print)):471–479, Aug. 1974. URL PM:4549929.

J. Woodman, J. Allister, I. Rafi, S. de Lusignan, J. Belsey, I. Petersen, and R. Gilbert. A simple approach to improve recording of concerns about childmaltreatment in primary care records: developing a quality improvement intervention. *British Journal of General Practice*, 62(600):e478–e486, 2012.

World Health Organisation. International statistical classification of diseases and related health problems, 2007.

C. Zahn-Waxler, B. Klimes-Dougan, and M. J. Slattery. Internalizing problems of childhood and adolescence: Prospects, pitfalls, and progress in understanding the development of anxiety and depression. *Development and Psychopathology*, 12(03):443–466, 2000.

G. Zilboorg. Depressive reactions related to parenthood. *The American Journal of Psychiatry*, 1931. ISSN 1535-7228.