The physical health of children of mothers experiencing mental illness in a UK primary care cohort

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ABBREVIATIONS

Abbreviation	Definition
AE	Accident and Emergency
BAME	Black, Asian and Minority Ethnic
CAMHEE	Child and Adolescent Mental Health in Enlarged Europe
CAPRI	Children and Adolescents with Parental Mental Illness
CPRD	Clinical Practice Research Datalink
CRD	Current Registration Date
DAG	Directed Acyclic Graph
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTaP	Diphtheria, Tetanus, acellular Pertussis
DZ	Data Zones
ERC	European Research Council
EU	European Union
FDAC	Family Drug & Alcohol Court
GMS	General Medical Services
GP	General Practitioner
GPRD	General Practice Research Database
HES	Hospital Episodes Statistics
Hib	Haemophilus influenzae type b
HPA	Hypothalamic-pituitary adrenal
HR	Hazard Ratio
HRA	Health Research Authority
ICD	International Classification of Disease
IMD	Index of Multiple Deprivation
IPV	Inactivated Polio Vaccine
IRR	Incident Rate Ratio
ISAC	Independent Scientific Advisory Committee
LCD	Last Collection Date
LSOA	Lower Super Output Area
MHRA	Medicine and Healthcare Products Regulatory Agency
MMI	Maternal Mental Illness
MMR	Mumps Measles Rubella
NCIN	National Cancer Intelligence Network
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
OCD	Obsessive-compulsive disorder
ONS	Office for National Statistics
OR	Odds Ratio
PS	Propensity Score
PSC	Propensity Score Calibration
PTSD	Post-traumatic stress disorder
QOF	Quality and Outcomes Framework
RR	Rate Ratio
SAPAS	Standardised Assessment of Personality-Abbreviated Scale
SCIE	The Social Care Institute for Excellence
SCIMITAR	Smoking Cessation for People with Severe Mental Illness
TOD	Transferred Out Date
UTS	Up to Standard

THESIS ABSTRACT

The physical health of children of mothers experiencing mental illness in a UK primary care cohort

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy (PhD)

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Background: In the UK, the prevalence of children living with Mothers with Mental Illness (MMI) is increasing and improving the lives of these children is an urgent concern. Although we know that children with MMI experience multiple challenges including congenital anomalies and neurodevelopmental problems, less is known about how and when mother's mental illness affects their child's physical health outcomes.

Aims: The main aim of this thesis is to better understand how MMI (depression, anxiety, psychotic disorders, substance and alcohol misuse disorders, personality and eating disorders) affects some of the common and rare physical health outcomes including preventative healthcare use as vaccination uptake along with childhood obesity, atopic disorders and childhood cancer in their children.

Methods: To address the aim of this thesis, cohorts were extracted from the Clinical Practice Research Datalink (CPRD-GOLD) which is the largest anonymous primary healthcare data source in the world and linked to external data sources namely Hospital Episode Statistics (HES) and Index of Multiple Deprivation (IMD). The effects of MMI on childhood vaccination uptake were quantified using logistic regression models. The risk of other physical health outcomes which are atopic disorders and childhood cancers among children with MMI were investigated using Cox proportional hazard models.

Results: Maternal mental illness was found to have a considerable effect on childhood physical health outcome and the risk of outcome varied on the type of maternal mental illness to which the child is exposed. Children exposed to maternal addiction disorders were the most vulnerable group as they have the highest risk of missing vaccinations and risk of developing cancer in childhood. In terms of atopic disorders, children exposed to maternal depression and anxiety were at highest risk compared to children exposed to other types of MMI. It was also observed that children with MMI were more likely to be from most deprived areas and had mothers who actively smoke, which are highly associated with mental illness and physical health outcomes.

Conclusion: Findings of this thesis indicate that in the UK, children living with maternal mental illness are at risk of missing necessary vaccinations and developing various physical illnesses including atopic disorders and childhood cancers. The public health interventions and policies could benefit from acknowledging the effects of MMI on children's health which may play an important role in reducing the health inequalities that are associated with this group by developing better resource allocation and service provision.

DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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PREFACE

This thesis is submitted in the alternative format because the area that has been investigated was suitable for production of academic papers to be published in peer-reviewed journals. It was also considered that these would also contribute to the author's career development. The results chapter of this thesis contains five research papers (three substantial and two brief research papers) where the author of this thesis is the first- author as she have led the planning of each study, conducted all of the analyses and drafted all manuscripts.

For each paper presented in this thesis, a statement outlining the contributions of each author and description of the paper in the context of the thesis is provided. One of the papers has been published in European Journal of Epidemiology, three of them are submitted and the other is currently being prepared for submission.

All the papers in this thesis are reproduced as published/submitted, with the exception of the numbering of the tables, figures, references and appendices, as these have been changed to fit with the thesis formatting. All papers have been written during the PhD study. Other research papers that she has contributed during her PhD study have been cited in the text and included in the appendices.

ABOUT AUTHOR

I completed my BSc in Applied Psychology at the University of Durham in 2015 and MSc in Children and Young People's Mental Health at the University of Edinburgh in 2016. Before I started my PhD at the University of Manchester in 2018, I joined NHS Scotland as a data analyst and worked there for 14 months.

Being a data analyst at NHS Scotland was really rewarding because I was contributing to Scotland's public health through data. I enjoyed being a data analyst and was very motivated to gain more skills and knowledge so I could become an expert in this area in the future. At this point, I came across Prof Abel and Dr Pierce's PhD project in psychiatric epidemiology which was perfect for me as it covered my interests in mental health and the use of 'big data'.

Now, looking back over my three-year PhD journey in this amazing research team, I realise how much I have changed and evolved academically, emotionally and, of course, personally. I deeply appreciate the work I have undertaken: I believe I have played an important role in raising awareness about a very special group of children that rarely have their voice heard – the children living with parental mental illnesses.

When COVID-19 hit the UK, I think the importance of my work only increased more: having access to such a large prospective electronic health care dataset allowed me to conduct important studies which would be very hard to do using traditional methods. With COVID-19, as a society, I think we are beginning even more to appreciate the availability and importance of national healthcare datasets; these are already playing an important role in tackling the pandemic. Yet, this is not readily available in many other countries. I am from a tiny island in the Mediterranean Sea, Cyprus; and I have had many moments of thinking that if we too had such data availability, like in the UK, how so many things could have been achieved in public health. This makes me think that, in future, this could be a goal for my career: to develop such a system in Cyprus.

Finally, with COVID-19, I believe we have entered a new era of digital transformation; this has led me to a better understanding and appreciation of agile working in epidemiology, an area which I believe will become more recognised and only more of an essential practice in the near future; so I am delighted to have started my journey in becoming an expert in epidemiology through this doctorate. I am so grateful that I was able to conduct my research and become a member of a research team led by Prof Abel. Knowing that I could help one of the most vulnerable groups in the UK with my research is the most satisfying feeling and I hope you as readers will see this reflected in my thesis.

ACKNOWLEDGMENTS

This thesis is the culmination of three years of study and it would have not been possible without so many people in my life and acknowledging these people with few words is not a fair task; however, I will try my best.

First and foremost, a heartfelt thanks to my supervisors, Dr **Matthias Pierce**, Prof **Kathryn M Abel** and Professor **Darren M Ashcroft.** It has been a privilege to work with you all. Hope to be able to work with you again in the near future.

Matthias, special thanks to you, for trusting and having faith in me. Working under your guidance was such a joyful experience, I learned so much with you… Many thanks for always being there, no matter how busy life was.

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Darren, thank you so much for contributing a different perspective to my PhD; your input on each research has been so valuable. Thank you so much being very responsive and kind to me. I am also profoundly grateful for the hard work of Dr **Holly Hope** for her valuable contribution to the studies presented in this thesis. It was such a pleasure to work with you, Holly. Thank you for your support all the way. I would also like to thank my postgraduate advisor Dr **Kimberly Dienes**, who has supported me all the way and made sure I was doing well.

Fortunately, I have also the privilege of having a lovely family and friends who helped me in getting through this PhD journey:

Mum and dad, it is just impossible for me to type these words without getting my eyes filled with tears. I would not become who I am today without your immense efforts for me. Thank you so much for supporting and loving me unconditionally. I love you both to the moon and back. This thesis is dedicated to you.

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My dear friend **Jasmine Dinand** from Cyprus, **Franka Gerhard** from Switzerland and my beloved colleagues **Amye Thomson** and **Carolanne D'arcy** from Public Health Scotland. Thank you so much for your close friendship and work support. I love you all!

STRUCTURE OF THESIS

The thesis is presented in eight chapters (numbered 1 to 8). Each chapter contains numbered sections (e.g. 1.1) and subsections (e.g. 1.1.1).

Chapter 1 introduces the reader to the existing literature on effects of maternal mental illness on child's physical health outcomes and provides an overview of the research aims of the thesis. Chapter 2 describes in detail the data and different methodologies used in the following results chapters.

Chapters 3 to 7 contains the thesis results and are prepared for publication in high impact academic journals. Chapter 3 examines the effects of maternal mental illness on childhood vaccination uptake. This chapter also includes a commentary on childhood vaccination uptake in the context of the COVID-19 pandemic. Chapter 4 investigates the feasibility of a study to examine the effects of maternal mental illness on childhood obesity using the primary care data. Chapter 5 considers the effect of maternal mental illness on childhood atopic disorders. Chapter 6 examines the perinatal smoking rates of women with and without mental illness and Chapter 7 investigates the effect of maternal mental illness on childhood cancers. Finally, Chapter 8 summarises the key findings of the thesis, discusses the strength and weaknesses of studies and discusses the findings in the context of public health.

CHAPTER 1- INTRODUCTION TO MATERNAL MENTAL ILLNESS AND CHILD PHYSICAL HEALTH

The effect of maternal mental illness on children's physical well-being has started to receive recognition by researchers, policymakers and healthcare providers. Whilst, there is evidence from high quality longitudinal data that the children of mentally ill mothers are at high risk of developing congenital anomalies[1], of being stillborn and of premature death[2], the risk of more common child physical illnesses are less well understood. Therefore, this chapter intends to provide an overview of the relationship between maternal mental illness and child physical illnesses. This thorough overview will be provided in five sections. In section 1.1, prevalence rates for mental illness among mothers are reported. In section 1.2, the different types of maternal mental illnesses are described. In section 1.3, the current evidence on the impact of maternal mental illness on specific child's physical health outcomes is compiled and evaluated. Then, in section 1.4, current policies for children and young people in the UK are discussed with reference to the physical health of children with mentally ill mothers. Finally, in section 1.5, thesis rationale and in section 1.6 thesis overview and objectives are stated.

1.1 HOW MANY CHILDREN ARE LIVING WITH MOTHERS EXPERIENCING MENTAL ILLNESS?

Up until 2019, population estimates of children exposed to maternal mental illness [3,4] were based on surveys. Considering the fact that mentally ill people are less likely to participate in such surveys because of social stigma [5,6], it is possible that these studies underestimated the number of children exposed to maternal mental illness. Moreover, surveys also tend to under-sample those from low socio-economic background [4] because, those from low socio-economic background are less likely to respond to surveys [7] which leads to a study sample which is systematically different from the general population.

Taking into account these limitations, in June 2019, we published the largest study in the UK reporting the estimated numbers of children living with maternal mental illness. We estimated that one in four UK children are living with a mother experiencing mental illness [8]. We also report that this number is increasing, from 22% between 2005-2007 to 25% between 2015-2017. Reasons for this increase are unclear, however may be a result of psychotropic medications that have lower effect on fertility.

Routinely estimated prevalence rates of children exposed to maternal mental illness is crucial to plan policy and allocate resources for existing as well as new services serving children exposed to maternal mental illness. Moreover, better-targeted support can be achieved by understanding the likely kinds of maternal mental illness to which children are exposed. Furthermore, when planning public health policies such as Healthy Child Programme [9] (*see section 1.4*) for these children, it is important to consider the rate, range, severity and frequency of maternal mental illnesses and their association with socio economic variables [10]. Each step—from establishing routine prevalence rates to designing intervention and support policies—can be accomplished at a population level by using routinely-collected health data.

Repeated epidemiological examinations based on routinely collected data could monitor trends in the number of children with mentally ill mothers along with variations in possible risk factors. These studies could not only inform policymakers to formulate more appropriate public health initiatives and care pathways for children and young people, but also be used to assess policy effectiveness [10]. The next section briefly describes different types of maternal mental illnesses.

1.2 TYPES OF MATERNAL MENTAL ILLNESSES

An understanding of maternal mental illness is essential when developing public health policies for vulnerable children [11]. Some mental illnesses are chronic and some of them can develop during the perinatal period [12]. In this section, the prevalence of depression, anxiety, psychotic disorders, substance misuse, eating and personality disorders among mothers is reported.

Depression and anxiety disorders are the most common mental illnesses observed among women as they are twice more likely to experience these common mental illnesses than men [13]. The lifetime prevalence of depression among women is estimated as 20% [14] and the prevalence rate of depression among mothers during pregnancy is estimated to be 11% [15] and 7% over the first three post-partum months [16] while in our prevalence study [17] we found that 18% of mothers experience depression between birth and two years postnatal.

Anxiety disorders, such as generalised anxiety disorder (GAD), among new mothers usually involve worries about the health of the baby; or post-traumatic stress disorder (PTSD) which may present itself after a traumatic birth experience, or can be triggered if pre-existing symptoms of past trauma exists. Longitudinal studies report that 9%-22% of new mothers experience anxiety disorders during pregnancy [15,18,19] and 17%-22% during the post-partum period [20,21]. Using the primary care data [17], we observed that 8% of mothers experienced anxiety disorders between birth and two years postnatal.

Psychotic disorders is an umbrella term for disorders such as mania, mixed episodes, bipolar, schizophrenia and post-partum psychosis [22] and they are considered to be the most severe mental illnesses [23]. Psychotic disorders are relatively rare in mothers [24] as the fertility in women with psychosis is greatly reduced [25,26]. For instance, prevalence rates of schizophrenia among mothers was estimated at 0.3% in the UK [25] and post-partum psychosis was estimated to affect 1 in 1000 women [27,28]. We reported affective psychotic disorders among mothers from birth to two year postnatal as 0.1% and non-affective psychotic disorders as 0.2%. Specifically, women with a bipolar disorder have high risk of experiencing post-partum psychosis when compared to women with other mental illnesses as it is estimated that the relapse of bipolar disorder risk during post-natal period is 37% [23].

Eating disorders are associated with severe disturbances in eating behaviour and body image. There are three types of eating disorders, namely anorexia nervosa (AN) which is characterised by extreme food restriction and underweight; binge eating (BE) which involves recurrent cycles of binge eating accompanied by a loss of control and bulimia nervosa (BN) which involves purging after binge eating. Women with eating disorders can experience persisting symptoms during pregnancy [29] and post-partum [30]. Although information on the prevalence of eating disorders among child bearing women is limited, existing studies report lifetime eating disorders among women as 3% and during pregnancy as 0.4% [29] and 0.1%between birth and two year postnatal [17]. Women with eating disorders are also known to have high risk of post-partum depression and anxiety [31].

Personality disorders (paranoid, schizoid, schizotypal, histrionic, narcissistic, borderline, antisocial, avoidant, dependent, obsessive-compulsive) can be characterised with inflexible, pervasive, deviant patterns of behaviour and social relations. Prevalence of personality disorders among mothers is uncommon relatively. In the UK, population estimates of personality disorders among women were reported as 3% [32]; however, the prevalence of disordered personality traits among pregnant women was estimated as 16% in one London based study (N=541) [33]. Our recent study (N=783,710) found that the prevalence of personality disorders among mothers during birth and two year postnatal as 0.1% [17] while a Swedish study (N=625) reported the prevalence of personality disorders during perinatal period as 6% [34].

Substance-misuse disorders are related to alcohol and drugs such as cannabis, hallucinogens, inhalants, opioids, sedatives, hypnotics, stimulants and tobacco. According to latest adult psychiatric morbidity survey in England, 13% of women reported hazardous levels of drinking and 3% reported alcohol symptoms indicating dependence [35]. Illicit drug use among women was 6% according to 2018/19 crime survey for England and Wales [36]. The information on prevalence rates of substance misuse during perinatal period is limited. We reported the prevalence of alcohol misuse among mothers from birth to two year postnatal as 0.1% and drug misuse as 0.2% [17]. In England, the prevalence rate of neonatal drug withdrawal syndrome, which is caused by exposure

to drugs in utero, was reported as 2.7 per 1,000 live births in 2011 [37]. Substance-misuse disorders contribute to poor physical health outcomes for children. For instance, lilicit drug and alcohol addiction are linked to childhood cancer [38,39].

Maternal age is one of the most important risk factors for maternal mental illness. In our recent retrospective matched control study [40], we reported the effect of having a child on post-partum mental illness is highly age dependent. For example we found that mothers aged 15-19 were seven times more likely to experience depression (adjusted Hazard Ratio (aHR) 7.09, 95%CI 6.65–7.56) than non-mothers of the same age, whereas for older women the increase in risk was (aHR 2.37, 95%CI=2.28–2.46) [40].

Other factors, such as poverty, environmental inequalities (e.g. inadequate housing, exposure to air pollution) and inadequate social support may also contribute to poor maternal mental health and mother-infant interactions [41,42], which could then adversely affect the physical health of the child. The next sub-section reviews the current literature on the effects of maternal mental illness on children's physical health outcomes.

1.3 THE ROLE OF MATERNAL MENTAL ILLNESS IN CHILDREN'S PHYSICAL HEALTH OUTCOMES

In the UK, children of mentally ill mothers face many challenges and deprivations that decrease their quality of life. As previously mentioned, children of mentally ill mothers are at risk of developing congenital abnormalities and of being stillborn or born prematurely [2] yet, little known about the risk of common child physical illnesses among this group. Moreover, the poor health of children who have mentally ill mothers has the potential to negatively impact children in vital developmental domains such as cognitive, language and social-emotional [43,44]. Also, poor health during childhood often persists into adulthood leading to lower life expectancy [45]. This high-risk group could be easily identified and supported by early interventions [46]. Unfortunately, there is limited information on their health needs. Thus, we conducted a systematic review and a meta-analysis to investigate the current literature around maternal mental illness effects on their

offspring's physical health [46]. This informed the specific preventative health care use and disease categories where more information is needed: vaccination uptake, childhood obesity, atopic disorders and childhood cancer. In the following sub-sections, the epidemiology of each outcome, current evidence and possible mechanisms linking maternal mental illness them are discussed. This section concludes with a discussion of limitations and gaps in the current literature.

1.3.1 Vaccination

Globally, every year, around two to three million lives are saved thanks to childhood vaccines and this has helped reduce infant mortality rates from 65 per 1,000 live births in 1990 to 29 in 2018 [47,48]. The benefits of childhood vaccines not only includes disease prevention but also better schooling, cognitive development, improved fertility and economic productivity [49].

The vaccination schedule for children until pre-school age in the UK is summarised in Table 1. In 2016/17 Public Health England reported the completed vaccinations by age of five was 96% for 5-in-1 primary dose, 87% for 4-in-1 booster, 95% for MMR first dose, 88% for MMR second dose and 93% for Hib/Men C [50].

Table 1 NHS England Vaccination Schedule as of August 2017 [53]

Type of vaccination	Protects against	Age given
5-in-1 [until 31 July 2017] (DtaP/IPV/Hib)	Diphtheria, tetanus, whooping cough, polio and Haemophilus influenzae type b (Hib)	8, 12 and 16 weeks
6-in-1(DtaP/IPV/Hib/HepB)	Diphtheria, tetanus, whooping cough, polio, Hib and hepatitis B	8, 12 and 16 weeks
Pneumococcal or pneumo jab (PCV)	Pneumococcal infection	8 weeks, 16 weeks, one year
Rotavirus vaccine	Rotavirus infection	8 and 12 weeks
Men B vaccine	Meningitis	8 weeks, 16 weeks, one year
Hib/Men C vaccine	Hib and meningitis	One year
MMR vaccine	Measles, mumps and rubella	One year, three years and four months
4-in-1 pre-school booster (DtaP/IPV)	Diphtheria, tetanus, whooping cough and polio	Three years and four months

Mothers are usually the primary caregiver and most likely to make decisions about children's health and health care service use [51]. It is important to understand what factors affect mother's decision-making about health care use. For instance, socio-economic status, education level, marital status, mother's employment, media and history of obstetric complications are reported to be specific factors that affect the mothers' use of preventative health care services [52]. Evidence about the association between maternal mental illness and childhood vaccination is limited, however.

A retrospective cohort study by Minkovitz *et* al [53] from the US examined the impact of maternal depression on children's health care service use in a cohort of 4,874 mother-child pairs. Findings showed a decrease in receiving the recommended vaccination schedule, which included one dose of MMR, three doses of polio, and four doses of diphtheria, tetanus and pertussis (Odds Ratio (OR) 0.79, 95% CI= 0.68–0.93) when compared to children who did not have mentally ill mothers. In the same manner, a prospective cohort study by Turner *et* al [54] from Australia with 159 mother-baby pairs reported that mothers were more likely to either vaccinate their children later than scheduled or never vaccinate if they had anxiety (OR 4.7, 95% Cl= 1.49–14.50), depression (OR 4.9, 95% Cl= 1.39–17.39) or anxiety and depression together (OR 3.59, 95% Cl= 1.11–11.60) compared to children who did not have mentally ill mothers. Moreover, a matched-control cohort study by Howard *et* al [55] from the UK reported that children of mothers with psychotic disorders were less likely to get vaccinated within 90-270 days of birth (Risk Ratio (RR) 0.94, 95% CI= 0.88–0.99). These results highlight that mental illness could be one factor influencing mothers' healthcare seeking decisions about their children, which could be targeted by early screening for maternal depression and anxiety disorders along with support to the mother and family.

To better understand the relationship between maternal mental illness and child vaccination status, more studies with solid methodological techniques are needed. For instance, existing studies [53,54] used self-report to determine maternal mental illness and parental report to identify the child's vaccination status instead of medical records. Therefore, responder bias might have significantly affected the results by providing inaccurate information on their mental health status

and their child's vaccination uptake as they may felt guilty, embarrassed or thought that this is socially unacceptable. Moreover, small sample sizes (<5000) [54] mean the results may not be reliable.

Maternal mental illness could be linked to decreased rates of child vaccination because of the cognitive effects of maternal mental illness: these mothers may experience difficulties keeping vaccination appointments or struggle to plan for scheduled vaccinations. Moreover, the chronicity of maternal mental illness [56] could lead mothers to be less engaged with infant health, which could significantly affect infants' vaccination uptake.

1.3.2 Overweight/ Obesity

Globally, it is estimated that four million children under age-five are overweight or obese [57] and in the UK it has been reported that one in five children under the age of five are overweight or obese [58]. Parenting practices play a key role in determining healthy lifestyle, including weight. Maternal mental illness affects parenting practices which may mean it affects children's weight too [59–62]. It is important to understand the ink between maternal mental illness and childhood obesity because, it would guide the health practitioners to provide necessary support these children and their families as well as to develop better preventative strategies for children at risk of obesity.

The link between maternal mental illness and child obesity has been examined by a number of researchers [63–67]. For example, a prospective cohort study by Santos *et* al [63] examined 3,792 mother-child pairs in Brazil and reported an increased risk for childhood obesity for chronic maternal depression symptoms (OR 1.6, 95% CI= 1.0–2.5). Similar results were found in a case-control study by De Sousa [64]. Meanwhile, although a prospective cohort study by Guxens *et* al [65] found an association between maternal depression and childhood obesity, this association disappeared when they controlled for maternal ethnicity. Moreover, two prospective population-based studies did not find an association between maternal depression and childhood obesity [66,67].

More research in this area is needed as there is mixed evidence for the role of maternal depression in childhood obesity. One explanation for these inconsistent findings may be the use of self-report measures to measure depression, which could lead to misclassification of the exposure and this would lead to over or under-estimate the impact of maternal mental illness. Another explanation may lie in how researchers have managed missing data. For example, Ertel *et* al [67] showed how failing to model missing data affects study results by conducting two analyses: one based on complete cases and the other with imputed data. The complete case analysis showed an association between maternal depression and child obesity, however this association disappeared once the researchers used multiple imputation [68]. This study illustrated how crucial it is to consider methods to deal with missing data by highlighting how failing to do so would have overestimated the association between maternal depression and childhood obesity. This finding may be indicating that those with BMI/ weight record were more likely to be overweight and those with missing information may had normal weight record which means an opportunistic data recording may have led to a biased sample.

There are possible mechanisms that could link maternal mental illness and childhood obesity. For instance, mothers with depression may lack a support network (family and friends) which would make it harder for these mothers to cope with parenting life. In addition to this struggle, negative affect as a symptom of maternal depression during the postnatal period could lead to inadequate caregiving among mothers, which may adversely affect infant feeding practises [69]. Moreover, an unhealthy maternal diet that includes sweets, fast foods, refined grains and high-energy drinks significantly contributes to depression in the mother [70], which can affect infant feeding practises. An unhealthy diet also may lead to established maternal risk factors for childhood obesity such as pre-pregnancy weight gain [71], gestational weight gain [72] and gestational diabetics [73].

Other mechanisms linking maternal depression and childhood obesity are low energy, lifestyle and parenting practises. Low energy among mothers with depression promotes decreased physical activity in their children [74], which would contribute to overweight/obesity. An unhealthy lifestyle because of depressive symptoms may increase the time children spend viewing television, which is

associated with children's weight problems [61]. Finally, childhood obesity and maternal depression can be linked to permissive parenting practises, with maternal depression, socio economic status and education of the mother contributing to this parenting style [75].

1.3.3 Atopic disorders

Childhood atopic disorders are group of disorders sharing common pathogenesis [76,77] which leads to heightened immune response to common allergens. Their main characteristic involves development of a specific immunoglobin (IgE) targeting allergens that are generally not harmful. Over the past decades, incidence of atopic disorders and related comorbidities has increased rapidly in developed countries and have been recognised as a global health concern [76,78]. Asthma, allergic rhinitis, atopic dermatitis and food allergy are the main atopic disorders.

Asthma is a chronic inflammatory respiratory disease occurring as a result of infected small air passages in the lungs and overreaction to infections and allergens [79]. It is estimated to affect 1.1 million children in the UK [80] and yearly health care costs to the National Health Service (NHS) have been estimated at £1.1 billion [81]. Allergic rhinitis which is also known as "hay fever" is strongly associated with asthma [82] and in a broader perspective, it can be defined as inflammation of the nasal mucosa [83] which affects approximately 20% of the UK population [84]. Atopic dermatitis, also known as "eczema", is a chronic inflammatory skin disease resulting from disruption of the skin barrier as a result of elevated IgE levels. Atopic dermatitis is one of the most common disorders among children below age five and it affects one in five children in the UK [85]. Finally, food allergies are characterised by adverse immunologic reaction to certain foods like milk, egg, peanuts, tree nuts, fish, and shellfish. In the UK, food allergy prevalence among children below age five was reported as 4% [86].

Common risk factors for atopic disorders are: being male, being from an ethnic minority group, maternal or paternal atopy history, exposure to house dust, dust mites, mould, cockroaches, tobacco smoke [87,88]. However, these risk factors are not only the explanation for atopic

disorders as there are still unknown risk factors. Therefore, a number of studies have investigated if maternal mental illness is one of the risk factors for childhood atopic disorders.

Magnus *et* al [89] investigated the association between postnatal stress and asthma in children by analysing a prospective Norwegian cohort of 63,626 mother-baby pairs. Study results revealed that maternal major depressive symptoms was associated with asthma in children at age seven (Rate Ratio (RR) 1.19, 95% Cl= 1.09–1.30) as well as depression and anxiety during pregnancy (RR 1.17, 95% Cl= 1.06–1.29). Similarly, a Swedish retrospective population study [90] with 360,526 mother-baby pairs revealed that exposure to postnatal anxiety and/or depression was significantly associated with the risk of developing asthma (OR 1.44, 95% Cl= 1.38–1.52). An association between maternal depressive symptoms and the risk of developing asthma in children (OR 2.36, 95% Cl= 1.61–3.45) was also found in an Australian prospective cohort study [91]. In another Australian cohort study [92] (N=1,587) an increased risk of asthma among children with mothers experienced stressful life event was observed (OR 2.24, 95% CI= 1.33–3.75).

In terms of allergic rhinitis, study by deMarco [93] reported that there was an association between maternal stress and child allergic rhinitis among children at age of eight years average (OR 1.36, 95% Cl= 1.08–1.71) in a sample of 3,854 Italian mother-child pairs. However, Hartwig *et* al [92] reported that there was no significant increased risk of allergic rhinitis among children with mothers experienced maternal stress during pregnancy. In a longitudinal birth cohort study by Cheng *et* al [94] investigated 1,152 mother-child pairs, and reported that mothers who experienced anxiety during pregnancy had an increased risk of infantile allergic rhinitis (OR 1.42 95% Cl= 1.04–1.93), however, this was not the case for the maternal depression.

Atopic dermatitis has received more attention from researchers. Wang *et* al [95], in a prospective cohort study of 18,024 mother-baby pairs, reported increased risk of atopic dermatitis among children exposed to postpartum depression by age three (OR 1.42, 95% Cl= 1.21–1.66). Similar results were also found in another prospective cohort studies for anxiety during pregnancy [96] (OR

1.21, 95% Cl= 1.05–1.39) as well as for postnatal anxiety [97] (OR 1.13, 95% Cl= 1.01–1.28). Studies that identified anxiety as a risk factor for atopic dermatitis also reported that maternal depression was not a risk factor for atopic dermatitis [96,97]. At the same time, another study by Chang *et* al [98] produced contradictory findings: there was a positive association between prenatal anxiety and depression as well as the risk of children developing atopic dermatitis.

Food allergies have received considerably less attention. In a case-control study (N=72), Alviani *et* al [99] reported antenatal stress was linked to childhood food allergies but this observation did not reach statistical significance. In a bigger sample (N=5,205), Elbert *et* al [96] found no association between maternal stress during pregnancy and offspring food allergy.

To summarise, there is contradictory evidence for the role of maternal mental illness in childhood atopic disorders. These inconsistencies in research results may be explained by measurement bias. For instance, only two out of eleven studies [90,96] used a standardised clinical diagnosis of atopic disorders and maternal mental illness. In the remaining studies maternal self-reports were used, which may have increased the likelihood of responder bias and may have led to underestimation of the effects of mental illness as the mothers may not have provided accurate information.

The possible links between maternal mental illness and childhood atopic disorders could be explained by the interaction of biological and environmental risk factors. It is evidenced that high levels of stress during pregnancy lead mothers to have elevated levels of inflammatory cytokines [100], which may affect fetal immune development leading to atopic disorders in later in life. Moreover, maternal smoking during pregnancy is much more prevalent amongst women with mental illness (Chapter 6) and is a risk factor for childhood asthma as it impairs the development of the foetal respiratory system, lung development and immune system [101–104].

Living conditions of mothers with mental illness may play a significant role in childhood atopic disorders. For example, not being able to provide a healthy home environment due to mental illness and living in low-income areas might increase indoor allergens such as mould, dust, dust mites and cockroaches, which are strongly linked with elevated atopic disorders [105]. Also, mothers with mental illness may struggle to care their children which may lead them to: use inappropriate products in the care of their infants; feed them inappropriate food [106]; have poor breastfeeding practises[107], and expose infants to indoor tobacco smoke [106]. The role of maternal mental illness in childhood atopic disorders is not limited to these mechanisms and more studies are required to understand these associations.

1.3.4 Cancer

Cancer can be described as a group of diseases where cells grow and divide in an unrestricted manner and occupy healthy cells and organs, which consequently spread throughout the body [108]. Even though childhood cancer is rare, it is the second most common cause of death in children in economically developed countries [109]. In the UK, childhood cancer incidence rates have increased since 2007 from 150 to 165 per million in 2017 [110]. Leukaemia and brain/intracranial tumours are the most common types of cancers observed in children.

In addition to genetics, prenatal and post-natal exposures to pesticides, radiation and viruses are known to increase the risk of some childhood cancer types [111,112], however, most of the risk factors for childhood cancer remain unknown. Mother's role in child's life starts from early conception but the impact of maternal mental illness on childhood cancer has not been examined. Currently there is only one study investigated the association between parental mental illness and the risk of cancer among offspring, which found no differences in the risk [113]. However, this study specifically focused on serious mental illness, such as schizophrenia, bipolar disorder, and unipolar depression among parents and included adult offspring.

Other studies have examined cancer in relatives with mental illness. For example, Levav *et* al [114] reported that parents and siblings of people with schizophrenia had a reduced risk of cancer compared to the general population. Mothers and fathers had roughly similar reductions in the cancer risk (Standardised Incident Ratio (SIR) 0.86, 95% CI= 0.79–0.94 for mothers; SIR 0.84, 95% CI= 0.76–0.91 for fathers). The greatest risk reduction was observed among siblings (SIR 0.74, 95% CI= 0.63–0.86). Similarly, Ji *et* al [115] reported significant reduction in cancer risk among parents (SIR 0.96, 95% CI= 0.94–0.98) and siblings (SIR 0.92, 95% CI= 0.89–0.96) of people diagnosed with schizophrenia in Sweden. However, other studies that have found no difference in the cancer risk among first degree relatives of people with schizophrenia compared to general population [116,117]. To-date, there are no studies that examined whether specific maternal depression, anxiety, personality disorders, eating disorders have an impact on the childhood cancer.

The link between maternal addiction and childhood cancer is more established. In terms of alcohol addiction, there are no studies which have specifically examined mothers with maternal alcohol addiction; rather, they have examined mothers who drank alcohol more than one unit of alcohol during pregnancy. For instance, a case-control study by Menegaux *et* al [118] with a sample of 1,039 (567 controls) found that maternal alcohol consumption during pregnancy was associated with increased risk of childhood leukaemia (OR 2.8, 95% CI= 1.8–5.9). In another study, with a sample of 798 (399 controls) [119], it was reported that maternal alcohol consumption during pregnancy increased the offspring's risk of childhood leukaemia (OR 1.39, 95% CI= 1.01–193). A meta-analysis by Martel *et* al [120] highlighted that maternal alcohol consumption during pregnancy is significantly associated with acute myeloid leukaemia in offspring (OR 1.56, 95% CI= 1.13–2.15). In a similar manner, Karalexi *et* al [121] reported a dose-response relationship between maternal alcohol use during pregnancy and acute myeloid leukaemia (moderate consumption:OR 1.64, 95% CI= 1.2–2.17; high-consumption: OR 2.36, 95% CI= 1.60–3.49). Moreover, maternal illicit drug use was reported to be associated with the risk of offspring's leukaemia risk (HR 1.63, 95% CI 0.79–3.36) in a cohort of 785,438 mother-baby pairs [39] from Canada. Likewise, Bluhm *et* al [38] conducted a case-control study with a sample of 1,042 mother-baby pairs and found that maternal

use of marijuana during pregnancy increased the offspring's risk of neuroblastoma (OR 4.75, 95% CI= 1.55–16.48).

Taken together, to better understand the relationship between maternal mental illness and childhood cancer, more studies with better methodology are needed because, except three studies [39,114,115], none has used mental health registry data or clinical diagnosis to retrieve maternal mental illness exposure; instead, they used self-reporting questionnaires. It is almost impossible to rule out the recall biases as a result of the stigma associated with alcohol consumption during pregnancy meaning that many mothers who were drinking during pregnancy may not have responded accurately to questionnaires. Moreover, a number of known risk factors such as pesticide use, air pollution and maternal age were not controlled for in any of the studies.

Despite the fact that most risk factors for childhood cancer are obscure, there are possible mechanisms that may explain why different types of mental illnesses may have a different effect on childhood cancers. Current evidence highlights that relatives of people with schizophrenia have reduced cancer risk and this may also be valid for children exposed to maternal schizophrenia. Also, the relationship between schizophrenia and reduced cancer risk is very unexpected, because there is evidence that people with schizophrenia also have reduced cancer risk- despite the fact that they are twice as likely to smoke tobacco compared to general population, yet they still have reduced lung cancer risk [122]. These findings have led researchers to focus on genetic factors and found that gene P53 may be responsible for such observations. Briefly, gene P53 is a tumour suppressor gene that controls the cell divisions that are happening too fast. In other words, gene P53 prevents the development of tumours and has been given the nickname "guardian of the genome" [123] but this gene is also strongly associated with the schizophrenia [124]. Further research is required to confirm the role of gene P53.

In terms of maternal addiction and childhood cancers, the mechanisms may be relatively more straightforward. Alcohol and illicit drugs are classified as "teratogens" which means specific substances that interrupt the development of fetus [125]. Exposure to alcohol and illicit drugs in

utero can cause DNA damage and alter the immune system, which may play a role in development of childhood cancers [126].

Other mechanisms involve, exposure to pesticides, tobacco smoke and traffic related pollution which are also considered to be teratogens. Specifically, there is consistent evidence that prenatal maternal exposure to pesticides is linked to childhood cancers [127–129] although, there is no study to date reporting a possible link between maternal mental illness and prenatal exposure to pesticides. However, there is evidence that, in the UK, children exposed to maternal mental illness are more likely to be living in the most deprived areas [17]; and the air quality of these areas is reported to be poorest [130]. Overall, the rarity of childhood cancers in general makes it very difficult to investigate the possible mechanisms.

1.3.5 Limitations and gaps in the current literature

The literature reviewed in previous sections mainly focused on common mental illnesses such as perinatal/postnatal depression. However, it is vital to examine the other type of maternal mental illnesses because each mental illness has its own aetiology and may have differential effects on children.

Very few number of studies has examined the association between maternal mental illness and rare childhood health problems including diabetes, epilepsy and cancer, although rates of these diseases among children are increasing rapidly [131,132]. Investigation of this relationship could contribute significantly to improved prevention, diagnosis and treatment of these diseases among children.

Moreover, current evidence primarily comes from the USA, Canada and Australia. Similar studies are needed to examine European, Asian, African and Middle Eastern populations. Such studies would advance understanding of the association between maternal mental illness and children's physical health among populations that may vary genetically and across geographic and cultural

contexts. Lastly, some childhood diseases are rare. Therefore, although difficult to achieve, research based on larger sample sizes would enable researchers to understand the nature of these childhood disorders more conclusively.

1.4 PUBLIC HEALTH POLICIES AND GUIDANCE FOR CHILDREN IN THE UK

Epidemiological research can inform public health policies for children exposed to maternal mental illness by providing information about how the child's physical health is linked to the mother's mental health or other aspects of the early environment [133]. Relevant public health policies for children in the UK are described below.

Every Child Matters is a policy initiative launched in 2003 by the UK government as a result of eight-year-old Victoria Climbie's death. This policy sets out that every child no matter their background or their life circumstances, from birth to age 19, should receive the necessary support they need to: **be healthy** physically, emotionally, sexually and mentally; **stay safe** from neglect, violence, sexual abuse, accidental injuries, bullying and crime; **enjoy and achieve in life** by attending school, reaching national educational standards, achieving personal and social development; **make a positive contribution to society** by engaging and supporting their community and environment, obeying laws, develop self-confidence and positive relationships with people and **obtain economic security** by continuing further education and getting ready for employment after school [134]. In order to achieve these goals, all public services such as hospitals, schools and police, as well as charities providing child services, are required to work collaboratively to ensure that every child receives the required level of support and this is only possible by sharing information, protecting children from harm and guiding children to achieve their life goals [134].

National Service Framework for Children and Maternity Services is a best practise guideline published by the UK government in 2004 that highlights national quality standards for children, young people and maternity services [135]. Two standards within this framework specifically focus

on children's physical health: *Standard 1-Promoting Health and Well-being, Identifying Needs and Intervening Early* aims to intervene early and reduce the health inequalities faced by children [135] while *Standard 6-Children and Young People Who are ill* focuses on providing children who have an acute injury or illness as well as children who are at high risk of a chronic illness access with relevant services and advice to support their health, social, educational and emotional needs during the period of their illness [136].

Think Child, Think Parent, Think Family [137] is a part of the policy guidance published in 2011 by The Social Care Institute for Excellence (SCIE), which aims to enhance the UK's social care services for adults and children. The goal of Think Child, Think Parent, Think Family is to target parents with mental illness and their relatives who are not engaging with social and health care services in order to improve outcomes and provide solutions, promote resilience and well-being among family members, offer support and crisis management, increase understanding of parental mental illness within the family and promote coping, and secure child safety [137]. This guidance not only aims to help families and their children but also to help relevant organisations (i.e. social and health care) to work smoothly and staff to be able to identify the needs of families so that service planning, delivery and practice can be improved [138].

The Healthy Child Programme (HCP) is an evidence-based early intervention and prevention public health programme. It is published in 2009 with an aim to help families and their children to access public health services by providing them advice and accessible information based on their needs [9], so that every child gets a good start they need. Broadly this programme aims to provide healthy pregnancy for every women as well as good breastfeeding practice, and a strong parent-child attachment; prevent infectious diseases; detect the developmental delays and ill health as well as providing better outcomes for children at risk of social exclusion. These aims are achieved through health promotion, surveillance screenings, immunisations and developmental reviews**.** Successful implementation of this programme leads to reduced inequalities and improved health outcomes in the first five years of life. This programme also extends for children until age of 19 where they would be included in the National Child Measurement Programme in the England

region at the age of five, then they would have school transition review during the ages of 11 and 12 and they would have immunisation status review between the ages of 16 and 19. This programme is delivered mainly by the health visitors in the first year of life but the GPs, practice nurses, midwives, health visitors, community nursery nurses, early years practitioners and family support workers also play an important role in the delivery of the HCP.

All policies discussed above aim to support children and provide necessary early interventions to make sure that each child has equal opportunities in every aspect of life. However, currently these policies do not explicitly acknowledge effects of maternal mental illness on children's physical health. Recognising these effects is crucial because recent studies report that offspring of mothers with mental illness are at high risk of developing certain physical illnesses [89,139–141], which were discussed in sub-section 1.3. Moreover, the Child and Adolescent Mental Health in Enlarged Europe (CAMHEE) report recognised the effects of maternal mental illness on children's physical health and affirmed an urgent need to develop better policies, health and social care systems that identify and take care of the needs of children with mentally ill mothers [142]. Making these changes, however, requires large cohort studies that make significant contributions to the public health area. Such studies could investigate when and how children of mentally ill mothers are at risk of preventable illnesses as well as the mechanisms that link maternal mental illness and physical illnesses in children. Outcomes of such large cohort studies would allow resource allocation planning and help determine if new services are needed as well as the form these services should take.

1.5 THESIS RATIONALE

To improve the lives of children with MMI, there is an urgent need for methodologically sound research studies to understand how and when children with MMI at risk of developing physical health outcomes. Most of the current studies in this area are too small to examine effects of MMI and limited in their study designs [46]. Public health policies and interventions rely on methodologically robust and consistent evidence to take action. By considering gaps in the

research and public health needs, the following physical health outcomes in children were identified:

- Vaccination uptake
- Childhood obesity
- Atopic disorders (asthma, allergic rhinitis, eczema and food allergies)
- Childhood cancers

These particular physical health outcomes were selected to be examined in this thesis for several reasons. First, a key part of maintaining good physical health includes vaccination. Examining vaccination uptake among children with MMI identifies a purely non-biological pathway between MMI and childhood health, which is not possible to accomplish when investigating other poor physical health outcomes. Furthermore, we had the opportunity to examine the effects of the Andrew Wakefield scandal which had falsely linked MMR vaccination in children to later autism. Second, childhood obesity and atopic disorders were selected because these two physical health outcomes are both increasingly common and increasing priorities for public health in the UK: almost 1 in 11 children in the UK is currently receiving asthma treatment and 20% of children aged between 10-11 are suffering from childhood obesity. Therefore, it was considerd that these poor physical health outcomes are causing a significant burden on children and their families and to the health care system: costing between £1 to £6 billion per year to the NHS. Yet we do not know if MMI plays an important role in these poor physical health outcomes. Moreover, our systematic review [46] indicated that these outcomes were potentially raised for CAPRI, however these results were inconclusive (atopy: ORpool = 1.36, 95% CI 0.91–2.03, I2 = 92.9%; obesity ORpool= 1.16, 95% CI 0.97–1.39, I2 = 55.0%) because of small number of studies (N = 10), inconsistent findings and small sample sizes (N between 100 and 21,121). Finally, we wanted to exploit a rare opportunity to combine two high quality population datasets which would allow exmaination of potentially rare exposures (maternal schizophrenia) and rare childhood outcomes (cancer) of which had been examined in smaller underpowered samples. There is limited information on risks for these childhood outcomes and identification of risk in offspring of mentally ill parents might advance our future capacity to identify and consider preventive interventions early. Therefore, these outlined health outcomes were chosen for further investigation in the large population based CPRD sample and in Sweden where appropriate.

1.6 THESIS OVERVIEW AND OBJECTIVES

The overarching aim of this thesis was to investigate the physical health needs of children with MMI using primary care data. This involved not only exploring the risk of specific physical health outcomes among children with MMI but also investigating the data quality of outcomes of interest and exploring one of the main risk factors of poor physical health in offspring. The aim of each individual study was therefore as follows.

In Chapter 3, the aim of the study was to investigate: i) whether children exposed to MMI have reduced vaccination uptake compared to children non-exposed to MMI; ii) if maternal psychotic disorders would have more detrimental effect on childhood vaccination uptake compared to those with mothers with common mental illnesses (i.e. depression and anxiety) and iii) if the effect of MMI has changed over the time including the MMR scandal period.

In Chapter 4, the study aim was to explore whether the childhood height, weight and BMI measurements recorded in primary care are fit for research purposes before conducting a study investigating the effects of maternal mental illness on childhood obesity.

In Chapter 5, the aim of the atopy study was to investigate: i) if children with MMI have a higher risk of atopic disorders compared to children without MMI ;ii) whether the risk of atopic disorders among children of mothers with psychotic disorders would be higher than children of mothers with common mental illnesses (depression and anxiety) and iii) if atopic disorder related secondary care use would be higher among children with MMI than children without MMI

In Chapter 6, the aim of the study was to investigate perinatal smoking rates among mothers with and without mental illness. This brief study was developed during the atopy project where maternal smoking is one of the important risk factors. Therefore, this opportunity was utilised despite the fact that the outcome is not child physical health, but highly relevant to a child's health.

Finally, in Chapter 7, the aim of the cancer study was to investigate: i) if children with MMI have a higher risk of developing childhood cancer when compared to children without MMI; ii) whether the

childhood cancer risk is higher among children with mothers experiencing common mental illness (depression and anxiety) and whether the cancer risk is lower for children living with mothers experiencing psychotic disorders.

In order to address these aims, primary care data from the Clinical Practice Research Datalink (CPRD-GOLD) was utilised and following articles for publication in high-impact journals were produced.

1- The influence of maternal mental illness on vaccination uptake in children: a UK population-based cohort study (Published at the European Journal of Epidemiology)

2- Data recording in the UK general practices: the case of weight and height measures (Submitted to Pediatric Obesity)

3- The effect of maternal mental illness on child atopic disorders: a UK population-based cohort study (Submitted to BMJ)

4- Perinatal smoking: Its prevalence and link with maternal mental illness *(*Submitted to Addiction)

5- The effect of maternal mental illness on childhood cancer: a pooled analysis of England and Sweden national cohorts (In preparation to be submitted to JAMA)

In Chapter 2, the description of the data source and methods used to analyse this data are presented. Chapters 3 to 7 presents the results of each study conducted in this thesis and Chapter 8 provides a discussion around the overall findings from this thesis in research and public health context.

CHAPTER 2- METHODS

This chapter describes in detail the methods used for this PhD. Section 2.1 covers the database where study cohorts were extracted. It details the data provided in this database and specific linkages that were utilised. Section 2.2 describes the cohorts used in each study, including vaccination, obesity, atopy, perinatal smoking and cancer. Section 2.3 outlines the classification of exposure and outcomes. The final section 2.4 provides detailed information on study design and statistical analyses.

2.1 THE CLINICAL PRACTICE AND RESEARCH DATALINK (CPRD)

2.1.1 Background

The Clinical Practice Research Datalink (CPRD) is a UK primary care database of routinely collected anonymised, medical records. It is one of the largest databases of primary care records in the world [143]. The data collection started in 1987 under the name of General Practice Research Database (GPRD), then in 2012, GPRD became CPRD and expanded data collection by including different general practice computer systems increasing the size and coverage of the data. It is jointly funded by National Institute of Health Research (NIHR) and the Medicine and Healthcare Products Regulatory Agency (MHRA).

As of January 2019, the CPRD contained data for over 35 million patients, of which 10 million are currently registered, representing 15% of the UK population. Each patient has a median follow up time of 10 years. Latest figures show that every 1 in 10 GP practices across the UK have contributed data to the CPRD, which is equivalent to 1,150 registered GP practices [144]. In order to contribute to the CPRD, all GP practices are required to have the same computer system called Vision and all GP practices have to provide consent for CPRD to extract de-identified primary care data from their system. Also, patients at a participating GP have a right to opt-out of sharing their data with CPRD at any time. More recently CPRD-Aurum has been developed that uses data from GP practices using the EMIS computer system.

2.1.2 Information contained in the CPRD

The CPRD contains data on patient demographics, prescriptions, and clinical events, including symptoms, diagnoses, tests, immunisations, specialist referrals and hospital referrals. These data are recorded by general practice staff using Read codes [143], a hierarchical medical classification system established by Dr James Read in the 1980's. Information is provided in 10 files within the CPRD: clinical, additional, referral, immunisation, test and therapy files. Further information on practice level demographics, such as general practice region, is recoded by CPRD. Table 2 illustrates the major information contained in CPRD and Figure 1 illustrates the CPRD data structure.

Table 2 The information contained in the CPRD

Files	Information Contained
Practice	Details of each practice including region.
Patient File	Basic patient demographics and patient registration details for the patients
Consultation	Information relating to the type of consultation as entered by the GP from a pre-determined list.
Clinical File	All the medical history data entered on the GP system, including symptoms, signs and diagnoses.
Additional File	Additional information for a specific clinical event (e.g. BMI records, post-natal visit, contraception use)
Therapy File	All prescriptions issued by GP
Referral File	Patient referrals to external care centres (i.e. secondary care: hospital for inpatient or outpatient)
Immunisations	Immunisation records on the GP system.
Test File	Records of test data

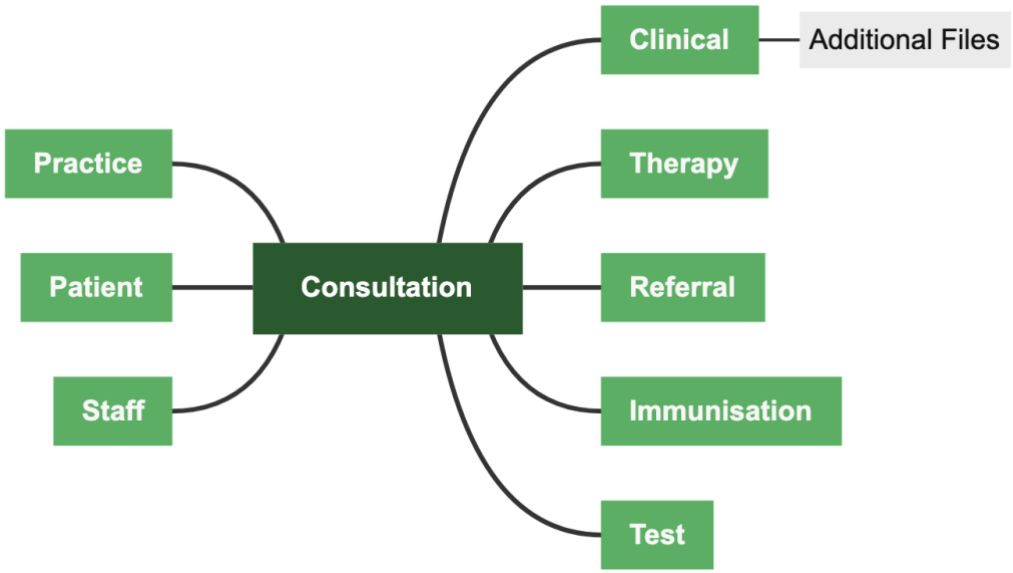

Figure 1 The structure of the CPRD

The CPRD provides data quality identifiers to researchers as the quality of information varies across the GP practices. These identifiers are the “acceptability flag” and “up to standard date”. The acceptability flag is a patient level data quality indicator, coded as 0=Unacceptable, 1= Acceptable. For a patient to be recorded as “acceptable”, they need to have i) a valid gender and birth date; ii) logically consistent and valid registration dates; iii) transferred out date and reason and iv) valid event date recording. This identifier is located in the “patient” file. In all studies, subjects only with acceptability flag=1 were included.

For each CPRD registered practice, an ‘Up To Standard’ (UTS) date is calcaulated, from which, data provided by the practice are considered to be of research quality. It is defined, such that, from the UTS date onwards: i) practice mortality rates lie within an expected range (which provides reassurance that data are being provided for patients who have died and that they have not been deleted from the system), ii) there is continuity (i.e. no gaps) in data recording within a practice. The UTS date is located in the “practice” file.

The Quality and Outcomes Frmework (QoF) was introduced in 2004 to improve the quality and completeness of data recoding in primary care as a part of new general medical services (GMS) [145] which is a voluntary financial incentive scheme in primary care. The QoF rewards the GP's for their performance in four domains of clinical, organisational, patient experience and additional services. For each domain, there are number of achievement indicators to measure the quality of health care provided to patients. The reward system involves collecting points based on GP's achievement in each domain which converts into a payment at the end of financial year. The higher the score, the greater payment received [145].

2.1.3 The Read code system

The Read Code system is widely used in UK primary care in coding and storing patient records electronically. It is based on a hierarchical structure and it involves "parent-child" concept of coding. Any Read term can only have one parent code. For instance, a five-byte Read code gives five levels of detail in a way that the code becomes more detailed as it moves away from the parent code [146]. Table 3 illustrates an example of five-byte Read code structure coded with alphanumeric characters to represent a specific neurotic disorder. The "E" chapter in the Read Code system stands for Mental Disorders and characters appearing after the letter "E" provides more information about the disorders in that chapter. Table 4 illustrates different chapters in the Read Code system. Medical history, examination, procedures and administration related information is recorded in chapters starting with numbers 0-9 while patient diagnoses are recorded in chapters starting with upper-case letters (A-Z) and prescriptions recorded with lower-case letters (a-z).

Table 3 Example of five-byte Read Code hierarchy

Hierarchy Level	Read Code	Description
1	E….	Mental disorders
2	E2…	Neurotic, personality and other nonpsychotic disorders
3	E20..	Neurotic disorders
4	E200.	Anxiety states
5	E2000	Anxiety state unspecified

Table 4 Chapters in Read Code System in (i) processes of care, (ii) diagnoses and (iii) prescriptions

I. Processes of care	
Chapter	**Contents**
0	Occupations
1	History and symptoms
2	Examinations and signs
3	Diagnostic procedures
4	Laboratory procedures
5	Radiology
6	Preventative procedures
7	Operative procedures
8	Other therapeutic procedures
9	Administration
II. Diagnoses	
Chapter	**Contents**
A	Infectious and parasitic diseases
B	Neoplasms
C	Endocrine, nutritional, metabolic or immunity disorder
D	Diseases of blood and blood-forming organs
E	Mental disorders
F	Nervous system and sense organ diseases
G	Cardiovascular system diseases
H	Respiratory system diseases
J	Digestive system diseases
K	Genitourinary system diseases
L	Pregnancy, childbirth and puerperal disorders
M	Skin and subcutaneous tissue diseases
N	Musculoskeletal and connective tissue diseases
P	Congenital anomalies
Q	Perinatal conditions
R	Symptoms, signs and ill-defined conditions
S	Injury and poisoning
T	Causes of Injury and poisoning
U	External causes of morbidity and mortality
Z	Unspecified conditions
III. Prescriptions	
Chapter	**Contents**
a	Gastro-intestinal system drugs
b	Cardiovascular system drugs
c	Respiratory system drugs
d	Central nervous system drugs
e	Drugs for infectious diseases
f	Endocrine drugs
g	Obstetric / gynaecological / urinary drugs
h	Malignant & immunosuppressant drugs
i	Nutrition and blood drugs
j	Musculoskeletal & joint drugs
k	Eye drugs
l	Ear, nose & oropharynx drugs
m	Skin drugs
n	Immunology drugs & vaccine
o	Anaesthetics
p	Appliances & reagents
q	Incontinence appliances
s	Stoma appliances
u	Contrast media
y	Drug release administration

In epidemiological studies using electronic health records, one of the critical steps is defining which codes will be used to identify clinical events of interest along with relevant covariates. This is a complicated process which involves searching for relevant codes in different types of files, because some complex clinical events may require multiple codes to correctly identify while some other clinical events can be easily identified from a single code [147]. Also, GP's differ in their recording of clinical events, for example depression can be either recoded as a diagnosis or it can be recoded as symptom with antidepressant prescription.

While flexibility and redundancy in coding medical events could be useful for the GPs [147], it is less so for researchers, because the Read Coding system is not developed for research purposes and researchers have to carefully go through the Read Codes and develop meaningful algorithms to capture all the relevant medical events. It is also important to mention that not all GP's are using Read Coding system efficiently. For instance, in the perinatal smoking study (Chapter 6), while defining mother's smoking status, there were mothers with "tobacco consumption status" record with no indication about the smoking status. In the hierarchical order, this read code is a parent code and it should be used with further codes indicating the smoking status. However, it was observed that some GPs only used this parent read code without using the subsequent codes to indicate the smoking status. As a result, it was not possible to identify the smoking status of the mothers with this read code only. A number of UK studies have also reported the same issue [148,149].

Accurate and consistent data recording across primary care is essential for improving health care services and research. Read code system has been in use since 1980 and over time it has gone through changes which have produced two versions (Read v2 and CTV3). Both versions exist in GP systems, however, not all GPs use the same coding system. NHS emphasized that one clinical terminology to be used across the UK GPs so that data can be exchanged across all care settings accurately and consistently. As a result, in April 2018, Read Codes were replaced by SNOMED CT.

2.1.4 Linkage with other datasets

Linkages to the CPRD can be used to get extra data on demographic, hospital events and death reasons. Patients can be linked to a number of data sources, for example the Office for National Statistics (ONS) [150] mortality data, that includes information on date and cause of death; the Index of Multiple Deprivation (IMD) and Townsend scores that provides area-level deprivation data; Hospital Episode Statistics (HES) [151] for hospital data; and disease registries like the National Cancer Intelligence Network (NCIN) [152]. These data sources can be linked to CPRD by the Health and Social Care Information Centre, which is classed classified as a trusted third party. In the below subsections 2.1.5 to 2.1.7, the external data sources that were utilised in this thesis are described.

2.1.5 CPRD Linkages: Mother- Baby Link

The Mother-baby link (MBL) is an algorithm that matches children to their mothers using delivery and birth records from primary care, and a family identifier based on home address. The MBL was utilised to estimate the maternal mental illness prevalence in the UK [17], healthcare utilisation of children with maternal mental illness (Hope *et* al), vaccination uptake in children with maternal mental illness [153], which is the first study of this thesis (see Chapter 3) as well as other studies presented in this thesis.

This linkage is established within CPRD by the UK Medicines and Healthcare products Regulatory Agency. There are three important steps in establishing the MBL: (i) maternal delivery identification, (ii) identification of babies, (iii) linking mothers with babies.

In the first step, maternal deliveries are identified using adult female (age 12 to 49) patients' clinical, referral and test records relating to deliveries. These were obtained if the female patient fulfilled patient-level data quality (see subsection 2.1.2 for acceptability flag). Delivery date is estimated from type of events. For example, if the recorded event was six-week postnatal visit,

then delivery date was estimated by event date minus 42 days, or if the event was a hospital discharge, then event date minus two days would be the estimated delivery date. From the identified records, those recorded before 1987 and historical records indicating delivery more than a year before the mother's registration, deliveries reported after the mother's transferred out date (TOD) or after the practice last collection date (LCD) (see section 2.2 for TOD and LCD date) were excluded. The first step was competed once the duplicated deliveries were dropped.

The second step was identifying the infants who were born after 1986. Infants were excluded if their registration year was before their birth year or their birth year was after the practice last collection year. In CPRD, full date of birth is not retrieved from the GP system as it is personally identifiable information. As a result, the birth date used is the 15th day of the recorded month and year. If offspring did not have a have a birth month, then 30th June as a month of birth along with the given birth year was accepted.

The third and final step was linking the mothers with their babies. Possible mother-baby pairs were created if: they were registered at the same practice; shared same family identifier, which is based on home address; and mother's delivery date and baby's birth date were within 60 days of each other. Following this matching, for each mother-baby pair, the closest delivery and birth date were kept, so that there was one record per mother-baby pair. If one delivery was matched with multiple babies, then only the baby with same birth date and registration date was included for that pair. If a baby was linked to more than one mother, then records where baby's birth month or year was not equal to mother's delivery month or year were excluded. Also, mother and baby pairs with different transferred out date were excluded as well. Remaining babies matched with multiple mothers were excluded as the true mother was not possible to identify. This linkage only includes pregnancies resulted in live births. Figure 2 illustrates the MBL creation process.

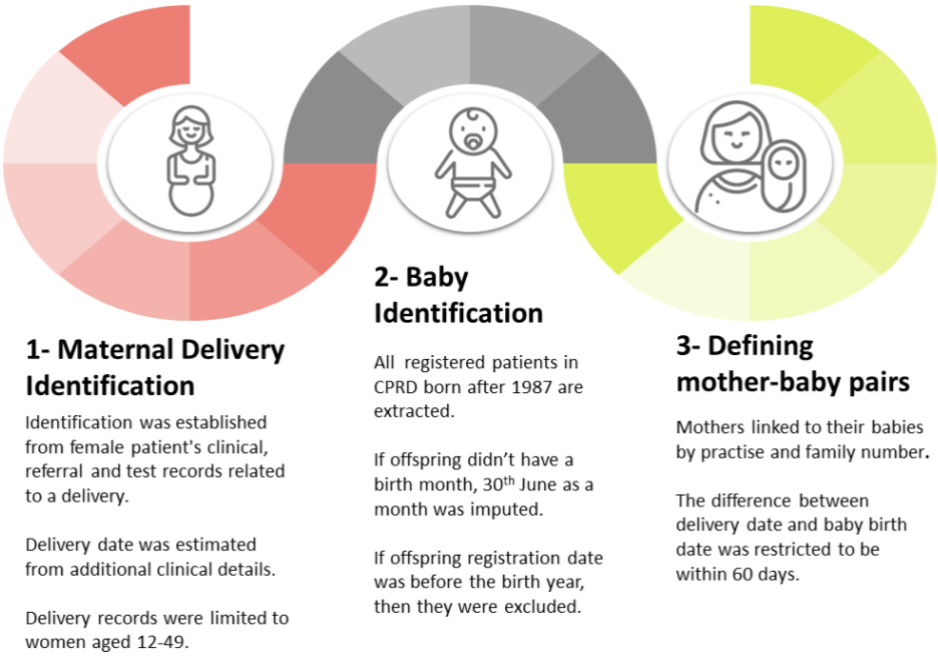

Figure 2 CPRD Mother-Baby Link Creation Process

2.1.6 Hospital Episodes Statistics (HES) dataset

The Hospital Episodes Statistics (HES) dataset collects information on date, duration and reason for patient's hospital admissions, A&E department attendances and outpatient appointments at NHS hospitals in England. General practices in England have access to HES data if their patients consented to HES linkage [143]. This linkage covers approximately ~75% of English practices. Primary care patients are linked to HES datasets using the NHS number: a unique patient identifier. Data for different HES domains are available from different starting dates. For instance, hospital inpatient admission data collection was started on 1 April 1997, outpatient appointments on 1 April 2003 and A&E department on 1 April 2007. The inpatient admissions dataset was utilised in the atopy (Chapter 5) and cancer (Chapter 7) research papers in this thesis to capture the secondary care use among children with atopic disorders and to capture the cancer diagnosis among children.

2.1.7 Index of Multiple Deprivation (IMD)

The Index of Multiple Deprivation (IMD) is a synthesised measure of area-level deprivation, obtained from eight domains: employment, income, housing, access to services, education, skills, crime and living environment [154]. Each domain has a composite score derived from two or more sub-domain indicators. The IMD score is calculated at Lower Super Output Area (LSOA) level in England, Wales and Northern Ireland [155]. In Scotland, Data Zones (DZ) are used as calculate IMD score. The CPRD provides linkage to two IMD datasets: patient level IMD and GP level IMD. Briefly, the patient level IMD score is only available for patients living in the English region, registered to the GP practices that have consented for patient level linkage and have a valid postcode record in the GP practice system. Patients who fulfil these criteria, then their postcode is mapped to the 2001 and 2011 LSOA boundaries through the postcode lookup file. GP level IMD score is available for all GP practices contributing to the CPRD-GOLD. Postcode of registered practices are linked to LSOA or DZ by using the postcode lookup file which allows linkage to English Indices of Deprivation 2010 [156], Northern Ireland Multiple Deprivation Measure (MDM) 2010 [157], Scottish IMD Deprivation 2012 [158], and Welsh IMD [159]. The IMD in the context of this thesis is very important because, deprivation is a key factor in physical health outcomes of children with maternal mental illness.

2.1.8 Ethics approval and funding information

In order to receive and supply data for public health research, CPRD requires annual ethnical approval from the UK's Health Research Authority (HRA). Then, researchers who would like to conduct research by CPRD data, a research protocol must be approved by Independent Scientific Advisory Committee (ISAC). ISAC provides scientific advice on research proposals to use CPRD data and assures that researchers have feasible plans that would not raise data governance issues. ISAC approval of this PhD study was granted on [31/08/17] to protocol title "Children and Adolescents with PaRental mental Illness: Understanding the 'who' and the 'how' of targeting interventions 'CAPRI'", ISAC protocol number: 17_187. This PhD project is part of CAPRI project which is funded by European Research Council (ERC) [GA682741 to KMA].

2.2 STUDY COHORTS

This section will first describe variables used to create each study cohort and outline the cohort delineation for each study. The study cohorts for each project have evolved throughout the course of this PhD thesis, each tailored towards individual research questions. All of the study cohorts were derived from the CPRD's 'mother-baby' link (see subsection 2.1.5); however, project-specific criteria were applied.

Along with the acceptability flag and UTS date which are described in subsection 2.1.2, three other relevant variables were used to create each study cohort. These variables were:

- Current registration date (CRD) which is the date that the patient is enrolled to the current GP practice.
- Transferred out date (TOD) which is the date patient left the GP practice.
- Last collection date (LCD) which is the last date of the GP practice contributed data to the CPRD.

In all cohorts, start and end dates for each mother and child were created based on these variables. Start date was the latest date of CRD or UTS and end date was the earliest date of LCD or TOD (including death date). It would be not possible to observe mother and baby pairs outside of these start and end dates, because, specifically CRD and TOD dates reflect the participants' physical registration and leave dates while LCD reflect the GP practice's data contribution. However, the UTS date is different than these dates. This date is unique to CPRD-GOLD and it reflects when the GP practice fulfils the data quality requirements (see sub-section2.1.2). Any recorded data before the UTS date is considered unreliable and should be not used. This means in CPRD-GOLD, left-censoring exists as some patients are registered and have clinical events recorded before their participating GP practice's UTS date, this can be seen in Figure 3, fictitious person A. Overall, how these variables were used in each study on two fictious people are also illustrated in Figure 3. For children, birth date was also included when defining the start date.

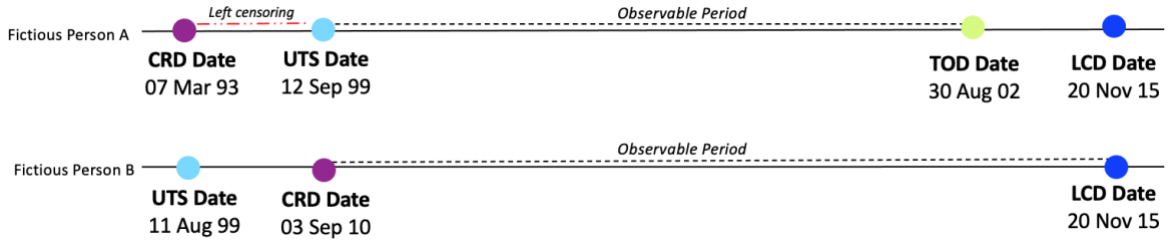

Figure 3 Observation period example of two fictitious people

In addition to CRD, UTS, LCD and TOD variables, some other study-specific variables were utilised to create start and end dates. For example, in the atopy study, child's end date included mother's death date, because in this study it was important that child continuously shared the same environment with the mother during the observable period. Similarly, in the cancer study, the child's end date included their 18th birthday in order to capture only childhood cancers, which was not the case in other studies. In the following section, cohort creation process of each study is briefly described. Table 5 below summarises cohort creation all of the studies presented in this thesis.

Vaccination study (Chapter 3) was the first research study of this thesis. The aim of the study was to investigate whether maternal mental illness has an effect on the vaccination uptake in children in the first five years of life. Therefore, two cohorts were constructed. The first included children with a complete follow up from birth to age two, and the second cohort included children with complete follow up from birth to age five. Mothers were required to be registered at a GP practice at least one year prior to birth to be included in the cohort in order to ascertain mental illness exposure.

The second study was the obesity study (Chapter 4) which examined whether it was feasible to look at the effect of maternal mental illness on childhood obesity/overweight using primary care data. The cohort involved children with a follow up period starting from their second birthday until the earliest date of TOD, death, LCD and they were excluded if they did not have minimum of five years follow-up.

The third study was the atopy study (Chapter 5) and it involved children who followed from birth until earliest date of TOD, LCD, 18th birthdate or mother's death. Children were excluded if their mother was not registered to participating practice six months prior to child's birth. This cohort was constructed differently than the first study as the aim of the study was to estimate the time to first atopy event (see Chapter 4). Also, a sub-cohort of children was identified based on their HES linkage in order to investigate their secondary care service use for atopic disorders.

The fourth study was the perinatal smoking study (Chapter 6) that was conceived of during the atopy study, where maternal smoking was one of the main risk factors for atopic disorders. The study involved examining prevalence of maternal smoking during perinatal period for women with mental illness compared to women without. Follow up was defined similarly as in the vaccination study, except that the child's birth was not used for the start date. For this study, only mothers who were observable during perinatal period were included.

The last study of this thesis was the Cancer study (Chapter 7) which was conducted in collaboration with colleagues in Sweden to investigate whether maternal mental illness has a role in childhood cancer risk. Cancer in children is a rare outcome [160] therefore, a meta-analysis study was considered necessary. For this study, UK and Sweden cohorts were constructed seperately. In this section, only the UK cohort is described; information on Sweden cohort construction can be seen in Chapter 7.

The cancer study cohort was constructed in a much different manner than the previous studies. In this study, children's follow-up began from the latest date of birth, HES inpatient hospital data start date or the mother's observation start date in CPRD. Children's follow up ended on the latest date of their 18th birthday, child's death or study end date. A cohort constructed this way allowed children to enter the study any time when they fulfilled the criteria until the age of 18. This was the only way to keep the maximum number of children and their mothers in the study.

However, due to cohort structure, not all children were not followed up from birth and some cancer cases might have been missed as children may have developed cancer before the observation period started, this is known as left censoring. Following children from birth would have been ideal; however, this was not possible because HES linkage was required in order to obtain child's cancer diagnosis status. While primary care data goes back to 1987, HES linkage starts only in 1997. This meant that if we followed up children who were born in or after 1997, we would have a very small sample which would not allow us to examine this rare outcome. Therefore, it was decided that cancer cohort would be an "open cohort" where children would be followed up from any age when they fulfil the inclusion criteria until age 18.

Table 5 Summary of cohort creation

Study name	Children born between	Child follow-up duration	Excluded if:
Vaccination	1st January 1993 and 31st December 2015	**Start**: Latest date of: Birth, CRD, UTS	Children born before UTS date;
		End: Earliest date of: TOD, LCD, Death	Children did not have minimum of two years of follow up; Mother was not registered at a participating GP for at least one year
Obesity	1st January 2005 and 31st December 2012	**Start:** Latest date of: Second birthdate, CRD, UTS	Children born before UTS date;
		End: Earliest date of: TOD, LCD, Death	Children did not have minimum of five years of follow up.
Atopy	1st January 1993 and 30th November 2017	**Start**: Latest date of: Birth, CRD, UTS	Children born before UTS date;
		End: Earliest date of: 18th birthdate, TOD, LCD, Death, Mother's death	Mother was not registered to participating practice six months prior to child's birth Children without a HES linkage [for the sub-cohort]
Perinatal Smoking	Mothers who had live birth between 1st January 2005 and 30th December 2015	**Start:** Latest date of CRD, UTS	Mother's follow up start before UTS date;
		End: Earliest date of TOD, LCD, Death	Mother was not observable during perinatal period (One year before and after birth);
Cancer	1st January 1987 and 30th June 2017	**Start**: Latest date of: Mother's observation starts in CPRD, child's conception date, birth or HES linkage start date (1st Apr1997)	Children who are not observable during follow up duration
		End: Earliest date of: 18th Birthdate, child's death, end of study date (31st July 2017)	Children without HES linkage

2.3 CLASSIFICATION OF EXPOSURE AND OUTCOME VARIABLES

This section describes exposure and outcome classifications used throughout this thesis. The main exposure in all research papers was childhood exposure to maternal mental illnesses and outcome variables were child physical health outcomes. Subsection 2.3.1 will describe how the maternal mental illness was defined and subsection 2.3.2 will outline how different types of physical health outcomes in children were defined.

2.3.1 Exposure

Maternal mental illness was defined by using a triangulation method which utilised four types of events in mother's primary care data: i) mental disorder diagnosis, ii) symptoms, iii) referrals to and use of psychological services or therapies, and iv) prescriptions.

Firstly, mental disorder was indicated if a consultation record had a recorded mental disorder diagnosis. These were identified using an a priori list of mental disorders as described in the international classification of diseases 10th Revision (ICD-10) categories of: alcohol and drug dependence (F10-19); non-affective psychotic disorders (F20-24, F28, F29)l affective psychotic disorders (F25,F30-33)l mood disorders, excluding those with psychotic symptoms (F32-F34,F38,F39,F52); anxiety and stress related disorders (F40-48); eating disorders (F50) and personality disorders (F60-68); and included general diagnoses of psychiatric disorder (*Appendix A1*). Illnesses as a consequence of alcohol or substance abuse were also identified under the diagnosis field (e.g. J612.00, "Alcoholic cirrhosis of liver") (*Appendix A2*).

Secondly, general practitioners are increasingly recording symptoms rather than diagnoses of mental illnesses in the CPRD [161]; therefore, symptoms of common and severe mental disorders (e.g. "Anxiousness", "Hallucinations") were captured (Appendix A3). A specific emphasis was given to symptom codes for depression and anxiety as these mental illnesses were the most common and had the greatest number of codes associated with them. Thus, we compiled a list symptom codes from three sources in addition to conducting a search with colleagues in the CPRD research

team. We prioritised symptom codes (depression: 2257, 1B1U.00, 1BT..00, 1BQ..00, 1BU..00; anxiety: 1B13.00, R2y2.00, 2259, 2258 and 1B12.00) which were included in the validated algorithm reported in John et al [162]. In addition, we also utilised codes from Windfur et al [163] for anxiety symptoms (E205.11 and E205.12) as well as depression symptom codes (1B17.11, 1B1U.11) from Kontopantelis et al's [164]. The remaining symptom codes for depression (1B17.12, 1BT..11, 1BT..12) and anxiety (1B12.12, 1466, 1B12.11, 1B13.11, Z7CG40, 1B1V.00, R2y2.11, Z4I7.00, Z4I7211, Z4I7200, ZV15400, 1468, Z7CG500, Z4I7100 and 1B13.12) were captured by our CAPRI research team and approved by our clinical lead Prof Kathryn M Abel.

Thirdly, referrals to and use of psychological services or therapies for common or severe mental disorders were identified (eg. 8HHs.00, "Referral to psychosis early intervention service" or Z4L..00, "Psychological counselling", Appendix A4). Fourthly and finally, all prescribing events for antipsychotics, sedatives, anxiolytics, hypnotics, antidepressants and mood stabiliser prescriptions were identified (*Appendix A5-8*).

Using an algorithm, the start date, daily dose and quantity prescribed were extracted and the stop date and duration of exposure was calculated for each class of psychotropic drug (antidepressants, antipsychotics, anxiolytics/hypnotics) [165]. Antipsychotic use indicated non-affective psychoses (F20-24, F26-29; *Appendix A5*), mood stabiliser use indicated affective psychoses (F30-F31; Appendix A6), an antidepressant prescription indicated depression (F32-33; *Appendix A7*) and an anxiolytic/hypnotic prescription was recorded as an anxiety disorder (F41; *Appendix A8*). In cases when there were overlapping prescriptions, the mean of the stop dates of the two closest prescriptions was utilised.

Once the information from four different types of events was gathered, we developed an algorithm to capture maternal mental illness. Diagnosis was enough to indicate the mental illness. However, symptom or prescription alone was not sufficient because symptom may not always be enough to indicate a mental illness, and psychotropic prescriptions are also used to treat non-mental illness related conditions. For instance, neuropathic pain is treated with amitriptyline, which is also used

for treating depression. Therefore, for symptom and prescription to indicate mental illness, mothers were required to have historical diagnosis of the relevant mental illness or symptom and prescription to be recorded within three months which indicated the same mental illness. Figure 4 illustrates the process of defining exposure.

Finally, mental illnesses were further classified into **affective** (Bi-polar, schizoaffective disorders, Depression with psychotic symptoms) and **non-affective psychoses** (schizophrenia, paranoia, psychoses, schizotypal disorders), **mood disorders** (depression and other mood disorders (including puerperal psychosis), **neurotic disorders** (anxiety, Obsessive-Compulsive Disorders, phobias, adjustment to stress, dissociative disorders), **eating disorders** (anorexia, bulimia, binge eating), **disorders of personality and behaviour** (DSM-V A, B and C clusters, other disorders of personality, habit and impulse disorders) and **alcohol abuse and substance abuse disorders**. Using this algorithm, we published an article titled *"Prevalence of maternal mental illness among children and adolescents in the UK between 2005 and 2017: a national retrospective cohort study*" [17] in Lancet Public Health in 2019.

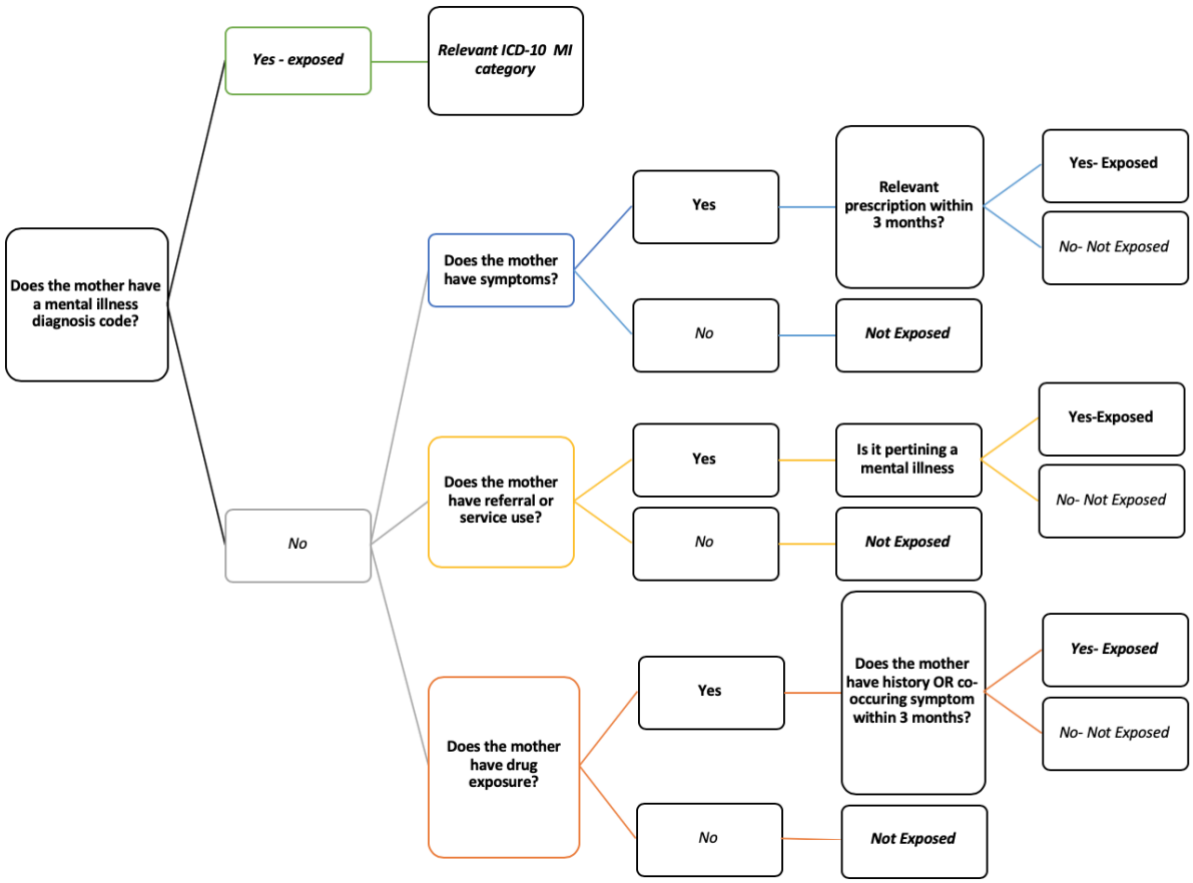

Figure 4 Process of defining maternal mental illness as an exposure

2.3.2 Outcomes

In this subsection the different types of physical health outcomes used in this thesis will be summarised, namely vaccination, obesity, atopy, perinatal smoking, and childhood cancer.

Vaccination study: The outcome variable in the vaccination study was child's immunisation status. Information on the child's immunisation status was retrieved from the "immunisation file" in the CPRD. In the UK, the vaccination schedule changed over the years (see *Appendix B*) ; therefore, we only examined the vaccinations that did not change through the study period (01 January 1993- 01 July 2015). These vaccinations were three doses of DTaP/IPV/Hib, which stands for 'Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine, Hib (Haemophilus influenzae type b)', also known as "5-in-1" given at two, three and four months of age; two doses of

Mumps, Measles and Rubella, which is known as MMR vaccine given at age one and three years and four months of age and one dose of DTaP/IPV, which stands for 'Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine, also known as “4-in-1 Preschool Booster”. These vaccines are recorded in primary care in two or three ways. They can be either recorded as one vaccine (e.g. MMR coded as 51) or each vaccine compound can be recorded separately (e.g. Mumps (9), Measles (7), Rubella(8). Table 6 illustrates the different combinations of vaccine recording in the primary care and these combinations were utilised in this study.

Table 6 Vaccine compound combinations

Vaccine	Code	Immunisation Type	Code Combinations
5 in 1 (DTaP/IPV/Hib)	80	DTAPIPVHIB	80
	79	DTAPIPV	79+6
	1	TETANUS	
	2	POLIO	
	3	DIPHTHERIA	1+2+3+5+6
	5	PERTUSSIS	
	6	HIB	
MMR (Mumps, Measles &Rubella)	51	MMR	51
	50	MR (MEASLES+RUBELLA)	50+9
	9	MUMPS	
	7	MEASLES	9+7+8
	8	RUBELLA	
4 in 1 (DTaP/IPV)	79	DTAPIPV	79
	1	TETANUS	
	2	POLIO	1+2+3+5
	3	DIPHTHERIA	
	5	PERTUSSIS	

A dichotomous variable was created for each child indicating whether they had a recorded dose of all the necessary vaccinations or not (yes/no) by age two and five. These vaccinations were investigated in two cohorts reflecting the different ages that children received their vaccination. The first involved children followed from birth up to the age of two and investigated three doses of 5-in-1 and one dose of MMR. In the second cohort, followed up from birth until age five, the outcome involved all necessary vaccinations by age two as well as second dose of MMR and one dose of the 4-in-1 preschool booster among children.

Obesity study: In this feasibility study, the outcome variable was child's obesity status. In order to define the obesity status, child's height, weight and BMI records were captured from child's "additional files". If the child did not have a BMI record, then it was calculated from weight and height records. The final step involved getting age appropriate standardised z-scores of weight and BMI of the children by using the Zanthro package in Stata [166].

Atopy study: The main outcome in this study was a diagnosis of an atopic disorder (asthma, eczema, allergic rhinitis or food allergy), which were identified from child's primary care clinical records using relevant readcodes from the repository clinicalcodes.org [147] (*Appendix C1-4*).

For secondary care health use for asthma, 'ICD-10 codes were used to identify asthma (J45, J46) and food allergy (T78) as ICD-10 codes are used in hospital inpatient admissions instead of read codes. Final diagnosis code lists were approved by a clinician (A.S). For each child, a dichotomous variable was created indicating whether they were diagnosed with atopic disorder or not (yes/no).

Perinatal smoking study: The perinatal smoking study was developed while conducting the atopy study, where maternal smoking is one of the risk factors for atopic disorders such as asthma. In atopy study, we observed that a very large proportion of mothers with mental illness smoked during the perinatal period and decided to specifically investigate perinatal smoking behaviour among mentally ill and non-mentally ill mothers. Capturing a patient's smoking status in the CPRD is not always straightforward, because the information may not be always reliable as a result of unstandardised terminology, changing attitudes towards smoking and patient's changes in smoking behaviour [167,168]. Moreover, the missingness of maternal smoking status in our dataset was around 50% when using only one data source. In order to tackle these two problems, I developed an algorithm which captures mother's smoking status using multiple data sources.

The first step in the algorithm involved capturing all smoking relevant read codes [169] (*Appendix D*) from mother's clinical, referral and test files. Then, from all the available data, a smoking status for each episode was assigned as "never smoked" *(coded as=0)*, "ex-smoker" *(1)* and "current smoker" *(2).* This action revealed a number of conflicting outcomes which were resolved in the second step of the algorithm as described below:

a) If a mother had multiple records on the same date such as "never smoked" and "health education for smoking", her smoking status was recoded as "never smoked". The reason for this recoding is that GP provides essential information during the consultation about the impact of smoking; it doesn't mean that the patient is a smoker.

b) Based on date of records, if the mother had a "never smoked" status after "current smoker" or "ex- smoker" status, they were recoded as "ex-smoker". In terms of logical order, current or ex- smokers cannot be classified as "never smoked" afterwards.

Once these conflicts were resolved, mother's smoking status during child's life, including pregnancy, was captured. Simply, the highest smoking status (0|1|2) during child's life, including pregnancy was used in the atopy and cancer studies. Using this algorithm, the missingness dropped to 6%.

For the perinatal smoking study, specific time periods (prenatal, perinatal and postnatal) were identified. Prenatal period covered one year prior to birth until birth; perinatal period covered one year prior and after the birth and postnatal period covered one year after the birth. Because the follow-up time for each period was relatively short it was necessary to have further assumptions to reduce missingness in these periods. These assumptions were:

a) If the mother did not have a record during the prenatal, perinatal or postnatal periods but had a record outside these time periods during the study as "Never Smoked", then her missing record was imputed as "Never Smoked".

b) If the mother did not have a smoking record during the perinatal period but had a record prior their pregnancy as ex-smoker or current smoker, then the missing record assumed to be “Ex-Smoker”.

c) If the mother had “Never Smoked” record before pregnancy but had a record of “Ex- Smoker” during postnatal period, then her prenatal smoking status was recorded as “Ex-smoker”.

Cancer study: This is a collaboration study with Sweden where the effect of maternal mental illness on childhood cancer was investigated in two national cohorts. In both cohorts, childhood cancer diagnosis was captured from the hospital inpatient admission datasets. Specifically, in the English cohort, children were linked to the HES inpatient hospital admission dataset and cancer diagnosis was captured using the ICD-10 codes from Chapter II- Neoplasms (C00-C97) excluding in situ neoplasms (D00-09), benign neoplasms (D10-36) and neoplasms of uncertain or unknown behaviour (D37-48). Similarly, in Swedish cohort, ICD-10 codes captured childhood cancers (*Appendix E*). For each child, a dichotomous variable was created indicating whether they were diagnosed with cancer or not (yes/no).

2.4 STUDY DESIGN AND STATISTICAL ANALYSES

In this final section of the methods chapter the main type of study design used; subsection 2.4.1 will describe cohort study design. Then, information on the statistical measures used in each research paper will be provided in subsections 2.4.2- 2.4.5. Subsection 2.4.6 will describe how clustering in the data was controlled for and finally, methods chapter will end with the subsection 2.4.7 by describing how confounding adjustment took place in all research papers.

2.4.1 Cohort study

A cohort study involves people who are followed up for a period of time and the outcome is judged at the end of a study between levels of exposure. Thus, the aim of cohort study is to measure the event of interest within unexposed and exposed cohorts during the specified time period [170] and they can be conducted retrospectively or prospectively. The retrospective cohort study involve

looking back in time for the outcome of interest. Retrospective cohort studies are relatively less expensive and quick to conduct. However, the researcher would not have any control on the data collection as the data would be collected in the past which could involve missingness and inaccuracy. All research papers produced in this thesis used retrospective cohorts.

Cohort studies have advantages over other study designs. For example, a cohort study can look at various outcome variables while case-control asses only one outcome variable. The probability of developing outcome of interest can be also calculated in cohort studies. Also, cohort studies provide clarity of temporal sequence and allow examination of incidence and the natural history of disease.

Yet, there are important points to consider when analysing cohort studies using electronic healthcare databases. In cohort studies, the ideal observation period involves from birth to death with no gaps. However, this is was not possible in the studies presented in this thesis because, once the participants leave their participating GP practice, we are not able to follow them anymore even if they register to another participating GP practice, which is one of the biggest drawbacks of the CPRD. Moreover, in the CPRD, UTS and LCD dates (see subsection 2.1.2, and section 2.2) are also needed to be considered when defining the observation period because data quality and availability relies on these dates. Whereas, some data sources that are not affected with these problems, for instance, Sweden's Total Population Register [171]. They have almost a complete follow up data on mothers and their children and the only reason that they would be not followed up if they leave the country. This cohort is utilised in Chapter 7 study where a collaboration between two countries took place.

Another important factor to consider in cohort studies is timing of exposure and outcome of interest. In this thesis, child's birthdate, mother's delivery date variables played an important role in defining exposure and outcome variables. However, patient's birthdate information in CPRD is not fully provided to the researchers to protect patient confidentiality. Although, in CPRD's mother-baby

link, child's birthdate is estimated using an algorithm (see subsection 2.1.5). As a result, the timing of the exposure or the outcome may slightly vary from the reality.

2.4.2 Logistic regression

In epidemiology, logistic regression is one of the most common statistical techniques to estimate the association between the likelihood (odds) of an event of interest and independent variables. Logistic regression is used when we have a binary outcome and one or more independent variables and when we do not have to account for differential follow-up time (i.e. each subject is followed up for the same length of time). The logistic regression model estimates the chance of the outcome depending on specific predictors by:

$$\log\left(\frac{\pi}{1-\pi}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots \beta_m x_m$$

where π denotes the probability of the specific event (e.g. vaccination), χ are the explanatory variables (e.g. maternal mental illness, ethnicity, gender etc) and β_i represents the association between the explanatory variables and the log odds. The reference group involves individuals with zero values for all $\chi_{1...m}$ and the log odds in this group is given by β_0.

The logistic regression parameters are expressed in odds ratios. In order to explain the odds ratios, it is vital to know the concept of odds. An odds is an expression of the likelihood of an event happening and is defined as the ratio of the likelihood of that event happening with the likelihood that it did not. For example, an odds of two shows that there is twice the chance of the event happening than not. This could be re-expressed as a proportion as: 66%. Odds ratios compare the odds of an event happening in the presence of the exposure, to the odds of the outcome happening in the absence of exposure [172]. Suppose *y,* is a categorical independent variable coded as 0 and 1.

The odds ratio would be describe as the ratio of the odds for y=1 to the odds for y=0 [173] which is formulated as:

$$OR = \frac{\pi\,(1)/\,1-\pi(1)}{\pi\,(0)/\,1-\pi(0)}$$

An OR equal to 1 indicates no association between the exposure and the outcome while OR >1 indicates exposure is linked with higher odds of the outcome and OR<1 suggests lower likelihood of outcome as a result of association with exposure.

Considering the vaccination study presented in Chapter 3, the parameters of a logistic regression (Table 7) model would be interpreted as follows. Those with maternal alcohol addiction have half the odds of getting vaccinated compared to those without [exp (β_1) **=** exp (-.6911818)= 0.50] and girls have a ten per cent higher odds of getting vaccinated [exp (β_2) = exp (.0725685)= 1.10]

Table 7 Vaccination study multivariate logistic regression model containing explanatory variables

Term	**β estimate**	**Standard error**	**P value**
Intercept ($\beta_{0)}$	1.958071	.0072894	<0.001
Maternal alcohol addiction ($\beta_{1)}$	-.6911818	.066688	<0.001
Child sex: Female ($\beta_{2)}$	.0725685	.0072894	<0.001

When multiple variables are involved in the regression, the interpretation of the beta coefficients is taken at the reference value for the other variables (e.g. β_1 is the relationship between maternal alcohol and vaccination when all the children are male). Logistic regression is estimated using maximum likelihood and the main assumption is that is the relationship between the log odds and the X variables is correctly specified (e.g. there are no missing squared terms). Also, standard methods assume that the observations are independent of each other.

2.4.3 Cox proportional hazards model

The Cox proportional-hazards model [174] is a semi-parametric model, which aims to answer the question “which particular factors have impact on the likelihood of an event of interest happening at a specific time period?” and useful when participants have different follow up times because they are ‘censored’ from the study. Censoring occurs when there are time periods that we do not observe when a subject may experience the outcome of interest. In the Cox proportional hazard regression model, the measure of effect is hazard rate which refers to instantaneous rate of an event happening, expressed as:

$$h(t) = \frac{f(t)}{S(t)}$$

where f(*t)* equals to the density of events at *t*, divided by the probability of surviving to that duration without experiencing the event s(t). Hazard rate is a conditional failure rate because, it indicates the rate which individuals fail by time (t) that they have survived until time (t) which is formulated as;

$$h(t) = \lim_{\Delta t \to 0} \frac{\Pr(t \leq T < t + \Delta t | T \geq t)}{\Delta t}$$

where h(t) illustrates the instant risk that the event happens in the time interval *t, t+Δt* at survival or after time *t.* The hazard ratio is an estimate of the ratio of the hazard rate in the exposed versus the unexposed group and it is expressed as

$$h(t) = h_0(t) \exp\{\beta_1 x_1 + \beta_1 x_1 + \cdots + \beta_m x_m\}$$

Where $h_0(t)$ is the baseline hazard and represents the hazard when all of independent variables) X_1, X_2 , X_p equal zero. Predicted hazard which is h(t)), or the rate of experiencing the event of interest in the next instant, is the product of the baseline hazard ($h_0(t)$) and the exponential function of the linear combination of the predictors. Thus, the predictors have a multiplicative or proportional effect on the predicted hazard.

Cox regression is a semi-parametric model because it assumes that predictor variables act multiplicatively on the hazard function, which is a parametric assumption, however, it does not make any assumptions about the shape of the baseline hazard function which is the non-parametric feature of the cox regression model.

$$h(t) = h_0(t) \exp\{\beta_1 x_1 + \beta_1 x_1 + \cdots + \beta_m x_m\}$$

Non- parametric | Parametric part

There are three key assumptions in cox regression model and if any of the following assumptions are not met, the results produced from the cox proportional hazards model may be invalid.

1- Event times (also referred to as failure times) are independent of one another.
2- Constant hazard ratio over time as it assumes the hazard of failure is proportional across levels of a given covariate.
3- Censor times are assumed to be independent of failure times, known as non-informative censoring.

2.4.4 Time-varying variables

The cox regression model was utilised in atopy (Chapter 5) and cancer (Chapter 7) studies. To accurately estimate the maternal mental illness effect in these studies, it was essential to include the maternal mental illness as a time-varying variable, because if we kept the maternal mental illness as a static variable, there would have been instances where mother develops mental illness after their child's diagnosis of atopy or cancer.

In order to do this, it was necessary to split the data on the day mother's mental illness status changed. To exemplify, assume that a fictious child is known to be exposed to maternal mental illness during study period. The child and its mother were followed up from child's birth and the mother experienced mental illness on day 300. This fictious child, therefore, would be recorded as unexposed to maternal mental illness between day 0 till day 300 and then recorded as exposed to

maternal mental illness from day 300 until the end of follow up, which is day 400. This data splitting process would create a new row for each child who was exposed to maternal mental illness. Table 8 illustrates how information about this fictious child would look like in the dataset: first, showing fixed-time (static) covariate version where the child is defined as exposed from beginning of the follow up until the end of the study, and second row illustrates how this time-varying covariate would look like.

Table 8 Fixed-time vs time-varying MMI covariate

Fixed-time covariate			
t_0	t	T	MMI
0	400	400	1
Time varying covariate			
0	300	300	0
300	400	100	1

In the table 8, _t0 refers to the beginning of the child's survival time while "t" refers to survival end time. "T" is the person-year contribution. In both atopy (Chapter 5) and cancer (Chapter 7) studies, time-varying maternal mental illness variable was used, and children were defined as exposed until the end of the study once they were exposed.

2.4.5 Meta-analysis

Meta-analysis is used to combine statistical results from independent studies that ask the same question [175] in order to derive a single estimate which was used in Chapter 7 to combine estimates from the UK and Sweden. Briefly, meta-analysis calculates the effect sizes from studies and weighted mean effect size across the studies included. Fixed-effect models and random-effect models are two ways to calculate the mean effect size. Decision of which model to use depends on the conceptualisation of the source of variation among study effect sizes and this determines how the estimate and error of estimate will be computed which directly affects the meta-analysis results.

The primary distinction between fixed-effect and random-effect model is the assumption of the source of error and how it is accounted for. In a fixed effect model, the observed variation is assumed to be within-study error and accounted by inverse variance weight. In random-effect

model, within-study error plus between-study error is accounted for. The variance, standard error and confidence intervals for the pooled effect estimate is always larger in random-effects model than in the fixed-effects model because of this extra source of variation [176].

In Chapter 7, after estimating the risk of cancer among children exposed to maternal mental illness in two separate cohorts, a meta-analysis procedure was undertaken to derive a pooled estimate of the risk among children using the Sidik-Jonkman random-effects model [177]

2.4.6 Clustering effects

In all regression analyses, accurate standard errors, unbiased and consistent estimates of the regression coefficients are vital. Briefly, the standard error is the standard deviation of the sample statistic and is used to calculate confidence intervals and p-values. This measures the statistics precision and is generally smaller for larger sample sizes. Clustering occurs when observations in the sample are non-independent. This means that, for example, the probability of an event occurring in one subject is correlated with the probability of it occurring in at least one other. If we ignore the clustering, then we would underestimate the true standard errors which means that we over-reject the null hypothesis. If data are analysed without adjusting for clustering, then it would violate the assumption of independence and lead to misleadingly small standard errors, confidence intervals that are too narrow and smaller p-values [178].

When looked into the research studies presented in this thesis from this perspective, it can be seen that they all investigate mother-baby pairs, including mothers with multiple children. This means there are siblings clustering on house level. In other words, there are sub-groups of siblings that are similar to each other. Hence, in all of the studies reported in this thesis, clustering effects of maternal sibships were accounted for to obtain accurate standard errors. Robust standard errors, also known as *Hubber-White Sandwich estimator* was utilised, which takes into account the intra-cluster correlation, and relaxes the assumption of independence of the observations [179]. In Stata,

robust standard errors were obtained by using the `vce(cluster clustvar)` command [180] at the end of each regression command as an option.

2.4.7 Confounding adjustment

Confounding is one of the biggest challenges that observational studies face. Confounding can be described as the bias emerging from the existence of common causes of exposure and outcome. A variable would be a confounder if it (i) causes the outcome of interest; (ii) causes the exposure. This excludes variables that are on the causal pathway between exposure and outcome/that mediates the effect of the exposure on outcome/that are caused by the exposure. [181]. Figure 5 illustrates an example of a confounder using Directed Acyclic Graph (DAG) where the association between exposure (maternal mental illness) and the outcome (child asthma) is confounded by maternal/child ethnicity. It is well evidenced that women from ethnic minorities are at high risk of experiencing mental illness [182] and also incidence rates of asthma among ethnic minorities in the UK higher than White ethnic group [183]. In this scenario, the confounding factor is ethnicity which is associated with both maternal mental illness and child asthma.

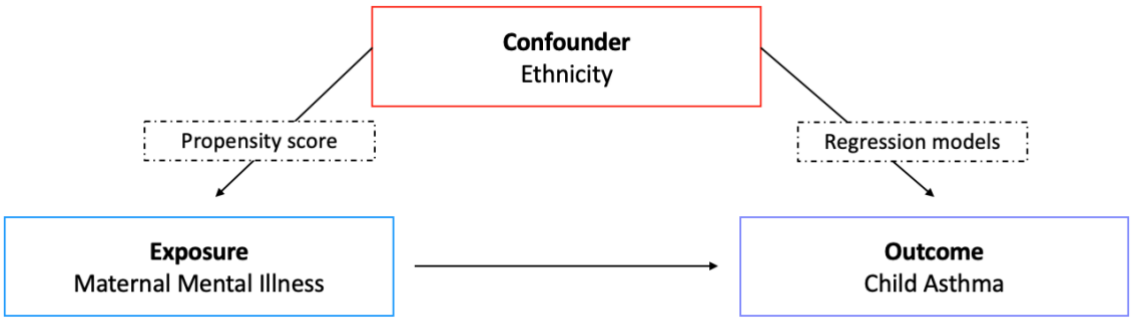

Figure 5 Example of a confounder presented on a DAG

An uncontrolled confounder would account for all or some part of the association observed. Also, it can lead to an over- or under-estimate or under-estimate of the true association. It can also reverse the direction of the exposure effect [184]. Potential confounders can be addressed through either study design or statistical methods. However, despite a well-developed study design, statistical methods are still required to address the potential confounders.

One way to control for confounders is covariate adjustment in a regression model, and this was used in all the research studies presented in this thesis. In Figure 5, these regression models target the arrow from confounder to outcome. However, it would be rather unrealistic to expect adjusted models to be completely free from confounder effects. It is very important to acknowledge the “unmeasured” confounder effects in epidemiological studies that rely on data from electronic health records.

The propensity score calibration (PSC) is a method for residual confounding adjustment. It would be appropriate to use when known confounders are not measured in both exposed and unexposed groups. The PSC aims to adjust for unmeasured multiple confounders by combining information from an external validation study sample using propensity scores and regression calibration methods.

The PSC method was seriously considered to be utilised for the atopy study (Chapter 5) as there was an opportunity to conduct an external validation study through a collaboration at the University of Manchester. Myself and our collaborator, Dr Wang designed a questionnaire-based study to be conducted by her final year psychology undergraduate students. The aim of the study was to investigate the risk of atopic disorders among children with and without maternal mental illness, same as the main atopy study. We also collected demographic information that exist in the main analysis as well as unmeasured potential confounders such as maternal education level, maternal occupation, income and marital status. Unfortunately, the validation study did not reach the optimal

sample size (N = 328) and it was not representative of the main analysis cohort in terms of deprivation and ethnicity. Therefore, I did not proceed with the PSC method.

However, if this study was to proceed, then the following steps would have been taken. First, propensity score of the main study would have been estimated by using logistic regression including all available covariates. Then, propensity scores would have been calculated for the validation study using the similar regression model. The first model would replicate the same regression model in the main study and second model would have been using the same covariates in the first model with additional information in the validation study (unmeasured covariates such as maternal education etc.). In the final step, we would have implemented score calibration using the regression calibration to correct measurement error in the propensity score of the main study. After this step, with a relevant Stata package, it would have been possible to obtain adjusted hazard ratios that are controlled for unmeasured confounding by using the propensity scores from both validation and main studies.

As a concluding remark, it is explicitly acknowledged that since it was not possible to control for unmeasured confounding in any of the papers presented in this thesis, unmeasured confounding may exist in each analysis.

CHAPTER 3- THE INFLUENCE OF MATERNAL MENTAL ILLNESS ON VACCINATION UPTAKE IN CHILDREN: A UK POPULATION-BASED COHORT STUDY

Journal Article

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Status: Published

Journal: European Journal of Epidemiology

Contributions: KMA gained funding for and conceived of the study, CSO wrote the study protocol, with input from KMA, MP, HH and DA. CSO carried out the analysis with support from MP and HH. CSO wrote the initial draft of the manuscript and all authors contributed to the final version.

Presentations: Doctoral Academy Conference 2019

3.1 DESCRIPTION OF STUDY IN CONTEXT OF THESIS

The following chapter presents the first published research paper of this thesis, which reported vaccination uptake among children exposed to maternal mental illness in the UK using a cohort of mother-baby pairs identified in the CPRD-GOLD (see subsection 2.1.5). The aim of the study was to quantify the vaccination uptake among children exposed to maternal mental illness using logistic regression models (see subsection 2.4.2).

The supplementary material for this study includes sensitivity analyses that were conducted to investigate effects of OQF on data recording (see subsection 2.1.2), late registered children as well as gender differences in MMR vaccine uptake.

After the publication of this study, I wrote a short commentary about the effects of COVID-19 on routine childhood vaccination uptake to highlight the importance of our findings, which is presented at the end of this chapter.

3.2 ABSTRACT

Background: Reduced vaccination uptake is a growing and global public health concern. There is limited knowledge about the effect of maternal mental illness (MMI) on rates of childhood vaccination.

Methods: This retrospective cohort study examined 479,949 mother-baby pairs born between 1993 and 2015 in the Clinical Practice Research Datalink (CPRD GOLD), a UK-based, primary health-care database. The influence of MMI on children's vaccination status at two and five years of age was investigated using logistic regression adjusting for sex of the child, child ethnicity, delivery year, maternal age, practice level deprivation quintile and region. The vaccinations were: 5-in-1 (DTaP/IPV/Hib) and first dose MMR by the age of two; and all three doses of 5-in-1, first and second dose of MMR vaccines by the age of five. Exposure to MMI was defined using recorded clinical events for: depression, anxiety, psychosis, eating disorder, personality disorder and alcohol and substance misuse disorders.

Results: The likelihood that a child completed their recommended vaccinations by the age of two and five was significantly lower among children with MMI compared to children with mothers without mental illness (adjusted Odds Ratio (aOR) 0·86, 95% CI=0·84-0.88, p<0·001). The strongest effect was observed for children exposed to maternal alcohol or substance misuse (at two years aOR 0·50, 95% CI= 0·44-0·58, p<0·001). In the UK, an estimated five thousand more children per year would be vaccinated if children with MMI had the same vaccination rates as children with well mothers.

Conclusions: Maternal mental illness is a hitherto largely unrecognised reason that children may be missing vital vaccinations at two and five years of age. This risk is highest for those children living with maternal alcohol or substance misuse.

Key Words: Maternal mental illness, child vaccination, primary care, CPRD

3.3 INTRODUCTION

Despite the fact that in most countries vaccines are provided free at the point of access [185], 15% of children remain unvaccinated globally [186]. Recent outbreaks of measles in Europe [187,188] and the US [189] indicate a significant decline in herd immunity as a result of reduced vaccination uptake in infants. Such trends of reducing childhood vaccination have been attributed to scepticism about the safety of vaccination, particularly following the falsified report by Andrew Wakefield [190] linking the Mumps, Measles and Rubella (MMR) vaccine with childhood autism.

People with mental illness are less likely to benefit from public health information campaigns [191,192] but it is unclear whether mothers with mental illness are more or less influenced by messages about vaccination safety. This is important because mothers are usually the primary caregivers and take a central role in their children's health [51] so the extent to which their children access preventative healthcare is of public health concern. Recently, using presence or absence of maternal mental illness (MMI) from primary care records, we estimated that almost one in four children in the UK has a mother with a mental illness [17] and this number may be growing. These estimates indicate the prevalence of children exposed to different types of MMI in the UK as: non-affective psychosis 0.2%; affective psychosis 0.3%, depression as 18%, anxiety as 8%; eating disorders 0.1%; personality disorder 0.1% and alcohol and substance misuse as 0.3% [17].

There is limited evidence about the extent to which MMI influences rates of vaccination uptake. Existing studies report associations between decreased vaccination uptake, maternal depression [53,54] and maternal psychotic disorder [55]. However, these rely on small samples (<5000), mostly use maternal self-report of mental illness and were ascertained more than a decade ago. If children with MMI remain at risk of significantly lower vaccination uptake, this represents an important public health concern in a group already known to be multiply deprived [193] and vulnerable to premature mortality of treatable cause [2,194]. We addressed this outstanding knowledge gap in a large, contemporary and high-quality population-based primary care cohort.

We hypothesised first that children with MMI would receive fewer vaccinations overall than children with healthy mothers. Second, we hypothesised that offspring of mothers with psychotic disorders would be significantly less likely to receive vaccination compared to mothers with common mental illnesses (i.e. depression and anxiety). Finally, we explore whether any effect that MMI has on vaccination rate has changed over time, and in the period including the MMR scandal.

3.4 METHODS

3.4.1 Data source

Data for this retrospective cohort study were delineated from the Clinical Practice Research Datalink (CPRD GOLD) which contains anonymised electronic health records from 10% of UK general practices and is considered demographically representative of the UK population [143]. CPRD holds data on clinical consultations, immunisations, prescriptions and external healthcare referrals. Data entries are made by general practitioners (GPs) using the Read Code [195] framework.

The cohort was identified from the CPRD mother-baby link; a previously developed algorithm [196] which identifies birth records for women and pairs those to babies if: the baby is registered at the same general practice as the mother; the baby's birthday is within 60 days of delivery date and the baby shares a specific family identifier based on residential address [197]. We also linked our cohort with Hospital Episode Statistics (HES) dataset to obtain additional information on the child's ethnicity.

3.4.2 Cohort selection

The cohort included a sample of children identified from the CPRD's Mother-Baby Link born between 1st January 1993 and 31st December 2015. Follow-up was defined from the date of birth until the earliest date that the child transferred out of the practice, died or the practice stopped contributing data to CPRD. Children were excluded from the cohort if: they were born before the participating general practice fulfilled the minimum data quality standards set by the CPRD; their

mother had not been registered at a participating general practice for at least one year prior to birth; or if they did not have a minimum of two years follow-up.

Two separate cohorts were constructed for children with complete follow-up data until age two and until age five years to reflect when children are vaccinated. The scheduled times for vaccination in this study are four, 13 and 40 months; therefore, the two and five year time points allow for delays in vaccination for legitimate reasons not associated with MMI (e.g. child infections). Moreover, these time points allow this study to be comparable with childhood vaccination statistics in different regions of the UK [50,198–200].

3.4.3 Maternal mental illness

Children were defined as exposed to MMI if their mother had a clinical event indicating mental illness between one year prior to birth up to the age of two (for the two year cohort) and five (for the five year cohort) as previously described [17]. Since children can exist in both cohorts, some of the following exposure categories may overlap. Mental illness was defined using the following categories (mapped to ICD-10 codes): *i) psychotic disorders* (ICD-10: F20-4, F25, F28-9, F30-31), ii) *depressive disorders* (F32–9), iii) *anxiety and stress-related disorders* (F40–48), v) *eating disorders* (F50), *iv) personality disorders* (F60-3, F67-9) and vi) *alcohol/drug dependence* (F10–16, F18-19). Final code lists used are available at www.clinicalcodes.org.

A recorded mental illness diagnosis by the GP was considered sufficient to identify mothers with mental illness. However, in the UK, there is an increasing preference among GPs to record mental illness symptoms instead of diagnostic labels [201]. Therefore, we adapted the algorithm created by Abel *et* al[17] which identifies mental illness if a mother has a symptom within three months of a prescription for medication such as antidepressants, antipsychotics and anxiolytics that has a recognised indication for the treatment of the same mental illness. The medications used and the relevant symptom-categories were antidepressants (depressive disorder); antipsychotics (non-affective psychosis), anxiolytics/hypnotics (anxiety disorders), mood stabilisers (affective psychosis); and drugs used to treat substance dependence.

3.4.4 Childhood vaccinations

We only selected vaccinations which have not changed during the study period, in the number of doses or child age at administration. These vaccinations were: three doses of 5-in-1; two doses of MMR; and one dose of 4-in-1 preschool booster (Table 9).

Table 9 Childhood vaccinations examined in the study

Vaccine *(active ingredients)*	**Given at age (in months)**	**Investigated for age-group (in years) for this study**
5-in-1 *(DTaP/IPV/Hib)* Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine and Hib (Haemophilus influenzae type b)	2,3,4	2
MMR Measles, Mumps and Rubella	13 (1st Dose), 40-60 (2nd Dose)	2, 5
4-in-1 *(DTaP/IPV)* Diphtheria, Tetanus, acellular Pertussis, Inactivated Polio Vaccine	40	5

Dichotomous variables were created for each child indicating whether they had a recorded dose of all the necessary vaccinations or not (yes/no) by the specified age by using the date of the vaccination recorded in the child's immunisation files. Children were recorded as having received all vaccinations if they had three doses of 5-in-1 and one dose of MMR by age two. Therefore, children aged five, were counted as "received all vaccinations" only if they had received all necessary vaccinations by age two as well as second dose of MMR and one dose of 4-in-1.

The proportion of those with recorded 4-in-1 was only around 10% which was considered unfeasibly low. This has been reported previously by Public Health England and the National Health Service [202,203] and it has been suggested that this relates to many children receiving 4-1 outside the recommended timeframe, or because some children only receive 3-in-1.Therefore, we assumed that data were not well recorded for this vaccine and excluded it from the analysis.

3.4.5 Covariates

Demographic data were extracted on maternal age at birth, child sex and geographical UK region of the general practice (categorised as*:* North East, North West, Yorkshire & The Humber, East Midlands, West Midlands, East of England, South West, South Central, London, South East Coast, Northern Ireland, Scotland and Wales). Child ethnicity (categorised as: Asian, Black, Mixed and White) was extracted from CPRD and HES. We prioritised HES data on ethnicity when data were available from both sources because HES data has been previously validated using other linked data sources [204]. The quintile of the Index of Multiple Deprivations (IMD) illustrates the deprivation at the local area level, based on employment, income, education, health and disability and crime, housing and the lived environment. These areas are rated and divided into quintiles from least to most deprived areas. The IMD of the registered practices was extracted based on their postcodes. The number of face-to-face GP appointments of the mothers nine months prior to birth was calculated with an aim to create a proxy for maternal engagement in primary healthcare services.

3.4.6 Analysis

The association between MMI and vaccination uptake was estimated using odds ratios calculated using logistic regression models. The first model adjusted for variables thought potentially to confound the relationship between MMI and childhood vaccination status: sex of the child, child ethnicity, delivery year, maternal age, practice level deprivation quintile and geographical region. In the second model we included, as an additional variable, the count of GP appointments nine months prior to birth to investigate whether part of the associations could be explained by maternal engagement in primary care services. We estimated how many extra children would be vaccinated over the study period (19 years) if children with MMI had the same vaccination rates as children with healthy mothers using the formula:

$$\sum_{y=1998}^{2017} LB_{y-5} * \pi_y * RD_y$$

Where π_y is the prevalence of MMI estimated in children aged five years in year *y*; LB_{y-5} is the number of live births in the five years prior, provided from national statistics [205–207]; and RD is the estimated difference in vaccination rate between those with MMI and those without, in year y. Confidence intervals for this estimate were calculated using the bootstrap procedure [208], using the normal approximation over 10,000 bootstrap samples.

In order to investigate whether the effect of MMI on vaccination has changed over the period covering the MMR scandal, adjusted odds ratio were calculated for each analysis year (1993-2015) using an interaction term between year and MMI.

In all regression analyses, continuous variables were centred, and a squared term was included; Wald-test statistics were used to determine 95% confidence intervals and p-values and chi-square test was used to test the interaction. Clustering by maternal siblings was dealt with by calculating the standard errors using the Hubber/White sandwich estimator [209]. Data were analysed using Stata SE 15.0.

3.4.7 Sensitivity analyses

Data recording in the CPRD has significantly improved from 2005 as a result of the introduction of the Quality and Outcomes Framework (QOF) in 2004 [210]. Therefore, a sensitivity analysis was conducted to investigate whether or not improvements in data recording affected results by repeating the analysis excluding those born before 2005. We also anticipated that some children may have registered to their participating practices later than age two even if their mothers were fully registered at the same practice. Vaccination records are back-dated when a child is registered at a general practice; however, we were concerned about the quality of vaccination history records for these late registered children. Therefore, we conducted a second sensitivity analysis to investigate the potential effects of late registered children by re-running the analyses excluding this group.

3.5 RESULTS

3.5.1 Demographics

The study cohort consisted of 479,949 mother-baby pairs in the cohort followed-up to two years old (the two-year cohort) and 326,082 pairs followed-up to five years old (the five-year cohort, Figure 6). The mean maternal age at delivery was 30.3 years (standard deviation = 5·8) and 48·8% of children were female (Table 10). Children exposed to MMI were more likely than those without to be registered at a general practice in the lowest deprivation quintile (30·7% vs 25·5%).

Twenty percent of children (95,435/479,949) in the two year cohort and 29·8 % of children (97,088/326,082) in the five year cohort had a mother with a mental illness recorded between one year prior to their birth up to their second and fifth birthday, respectively. The most common disorder was maternal depression (25·7% for the five year cohort); less than one per cent had a diagnosis of psychotic disorder.

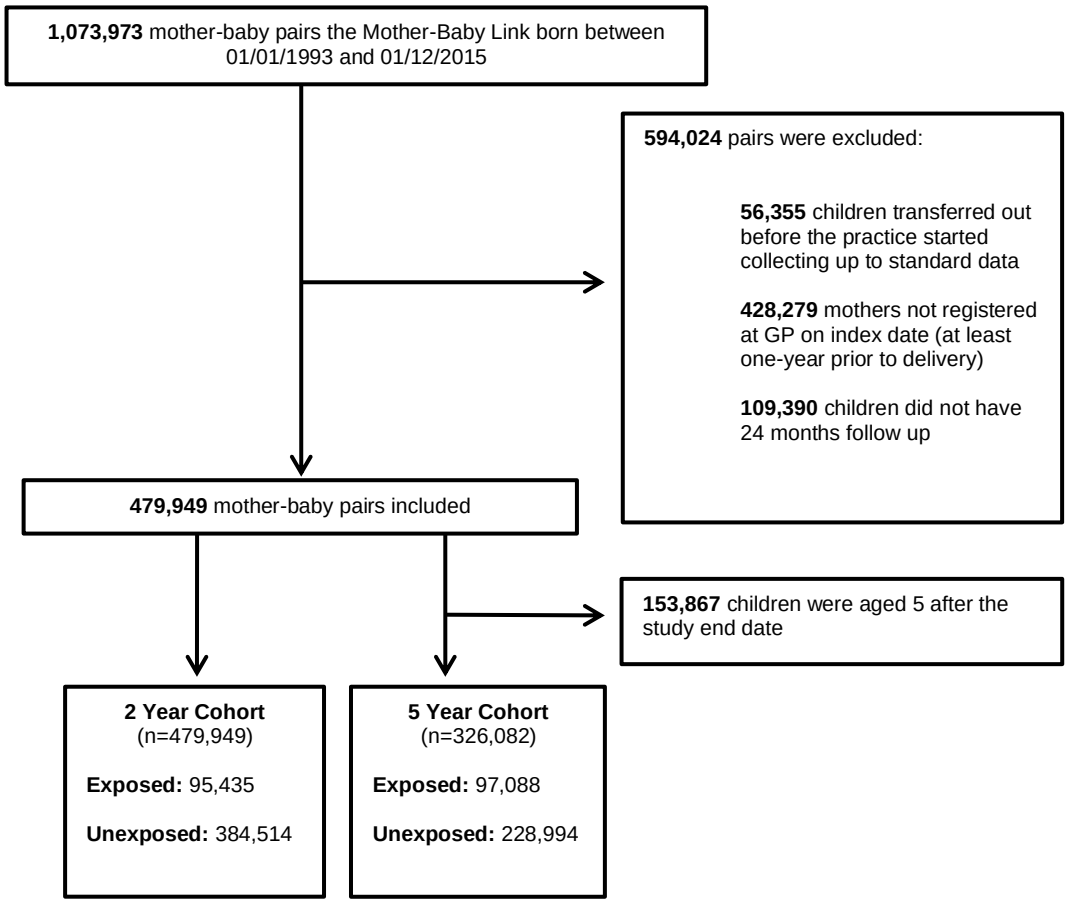

Figure 6 CONSORT diagram of the mother-baby cohort selection process

Table 10 Cohort demographics for the two and five year cohorts, by maternal mental illness status

	2 Year cohort (n= 479,949)				5 Year cohort (n= 326,082)			
	Children with MMI (n=95,435)	**%**	**Children without MMI** (n= 384,514)	**%**	**Children with MMI** (n=97,088)	**%**	**Children without MMI** (n= 228,994)	**%**
Child gender								
Female	46,299	48·5	188,058	48·9	47,229	48·7	111,951	48·9
Male	49,136	51·5	196,456	51·1	49,859	51·4	117,043	51·1
Child ethnicity								
Asian/British Asian	1,279	1·3	13,679	3·6	1,339	1·4	7,515	3·3
Black/ black British	604	0·6	5,991	1·6	549	0·6	3,026	1·3
Mixed	1,591	1·7	7,021	1·8	1,336	1·4	3,386	1·5
Other	511	0.5	3,565	0·9	474	0·5	1,876	0·8
White	62,479	65·5	236,265	61·5	62,740	64·6	139,957	61·1
Unknown	28,971	30·4	117,993	30·7	30,650	31·6	73,234	32·0
Maternal age at delivery								
<19	4,959	5·2	12,370	3·2	5,140	5·3	6,761	3·0
20-24	17,996	18·9	47,759	12·4	17,236	17·8	26,457	11·6
25-29	26,098	27·4	95,669	24·9	26,476	27·3	55,581	24·3
30-34	27,081	28·4	129,771	33·8	28,247	29·1	79,267	34·6
35-39	15,473	16·2	79,789	20·8	16,207	16·7	49,471	21·6
40>	3,828	4·0	19,156	5·0	3,782	3·9	11,457	5·0
Maternal mental illness								
Any mental illness*	95,435	19·9	-		97,088	29·8	-	
Psychotic disorder	1,120	0·3	-		1,319	0·6	-	
Depressive disorder	78,062	16·9	-		79,355	25·7	-	
Anxiety disorder	28,932	7·0	-		36,744	13·8	-	
Eating disorder	854	0·2	-		1,124	0·5	-	
Personality disorder	500	0·1	-		594	0·3	-	
Substance and alcohol abuse	1,549	0·4	-		1,943	0·8	-	
UK IMD quintile based on GP location								
1 least deprived	14,085	14·8	72,719	18·9	15,347	15·8	46,276	20·2
2	14,753	15·5	62,129	16·2	14,847	15·3	36,738	16·0
3	17,232	18·1	72,012	18·7	17,391	17·9	42,489	18·6
4	20,045	21·0	79,491	20·7	20,240	20·9	46,708	20·4
5 most deprived	29,320	30·7	98,163	25·5	29,263	30·1	56,783	24·8
Region								
North East	1,992	2·1	7,280	1·9	2,029	2·1	4,388	1·9
North West	13,323	14·0	46,544	12·1	13,811	14·2	28,979	12·7
Yorkshire & The Humber	3,137	3·3	13,693	3·6	3,148	3·2	8,144	3·6
East Midlands	4,222	4·4	14,688	3·8	4,074	4·2	8,433	3·7
West Midlands	8,886	9·3	36,298	9·4	8,987	9·3	21,911	9·6
East of England	7,536	7·9	35,376	9·2	7,573	7·8	20,536	9·0
South West	8,747	9·2	33,305	8·7	8,829	9·1	19,479	8·5
South Central	10,755	11·3	44,153	11·5	10,657	11·0	26,391	11·5
London	5,641	5·9	36,529	9·5	5,386	5·6	19,093	8·3
South East Coast	8,021	8·4	37,712	9·8	8,037	8·3	22,506	9·8
Northern Ireland	4,813	5·0	13,370	3·5	5,193	5·4	8,328	3·6
Scotland	9,222	9·7	31,700	8·2	9,401	9·7	18,906	8·3
Wales	9,140	9·6	33,866	8·8	9,963	10·3	21,900	9·6

***Note that maternal illness categories are not mutually exclusive

3.5.2 At two years

Across the study period between 1993 and 2015, the proportion of children with healthy mothers who had all their necessary vaccinations at 24 months was 88·0%; for children with MMI, it was 86·3% (Table 11).

After adjusting for sex of the child, child ethnicity, delivery year, maternal age, practice level deprivation quintile and region, the likelihood that children received both their 5-in-1 and MMR 1st dose by age of two years was estimated to be 14% lower in children with MMI, compared to children with healthy mothers (aOR 0·86, 95% CI=0·84–0·88). Children with maternal substance or alcohol misuse disorders were half as likely to receive these compared to unexposed children (aOR 0·50, 95% CI=0·44–0·58).

3.5.3 At five years

At age of five years, the proportion of children with healthy mothers who received all necessary vaccinations was 82·3% and for children with MMI, it was 79·9% (Table 11). After adjusting for sex of the child, child ethnicity, delivery year, maternal age, practice level deprivation quintile and region, children exposed to any MMI had significantly reduced likelihood of receiving all three vaccinations of 5-in-1, MMR 1st and MMR 2nd dose at five years (aOR 0·86, 95% CI=0·84–0·88). Mothers with a psychotic disorder were 29% less likely to vaccinate their children across the complete vaccination programme by age of five (aOR 0·71, 95% CI=0·62–0·82). Including the count of mother's GP appointments nine months prior to delivery in the models, for both the two and five year cohorts, did not substantively alter results (Table 11).

If children with MMI had the same vaccination rate as children with healthy mothers then, on average 5,010 additional children per year would have been vaccinated by age five (Table 12).

Table 11 Association between receiving vaccinations at age two and five years and maternal mental illness

			Unadjusted Model		Adjusted Model-1[a]		Adjusted Model-2[b]	
Up to Date Vaccinations at	**Number vaccinated (%)**	**Number not vaccinated (%)**	**OR (95% CI)**	***p***	**OR (95% CI) [a]**	**P**	**OR (95% CI) [b]**	**p**
2 Year								
Unexposed to MMI	338,398 (88·0)	46,116 (12·0)	**REF**		**REF**		**REF**	
Exposed to any MMI	82,361 (86·3)	13,074 (13·7)	0·86 (0·84-0·88)	<0·001	0·86 (0·84-0·88)	<0·001	0·86 (0.84-·0·88)	<0·001
Psychotic disorder	973 (86·9)	147 (13·1)	0·90 (0·75-1·08)	0·267	0·86 (0·71-1·03)	0·103	0·85 (0·70-1·02)	0·088
Depressive disorder	67,241 (86·1)	10,821 (13·9)	0·85 (0·83-0·87)	<0·001	0·86 (0·84-0·88)	<0·001	0·86 (0·84-0·88)	<0·001
Anxiety disorder	25,052 (86·6)	3,880 (13·4)	0·88 (0·85-0·91)	<0·001	0·86 (0·83-0·89)	<0·001	0·86 (0·82-0·89)	<0·001
Eating disorder	738 (86·4)	116 (13·6)	0·87 (0·71-1·06)	0·174	0·94 (0·77-1·16)	0·579	0·94 (0·76-1·15)	0·533
Personality disorder	430 (86·0)	70 (14·0)	0·84 (0·65-1·09)	0·181	0·75 (0·58-0·98)	0·037	0·74 (0·57-0·97)	0·029
Substance and alcohol abuse	1,218 (78·6)	331 (21·4)	0·50 (0·44-0·57)	<0·001	0·50 (0·44-0·58)	<0·001	0·50 (0·44-0·57)	<0·001
5 Year								
Unexposed to MMI	188,399 (82·3)	40,595 (17·7)	**REF**		**REF**		**REF**	
Exposed to any MMI	77,569 (79·9)	19,519 (20·1)	0·86 (0·84-0·87)	<0·001	0·86 (0·84-0·88)	<0·001	0·85 (0·84-0·87)	<0·001
Psychotic disorder	1,024 (77·6)	295 (22·4)	0·75 (0·65-0·86)	<0·001	0·71 (0·62-0·82)	<0·001	0·71 (0·61-0·81)	<0·001
Depressive disorder	63,302 (79·8)	16,053 (20·2)	0·85 (0·83-0·87)	<0·001	0·86 (0·84-0·88)	<0·001	0·85 (0·83-0·87)	<0·001
Anxiety disorder	29,291 (79·7)	7,453 (20·3)	0·85 (0·82-0·87)	<0·001	0·84 (0·82-0·87)	<0·001	0·84 (0·81-0·86)	<0·001
Eating disorder	884 (78·7)	240 (21·4)	0·79 (0·68-0·93)	0·004	0·83 (0·71-0·98)	0·024	0·83 (0·71-0·99)	0·018
Personality disorder	454 (76·4)	140 (23·6)	0·70 (0·57-0·85)	<0·001	0·64 (0·52-0·78)	<0·001	0·63 (0·51-0·77)	<0·001
Substance and alcohol abuse	1,354 (70·0)	580 (30·0)	0·50 (0·45-0·56)	<0·001	0·50 (0·45-0·56)	<0·001	0·50 (0·45-0·55)	<0·001

[a:] Adjusted for sex of the child, child ethnicity delivery year, maternal age, practice level deprivation quintile and region.
[b:] Adjusted for all variables in model one, plus number of GP visits nine months prior to the birth
See supplementary tables 4 and 5 for estimates relating to adjusted variables

Table 12 Number of children who would have been vaccinated if children with any maternal mental illness had the same vaccine uptake as children without

Year	Live Birth Rates in the UK*	MMI Prevalence rate in 5 Year Cohort, %	Vaccination rate in children with MMI, %	Vaccination rate in children with well mothers, %	Number of extra children would have been vaccinated in 5-year cohort
1998	761,526	27	76	72	8,888
1999	750,480	28	77	73	8,225
2000	731,882	28	76	74	5,923
2001	733,163	30	75	72	4,807
2002	726,622	30	76	74	4,554
2003	716,888	31	78	75	4,952
2004	699,976	31	76	72	8,430
2005	679,029	32	75	73	5,446
2006	669,123	31	75	73	3,360
2007	668,777	32	76	74	5,725
2008	695,549	31	79	76	5,451
2009	715,996	31	81	81	1,348
2010	722,549	30	85	83	3,798
2011	748,563	29	85	81	7,841
2012	772,245	29	87	85	5,148
2013	794,383	28	89	86	4,816
2014	790,204	29	89	88	4,003
2015	807,271	29	89	89	2,114
2016	807,776	29	90	89	4,239
2017	812,970	28	90	90	1,125
Total (95%CI)					**100,193 (85,903 to 114,482)**

*Live birth rates are five years prior to vaccination observation year (eg:1993 live birth rates for 1998 when child would be 5 years old)

3.5.4 MMR scandal

In our cohort, consistent with previous reports [50,198–200], we observed that the MMR vaccine rates in the UK declined considerably from 93% to 87% between 1993-1998 to 1999-2004 following the retracted report linking the MMR vaccine to autism [190].

The rate of MMR vaccination fell similarly in both MMI and healthy groups (Figure 7A). Some differences were observed: the reduction in MMR uptake was more pronounced following the scandal among children with healthy mothers compared to those with MMI; such that, those with MMI were more similar to those without during the period 1999-2004 than they were prior to 1998 (Figure 7B). After 2003, the rate improved for both groups, however the improvement appears slower for children with MMI (Figure 7A).

3.5.5 Sensitivity analyses

Excluding children born before 2005, in order to test the 'QOF effect', led to a very small decrease in the aORs for children exposed to any MMI at two years (see *Appendix F1*). The most distinct change was observed for the children exposed to maternal psychotic disorder: as the odds ratio decreased from 0·86 to 0·79. Excluding late registered children did not change the effect estimates (see *Appendix F2*)

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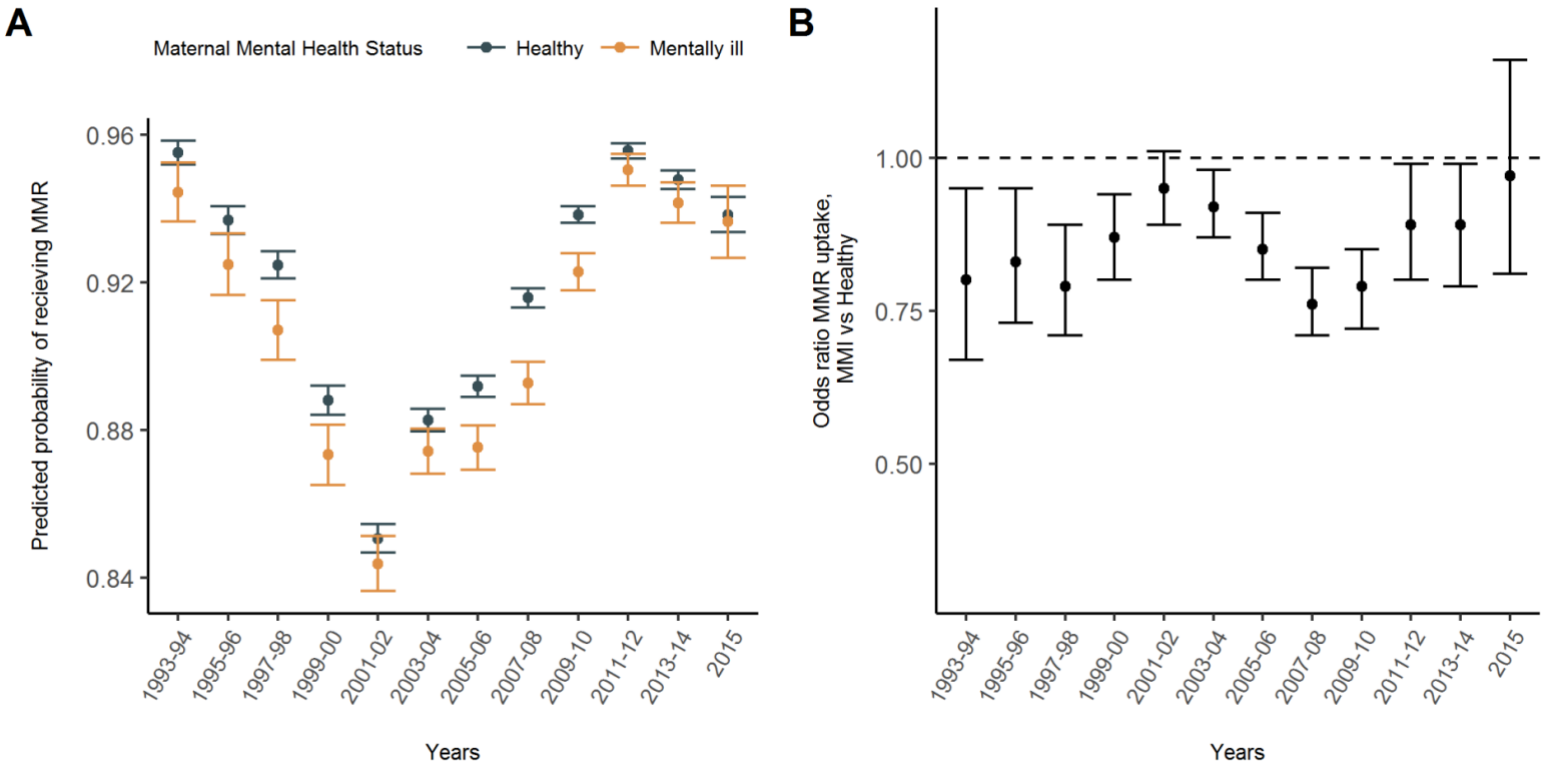

Figure 7 A) Predicted probability of receiving MMR vaccine by maternal mental illness and year; B) Association between MMR vaccine uptake and maternal mental illness by yea

3.6 DISCUSSION

3.6.1 Principal findings

We have conducted the largest contemporary cohort study to-date examining the association between MMI and childhood vaccination uptake in a primary care cohort of over 400,000 mother-baby pair. This study demonstrates that children with MMI are significantly less likely to receive preventative health vaccinations during the first five years of life.

Children exposed to maternal psychotic or depressive disorders had 14% lower likelihood of receiving necessary vaccinations at two years compared to children of well-women. There was some variability in likelihood of vaccination uptake according to type of MMI: children exposed to maternal eating disorders had only 6% lower likelihood of receiving complete vaccination doses when compared to children with healthy mothers and children exposed to maternal substance and alcohol abuse who had a 50% decrease.

We confirm previous reports: over the study period, there was a significant reduction in MMR vaccination uptake in children of both well and mentally ill mothers. The trends were similar; although we showed some evidence that the reduction was slower amongst children with MMI than with healthy mothers, and that the recovery was also slower. We conducted additional analysis to validate these findings by investigating the trends for girls and boys. This revealed that the reduction in MMR uptake was greater for boys, possibly because parents harbour greater fear about risk of autism in boys (see *Appendix F3*).

3.6.2 Strengths and limitations

The large sample size of this study allows for precision in the estimates and for us to examine the relationship by type of mental illness and by calendar period. Moreover, using administrative data eliminates the possibility of response or recall bias associated with previous studies using self-reported data.

However, there remain some limitations. The effect of MMI on the vaccination uptake in children may be underestimated for several reasons. First, we used only medical records of the mothers recorded by the GP; and mental illnesses may be under-reported in primary care [211]. This might have led us to misclassify some mentally ill mothers as healthy[140,141,193]. This is more likely to influence estimates for children of mothers with less severe mental illness which may be more likely to remain hidden; and also to underestimate effects in non-white mothers and migrant mothers who are less likely to use primary and preventative health services [212,213]. Also, it was not possible to differentiate between potential unstable mental illness diagnoses and true co-morbidities of mental illnesses in the dataset – if a diagnosis were to have changed over time this would not be distinguished from a comorbid illness.

Secondly, in order to capture MMI before the vaccination date, we excluded mothers who did not register to their participating practice at least one year prior to birth. More severe mental illness might be associated with moving-house and moving GP more frequently [214]; therefore, excluding these mothers might have underestimated the effect of MMI because the exclusion might have biased the sample to less severe MMI. Finally, we were not able to capture other potential confounders such as mother's education level, marital status, social support and parenting practices as these are poorly, or not routinely, recorded in primary care. This is an important gap in our knowledge and would warrant investigation in future studies [215].

3.6.3 Comparison with previous studies

Comparability with other studies examining MMI and vaccination uptake is limited, either because they were undertaken in different countries with different health systems; and using different exposure definitions; or with different analysis design or different study periods. Existing evidence heavily focuses on common mental disorder. For instance, Turner *et* al [54], in a small sample of 159 infants, reported children of mothers with depression were more almost five times more likely to be vaccinated late or not at all (OR 4·92, 95% CI= 1·39–17·39). Similarly, Minkovitz *et* al [53] reported 21% reduced likelihood of vaccination rate among two year-olds with depressed mothers

(OR 0·79, 95% Cl= 0·69–0·93); this is comparable to our finding of a 15% decrease in the likelihood of vaccination uptake among children aged two. Marginal decreased vaccination uptake among UK infants of mothers with psychotic disorder was reported in 2003 by Howard *et* al [55] (Relative Risk (RR) 0·94, 95% Cl= 0·88–0·99); in our study, we followed children through school age (five years). All these studies demonstrate a negative association between maternal mental illness and offspring vaccine uptake.

This is the first time the effects of the MMR scandal has been investigated in a large cohort study. Our findings show that MMR uptake in children of healthy mothers dropped post 1998, reaching the same level as that of mentally ill mothers before 1998. This adds to the growing body of evidence that public health information is not accessed in the same way by people with mental illness[191,192]; in this case, lack of engagement with misleading public health information may have protected some children in our cohort.

Our results are independent of potential measurable confounders of sex of the child and ethnicity, delivery year, maternal age, practice level deprivation quintile and region. We note that our estimates do not imply a causal link and may be subject to residual confounding. We have not been able to examine further mechanisms explaining the link between MMI and decreased childhood vaccinations. Existing literature suggests that severity of mental illness symptoms could influence a mother's parenting skills [216] and her decision making with respect to their children's preventative health-care.

3.6.4 Public health implications

Overall, our results suggest that MMI is associated with a reduced likelihood of vaccination uptake in offspring. Poor maternal mental health has wider cost and resource implications for public health interventions such as the Healthy Child Programme [9] which seeks to support families and children to access preventive public health services through parental advice and accessible

information; but it does not explicitly link MMI with a lack of uptake of preventive health care. Neither does the current Healthy Child Programme [9] include tailored approaches to mothers with specific mental illnesses.

Our results explicitly link MMI to illness prevention in children and demonstrate how important this link may be for child health. Children with MMI represent an easily identifiable group of children at risk of not receiving preschool vaccination; while screening of women for mental illness antenatally and postnatally is now part of routine antenatal and postnatal primary care. Public health policies and practice guidelines including the Healthy Child Programme [9] should be modified to target mothers with mental illness. For instance, children exposed to maternal alcohol and substance misuse were at the greatest risk of not receiving necessary vaccinations; therefore, expanding preventive programmes to target these mothers is another clear implication of our findings. Moreover, children exposed to any MMI at two years remained at risk of not receiving vaccinations at five years which suggests that screening and support for MMI is required beyond the postnatal period. Future research should examine whether the disparity in vaccine uptake in pre-school continues throughout childhood, using large population level data.

Our findings also imply that, as is the case for information about smoking cessation [191], public health information about vaccination needs to be personalised to women with mental illness who become mothers. Such a targeted approach could lead to thousands of additional children receiving their necessary vaccinations resulting in significant health and economic benefits. These results are timely following the secretary of state's recent invocation for a National Health Services (NHS) which is more focussed on preventive health, of which childhood vaccination uptake must play a role [217].

3.6.5 Conclusions

This study provides essential evidence for policy makers, service planners, commissioners and GPs. It suggests that there is a current and urgent need to improve vaccination uptake among

children exposed to MMI. Importantly, this research informs GPs and health visitors that children with MMI are at particular risk of starting school vulnerable to preventable diseases; and that these families are likely to require extra monitoring and support to reverse this health inequality.

3.7 COVID-19, PRE-SCHOOL VACCINATIONS AND MATERNAL MENTAL ILLNESS IN THE UK

Commentary

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Contributions: KMA gained funding for the study. CSO conceived of the study. CSO wrote the initial draft of the manuscript and all authors contributed to the final version.

“The two public health interventions that have had the greatest impact on the world’s health are clean water and vaccines.” (WHO)

As of January 2021, more than 83 million people worldwide have been infected with COVID-19 [218]. In the absence of an effective vaccine, this number continues to grow as the virus spreads across the globe. Social distancing measures and travel restrictions to prevent COVID-19 may have reduced, but will not have eradicated the risk of vaccine-preventable diseases such as measles, haemophilus influenzae type b (Hib) and whooping cough (pertussis). Most of the known vaccine-preventable diseases are significantly more infectious than COVID-19. For instance, the basic reproduction rate (R_0) of measles is between 9-18 [219] while COVID-19 R_0 is estimated as 2.5 [220,221]. Currently, vaccination is the only way of keeping the public safe; this means that when lockdown measures are lifted, there remains a risk of emerging vaccine-preventable diseases.

By the end of March 2020, routine childhood vaccination appointments were cancelled in the UK following the first national lockdown response to the pandemic. According to Public Health England (PHE), pre-school vaccination uptake subsequently reduced in England by 20% compared to March 2019[222]. If these low rates continue, there is the potential for a serious public health harm if vaccine-preventable disease and COVID-19 outbreaks co-occurr, whilst simultaneously public health and clinical practioners continue to tackle the wider health challenges associated with the imposed restrictions in response to COVID-19.

Prior to the pandemic, in the UK and elsewhere, uptake of freely available vaccination among pre-school children is largely a parental decision [223]. In this context, Pierce and colleagues [224] recently report that the prevalence of clinically relevant mental distress rose in the UK from 19% in 2018/19 to 27% in April 2020, one month into lockdown [224]. Moreover, women and parents of pre-school children experienced significantly more mental distress during lockdown [224]. These results are relevant to childhood vaccination rates because in our recent study we reported children with maternal depression or more severe maternal mental illnesses were 14% less likely to

receive preventive vaccinations by aged two years, compared to children of women unaffected by mental illness. The most affected group was children of mothers with alcohol and substance misuse disorders who were half as likely to receive necessary vaccinations by two years old, compared to children of unaffected women [153].

Public Health England (PHE) has now advised families that childhood vaccinations should continue during the pandemic and has issued *"Clinical guidance for healthcare professionals on maintaining immunisation programmes during COVID-19"* [225]. This covers how vaccination schedules should be maintained and what to do if children do not attend vaccination appointments. For instance, in the guidance [225] it is advised to re-invite parents and their children whose appointment was cancelled because of COVID-19. Also, since parents may be worried about coming to their general practitioner (GP) because of COVID-19, practitioners are advised to reassure parents about social distancing measures in waiting rooms and that GP premises are regularly decontaminated. Healthcare practitioners are also advised to plan appointments strategically to avoid crowded waiting rooms.

Maternal mental health is not mentioned in the current guidance [225] and we urge the public health teams of all four devolved nations to add a section which helps health practitioners to recognise that some parents experience mental health problems that may prevent them bringing their child for vaccination. In such situations, these parents and their children should be provided with a health practitioner to visit at home and administer the necessary vaccinations. Moreover, public health campaigns should go beyond advising parents that routine childhood vaccination continues. We suggest there is a need for more tailored public health campaigns which target vulnerable groups including parents and their children living with mental illness. Globally, we are tackling two major challenges: namely COVID-19 and increasing prevalence of mental illness [17]. We should act urgently not to add yet another challenge of vaccine preventable diseases.

CHAPTER 4- HEALTHCARE DATA RECORDING IN THE UK GENERAL PRACTICES: THE CASE OF WEIGHT AND HEIGHT MEASURES OF CHILDREN AND YOUNG PEOPLE

Short Communication Article

Authors: Cemre Su Osam, Matthias Pierce, Holly Hope, and Kathryn M Abel

Status: Submitted

Journal: Paediatric Obesity Journal

Contributions: KMA conceived of the study, CSO wrote the study protocol, with input from MP. CSO carried out the analysis with support from MP, KMA and all authors interpreted the results. CSO wrote the initial draft of the manuscript and all authors contributed to and approved the final version.

4.1 DESCRIPTION OF STUDY IN CONTEXT OF THESIS

This chapter contains the second research study illustrating the feasibility of conducting a study into the effects of maternal mental illness on childhood obesity using data from CPRD-GOLD's (see sub-section 2.1.5). This study is formatted as a short communication article so is considerably shorter than the other studies in this thesis. This study shows that height, weight and BMI records of children are poorly recorded in primary care thus we conclude that it is not feasible to conduct a study to investigate the effects of maternal mental illness on childhood obesity.

4.2 ABSTRACT

Using a large, primary care registry, this brief study reports that children's height, weight and BMI measurements are poorly recorded in UK primary care data. Thus, we judge that it is not feasible to analyse the effects of exposures on childhood obesity using this data source. The importance of routine data collection on height, weight and BMI measures in primary is discussed.

4.3 INTRODUCTION

Obesity among children and young people is a global health problem [226]. The prevalence of childhood obesity in England for the 2018/19 school year was reported to be the 10% for the children aged between 4-5 years and 20% for the children aged between 10-11years [226] and the impact of childhood obesity is estimated to cost NHS around £6 billion per year [227]. Childhood obesity is associated with many chronic illnesses and poor health outcomes therefore, in many epidemiological studies, obesity is a vital factor to be considered as an outcome, exposure or mediator.

Electronic healthcare databases are becoming increasingly important for epidemiology. In the UK, the Clinical Research Datalink (CPRD) is the largest primary care database and is used extensively for healthcare research. For instance, we utilised the CPRD to estimate the prevalence of children exposed to maternal mental illness in the UK [17] and also to report the effect of maternal mental illness on childhood vaccination uptake in the first five years of life [153]. In terms of childhood obesity, the CPRD has been utilised by Van Jaarssveld to reported the obesity trends in the UK [228] and others reporting multi-morbidities associated with obesity among children and young people [229]. Considering the fact that childhood obesity is a public health concern in the UK, it would be also important to investigate risk factors for childhood obesity using the data from CPRD. For instance, we propose that it is important to examine the effect of maternal mental illness on childhood obesity: it may be an important risk-factor, yet existing evidence restricted to small sample sizes and self-reported maternal mental illness [63,64].

In order to conduct such an investigation, BMI and obesity data should be of sufficient quality. However, in primary care, there is a tendency to record height, weight and body-mass index (BMI) only if they are clinically relevant, which means this data could be incomplete and biased [230]. Therefore, we use the CPRD to investigate if this is the case for children's height, weight and BMI measurements recorded in primary care, to ascertain whether these data are fit for purpose for use in research.

4.4 METHODS

4.4.1 Data source

For this feasibility study, we constructed a retrospective cohort analysis using data from the Clinical Practice Research Datalink (CPRD-GOLD) which, holds routinely collected primary healthcare data from approximately 15.3 million patients in the UK [143]. The cohort of children was drawn 1,254,209 children from the 'Mother-Baby link'- an algorithm that links children and their mothers based on pregnancy, delivery and birth records and a household identifier [140].

4.4.2 Cohort selection

The study period started on 1st January 2005 and ended on 31st December 2017. Follow-up began on children's second birthday and ended on the earliest date of: their 18th birthday, the day they transferred out of the practice, died or the practice stopped contributing data to CPRD. They were excluded if they were born before the participating general practice fulfilled the minimum data quality standards set by the CPRD; or if they did not have a minimum of five years follow-up. This resulted in 350,148 children available for follow-up.

4.4.3 Height, weight and BMI records

Children's weight, height and BMI records were extracted from the CPRD's 'additional files' that holds records on measurements made on clinical visits. Utilising the World Health Organisation's(WHO) child growth standards [231], average height based on age and gender was

used for children who had weight but not height record. The BMI of children was calculated for those who had height and weight records but not BMI, by using the formula *Weight (kg) / Height (m)²*.

4.4.4 Covariates

Demographic data were captured on maternal age at birth, child sex and geographical UK region of the general practice (categorised as*:* North East, North West, Yorkshire & The Humber, East Midlands, West Midlands, East of England, South West, South Central, London, South East Coast, Northern Ireland, Scotland and Wales).

Data were also obtained on maternal smoking status using mother's clinical, therapy files. Child ethnicity (categorised as: Asian/ British Asian, Black/Black British, White, Mixed and Other) was derived from CPRD and HES. Priority was given to ethnicity data from HES when data were available from both resources because, HES data has been validated by using other data sources [204]. The quintile of the Index of Multiple Deprivations (IMD) data was captured based on the participating practice postcode**.**

4.4.5 Statistical analysis

We obtained age and gender specific growth curves from the UK-WHO growth chart which uses a composite of the modified WHO growth chart [231] and the 1990 British Growth Reference (UK 90) dataset [232]. These provides BMI centile curves for children age 0 to 18. Children's z-scores were calculated by using the Zanthro package in Stata [166] which yields standardised z-scores for "BMI" as well as for "weight for age".

4.5 RESULTS

The study cohort involved 350,148 children and 48% of them were girls. Only 38% (133,825/ 350,148) of children had a weight record at any point over their follow-up. Children with a BMI measurement were more likely to be girls and children without were more likely to be boys (51% vs 53%). Child ethnicity was similar in both groups and, excluding those with missing data (39%) most children were from white ethnicity backgrounds (86%). Only 4% of children with BMI measurement were recorded to be from ethnic minority groups (i.e. Asian, black, mixed, other). Children with BMI measures were more likely to have a mother in the youngest age-groups than children without BMI measure (e.g. 44% vs 40% with mothers aged between 20-29). Also, children without BMI measures were more likely to have mothers with older maternal age (53% vs 49% in age group 30-39). Children with BMI measures were more likely to have a mother who actively smoked tobacco compared to children without BMI measure (38% vs 34%, Table 13). It was also observed that 65% (32,956/50,657) of children with BMI record had a mother actively smoking tobacco were exposed to maternal mental illness.

39% (52,349/ 133,825) of those with BMI records were observed to be either overweight or obese. The distribution of z-scores indicated that, following the 5th primary care consultation, children are more likely to be recorded if they are overweight or obese as the mean of distribution of z-score is skewed to the right, which means greater BMI (Figure 8).

Moreover, we further investigated the first BMI record of children before and after age five. The distribution of the mean Z-scores appeared to be heavier on the tails for both groups (i.e. before and after age five) however, it was worse for children who had their first BMI record after age five than those children had first BMI record before age five (Figure 9).

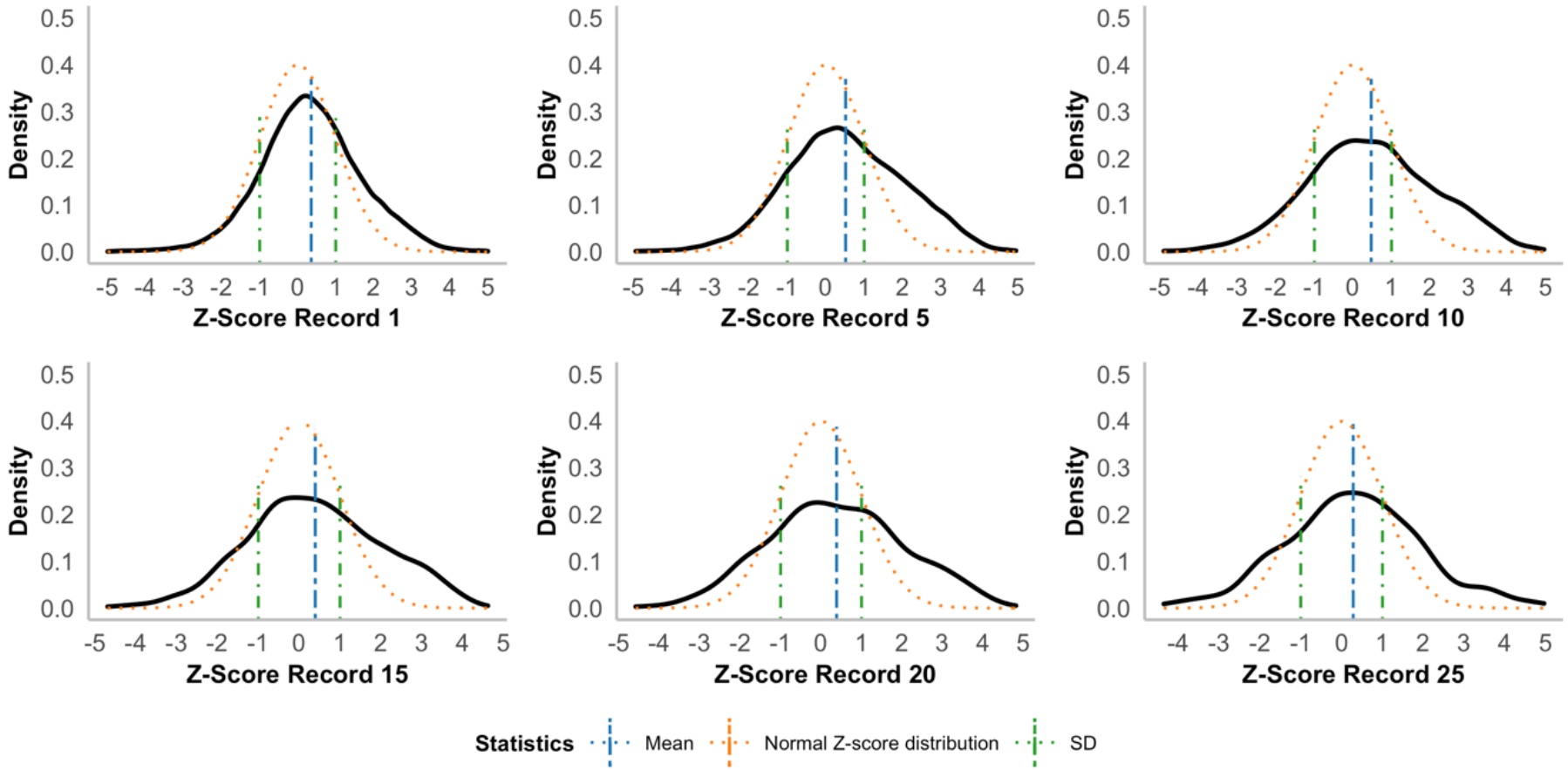

Figure 8 Density plot illustrating children's BMI Z-scores at 1st, 5th, 10th, 15th, 20th and 25th record

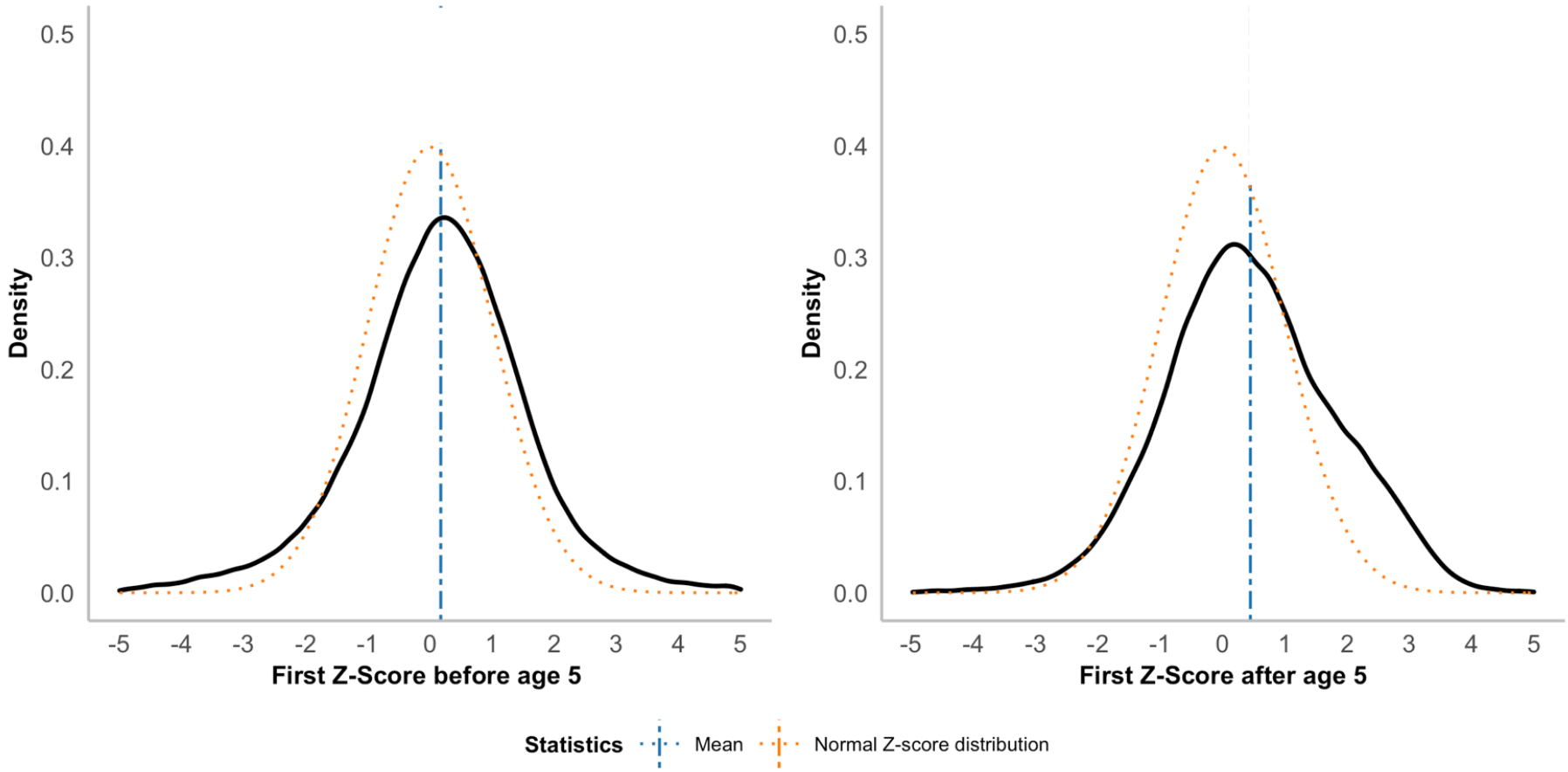

Figure 9 Density plot illustrating children's first BMI Z-scores recorded before and after age five

Table 13 Baseline cohort characteristics of children with and without BMI record

	Without BMI Record (N=216,323)		With BMI Record (N=133,825)	
	N	**%**	**N**	**%**
Gender				
Female	100,985	46.7	68,442	51.1
Male	115,338	53.3	65,383	48.7
Ethnicity				
Asian/British Asian	3,929	2.9	3,546	4.3
Black/ black British	1,967	1.5	1,681	2.0
Mixed	2,114	1.6	1,198	1.5
Other	1,328	1.0	879	1.1
White	115,364	85.9	71,032	86.2
Unknown	9,578	7.1	4,057	4.9
Maternal age				
<20	7,594	3.5	5,345	4.0
20-29	85,878	39.7	58,436	43.7
30-39	114,476	52.9	65,566	49.0
40>	8,375	3.9	4,478	3.4
Maternal smoking				
Never	112,194	51.9	66,687	49.8
Former	24,853	11.5	14,560	10.9
Current	74,253	34.3	50,657	37.9
Missing	5,023	2.3	1,921	1.4
BMI/Weight record				
Normal Weight	-	-	81,476	23.3
Overweight/ Obese	-	-	52,349	15.0
No Record	216,323	61.8		
IMD *				
1 (least deprived)	45,382	21.0	23,651	17.7
2	35,360	16.4	21,838	16.3
3	41,903	19.4	24,015	18.0
4	40,400	18.7	30,180	22.6
5 (most deprived)	53,278	24.6	34,141	25.5
Region				
North West	29,053	13.4	15,925	11.9
South Central	26,382	12.2	15,977	11.9
Wales	23,486	10.9	14,400	10.8
Scotland	20,669	9.6	14,439	10.8
South East Coast	23,195	10.7	9,923	7.4
West Midlands	18,545	8.6	12,286	9.2
South West	16,527	7.6	13,152	9.8
East of England	16,717	7.7	11,900	8.9
London	17,071	7.9	9,283	6.9
Northern Ireland	9,960	4.6	7,181	5.4
East Midlands	5,716	2.6	3,799	2.8
Yorkshire & The Humber	5,303	2.5	2,584	1.9
North East	3,699	1.7	2,976	2.2

*Based on GP practice postcode

4.6 DISCUSSION

This study demonstrated that more than 60% of children (aged two and over) had missing weight or BMI data in primary care. Whilst the proportion of missing data is concerning, more important to the inferences that can be made from any subsequent study is the potential mechanism underlying this missingness. 39% of those with a BMI record were either overweight or obese. This is considerably higher than the combined overweight and obesity rates reported by the NCMP between years 2006 and 2019 (22-23%) [233]. If we assumed that children with missing BMI records (N=216,323) had weight in the normal range (or were underweight), then the prevalence of children who are overweight or obese dropped to 14% (52,349/ 350,148), which is far lower than national statistics.

We demonstrated that those with BMI measurements were a biased sample: they were more likely to be girls, from a white ethnic background, with younger and actively smoking mothers. If we could model our missing data mechanism purely on observed variables, we could proceed with modelling techniques (such as multiple imputation or inverse probability weighting) with little worry about biased results. However, given that we suspect GP's record data when they are concerned about the child's weight, we have little data to capture this effect. It would be difficult to rule out that the reason for this missingness was unrelated to the exposure of interest (in our case parental mental illness). We therefore conclude that any study using the CPRD to ascertain risk factors for childhood obesity would be at high risk of bias.

Prior to conducting a large retrospective cohort study to investigate the effects of maternal mental illness on childhood obesity, it was essential to demonstrate that data is of sufficient quality. The reason for this feasibility study is that, existing evidence shows that in primary care, lifestyle factors such as height, weight and BMI of adults are not recorded routinely [230], yet no information exists on children. While these findings are important step towards understanding the patterns of weight, height and BMI recording of children in primary care, we recognize a specific limitation. We may have missed some of the height, weight or BMI records that were entered as "free text" as we did not analyse the free text information and also it could be possible that there have been some instance that child's BMI may have been measured but not entered to child's clinical records.

The UK government introduced National Child Measurement Programme (NCMP) to track children's weight at age five and ten in England, recognising childhood obesity as one of the UK's major public health priorities. Along with NCMP, a community-based weight management programme called *'Mind, Exercise, Nutrition, Do it* (MEND)' as well as *'Change4Life'* have been also developed as a part of UK government's "Healthy Weight, Healthy Lives" strategy to tackle obesity in children in 2008.

The CPRD could benefit from linkage to data from obesity prevention programmes (i.e. NCMP, MEND and Change4Life) as it would contribute to a better data in primary care which would not only contribute to a better surveillance system to tackle childhood obesity but also to better public health research opportunities. However, this may be only available in regions where there are obesity prevention programmes, for instance, NCMP is only available in England.

Another attempt to improve child measurement recording in primary care would involve getting all four nations of the UK to record child's BMI similarly as in NCMP at the GP practices. Such routine data in primary care would mean a representative, good quality data, which would be provided by CPRD to the public health researchers to conduct large-scaled research on childhood obesity. In healthcare research, height, weight and BMI measures are key factors determining the health status. Therefore, improved data recording as well as linkages between CPRD and obesity prevention programmes would allow epidemiologic research on child obesity which would produce valuable evidence to understand the risk factors of child obesity and also allow to assess and improve the obesity prevention and intervention programmes.

If we were able to proceed with our study, it might have highlighted the needs and changes required in this area which would not captured in small sample studies. Given the increase of childhood obesity and lack of epidemiological research in this area, linkages between NCMP and CPRD as well as possibility of routine BMI data collection in primary care should be urgently considered.

CHAPTER 5- MATERNAL MENTAL ILLNESS AND CHILD ATOPIC DISORDERS: A UK POPULATION-BASED COHORT STUDY

Journal Article

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Status: Submitted

Journal: BMJ

Contributions: KMA conceived of the study, CSO wrote the study protocol, with input from KMA, MP, HH and DMA. CSO carried out the analysis with support from MP and HH. CSO wrote the initial draft of the manuscript and all authors contributed to the final version.

5.1 DESCRIPTION OF STUDY IN CONTEXT OF THESIS

This is the third study of this thesis and reports on the association between maternal mental illness and childhood atopic disorders. Cox proportional hazard model was (see subsection 2.4.3) utilised to measure the risk of atopic disorders among children associated with maternal mental illness. In this model, the exposure which is maternal mental illness was considered to be time-varying exposure (see subsection 2.4.4 time-varying variable).

5.2 ABSTRACT

Objectives: To investigate the impact of maternal mental illness on the risk of childhood atopic disorders.

Design: Retrospective cohort study.

Setting: Electronic healthcare records from the UK CPRD-GOLD primary care database involving 674 general practices.

Participants: 590,778 children born between 1st January 1993 and 30th November 2017, linked to their mothers and followed from birth to their 18th birthday.

Exposure and outcome measures: Time-dependent exposure of Maternal Mental Illness (MMI) was identified from the earliest mental illness event present six months prior to pregnancy until the end of follow up. MMI included depression, anxiety, psychosis, eating disorder, personality disorder and alcohol and substance misuse disorders.

The outcome was time to atopic disorder (asthma, eczema, allergic rhinitis and food allergies) during follow up. The association between MMI and atopic disorders was investigated using Cox regression models, adjusted for maternal atopy history, maternal smoking, antibiotic use during pregnancy, maternal age, child sex, child ethnicity, birth season, birth year, area-level deprivation and region. Clustering by maternal siblings was accounted for using clustered standard errors.

Results: The risk of atopic disorders varied based on the type of maternal mental illness: children exposed to maternal common mental illness (depression/anxiety) were at highest risk of developing asthma and allergic rhinitis (aHR: 1.17, 95%CI=1.13-1.21). Children exposed to maternal addiction disorders were 9% less likely to develop eczema (aHR: 0.91, 95%CI=0.85-0.97) and 35% less likely to develop food allergies (aHR 0.65, 95%CI=0.45-0.93). The risk of hospital inpatient admission for asthma among children exposed to maternal common mental illness was 26%.

Conclusions: Our findings suggest that a child's risk of developing atopic disorders may depend on the type of maternal mental illness to which they are exposed. This raises interesting mechanistic questions about the aetiology of atopic disorders. Knowledge about risk of common physical

disorders in the children of mother with mental illness is important for GPs, other health practitioners and policy makers so that they can monitor children and target preventive measures early.

5.3 INTRODUCTION

Mothers play a key role in the development of their offspring from pregnancy to early adulthood and are most likely to be the primary caregivers. Accumulating evidence highlights the fact that children with maternal mental illness have poorer physical health than unexposed children [46]. Some evidence addresses the risk of child and adolescent atopic diseases, such as asthma, eczema, allergic rhinitis and food allergies [96,234,235]; which are increasingly prevalent and now occupy some of the commonest global health problems among children [78]. For example, asthma affects almost 14% of children worldwide and, in the UK, 1 in 11 children receives asthma treatment, costing the National Health Service (NHS) an estimated £1 billion per year [81]. The prevalence of eczema, allergic rhinitis and food allergies is also increasing [236]; it is currently that 20% of the UK population is affected by one or more atopic diseases [84].

Antenatal maternal stress, including maternal mental illness, has been linked to increased risk of offspring atopy [237,238]. The mechanism of this association is unclear because offspring of mothers with mental illness are also more likely to be exposed to a range of other potential risk factors: younger maternal age [40]; poverty and other socioeconomic and environmental factors [239]; poor antenatal care; maternal smoking [240]; fetal growth restriction [241]; as well maternal antibiotic exposure in pregnancy [242].

In the UK, almost one in four children is exposed to maternal mental illness [17]; we have estimated that the excess cost to the NHS of physical health care utilisation by these children is £560 million per year (Hope *et* al ,2020). Currently, there are three systematic reviews that report the link between common maternal mental illness (depression and anxiety) and child atopic disease [46,234,243]. However, existing, individual studies are based on relatively small samples, use self-report measures of common maternal mental illness and are focussed on childhood

asthma rather than examining the spectrum of atopic disease [90,91,95,244–248]. We addressed these important limitations and gaps in the current evidence base by using a large, contemporary UK primary care cohort to compare the risk of atopic diseases in children of mentally ill mothers and well mothers.

First, we hypothesised that children with mentally ill mothers would have a higher risk of developing atopic diseases overall compared to children with well mothers. Second, we hypothesised that the risk for children to develop atopic diseases would be higher among children exposed to serious maternal mental illness (affective and non-affective psychosis) compared to those exposed to more common maternal mental illnesses (depression and anxiety). Finally, we hypothesised that the secondary healthcare utilisation for atopic diseases among children with maternal mental illness will be higher than children with well mothers.

5.4 METHODS

5.4.1 Data source

For this retrospective cohort analysis, we utilised data from the Clinical Practice Research Datalink (CPRD) GOLD, which holds anonymised primary healthcare records on about 10% of UK general practices [143]. Clinical event data are routinely collected on consultations (including diagnosis), referrals and prescriptions. The analysis cohort was drawn from children identified in the CPRD's mother-baby link. The mother-baby link is an algorithmic linkage of children and mothers based on pregnancy, delivery and birth records and a household identifier [140].

Children in this cohort were linked to Hospital Episodes Statistics (HES) dataset using a unique NHS identifier, to ascertain inpatient, outpatient and accident and emergency visits. Linkage to the HES dataset is only available for English practices and practices that consented to linkage (75% of English practices). Socioeconomic data was used based on the Index of Multiple Deprivation (IMD) linked to the GP practice postcode. The IMD is a rank score of area-level deprivation, divided into

quintiles, derived using seven domains including: income, employment, education, health and disability, crime, barriers to housing and services and the lived environment.

5.4.2 Cohort selection

Eligible children were selected from all those born between 1st January 1993 and 30th November 2017 and whose mother was registered at a CPRD-participating general practice at the time of their birth. In order to have sufficient data to determine the exposure status, we excluded those whose mother registered at an up-to-standard general practice for less than six months prior to the child's birth.

Children's follow-up started at the latest date of: the child's date of birth; the date when the practice started collecting data that were deemed 'up-to-standard'; the date of the child's registration at that clinical practice; and the study start date (1st January 1993). Their follow up ended at the earliest date of: the date they transferred out of the general practice, their 18th birthday, their date of death, their mother's date of death, the practice data collection end date and the study end date (31st December 2017). In total, 590,778 children and 428,924 mothers were identified for analysis with an average follow-up time of 5.24 person years. A subgroup of 359,611 children eligible for HES linkage was identified to investigate the risk of secondary healthcare utilisation for atopic diseases among children with maternal mental illness.

5.4.3 Exposure

Children's exposure to maternal mental illness was identified using primary care data on each mother's recorded diagnoses, symptoms, prescription and referral to external services. Maternal mental illness was determined using four methods: diagnosis of a mental illness; a referral to psychiatric care services; a psychotropic medication or symptom if there was a related historical diagnosis; or a psychotropic medication and a related symptom within three months of each other. See Abel *et* al [17] for further details on the algorithm used to define mental illness. Children were

defined as exposed from the time of the first recorded event relating to depression, anxiety, non-affective and affective psychosis, alcohol and substance misuse, eating disorders and personality disorders between six months prior to pregnancy and the end of the child's follow up. For this analysis, mental illnesses were grouped into the following categories: common mental illnesses (CMI, anxiety/depression), serious mental illnesses (SMI, non-affective and affective psychosis), maternal addiction (alcohol and substance misuse), and other MMI (eating and personality disorders).

5.4.4 Outcome

The primary outcome was time to first diagnosis of child atopic disorder in primary care (asthma, eczema, allergic rhinitis and food allergy). Clinical codes that identify diagnoses within each category are available from clinicalcodes.org [147]. For analysis of hospitalisation, asthma related inpatient service visits were captured based ICD-10 codes: (J45 Predominantly allergic asthma; J46 Status asthmaticus) [249].

5.4.5 Covariates

Demographic data were extracted on maternal age at birth, child sex and geographical UK region of the general practice (categorised as*:* North East, North West, Yorkshire & The Humber, East Midlands, West Midlands, East of England, South West, South Central, London, South East Coast, Northern Ireland, Scotland and Wales). Data were also extracted on maternal atopy history, antibiotic use during pregnancy and smoking status. Child ethnicity (categorised as: Asian/ British Asian, Black/Black British, White, Mixed and Other) was extracted from CPRD and HES. Ethnicity data from HES were prioritised when data were available from both resources because HES data has been shown to be more accurate [204]. The quintile of the Index of Multiple Deprivations (IMD) data was captured based on the participating practice postcode.

5.4.6 Statistical analysis

Unadjusted and adjusted hazard ratios (HR and aHR) for the risk of atopy among children associated with MMI were calculated using Cox proportional hazard models. Two adjusted models were calculated. The first model adjusted for a priori potential confounders of: maternal atopy history, antibiotic use during pregnancy, maternal age at birth, child sex, child ethnicity, delivery year, practice level deprivation quintile and geographical region. Maternal smoking was considered as potentially on the causal pathway. Therefore, a second adjusted model included this additional variable as a covariate. In a sub-cohort of children with HES linkage, Cox proportional hazard models were used to calculate the risk of asthma related hospital inpatient admission associated with maternal mental illness.

In all regression analyses, continuous variables were centred and a squared term was included. Clustering by maternal sibships was accounted for by calculating the standard error using the Hubber/White sandwich estimator[209]. Data were analysed using Stata SE 15. This study reports in line with the requirements of the RECORD statement [250].

5.4.7 Sensitivity analysis

We considered whether any association with childhood eczema was accounted for by the association with infantile eczema, as opposed to eczema diagnosed later. Therefore, as a sensitivity analysis, we repeated our analysis starting follow-up on children's 3rd birthday.

Patient and Public Involvement

This study did not include patient and public involvement.

5.5 RESULTS

The study cohort consisted of 590,778 mother-child pairs (Figure 10) and 3,840,135 person-years of follow-up (median follow-up: 5.24 years; IQR 2.12 to 10.01). The mean maternal age was 30.3 years (standard deviation= 5.8) and 48.7% of children were female (Table 14). Children from most deprived areas were more common than children from least deprived areas (26.7 vs 17.6).

Overall, 39% of children (227,832/590,778) were exposed to CMI at some point over follow-up and less than one per cent was exposed to SMI. The prevalence of maternal smoking during pregnancy was 10% and the overall prevalence of maternal smoking (from the beginning of pregnancy until the child's end of follow up) was 36 % (Table 14).

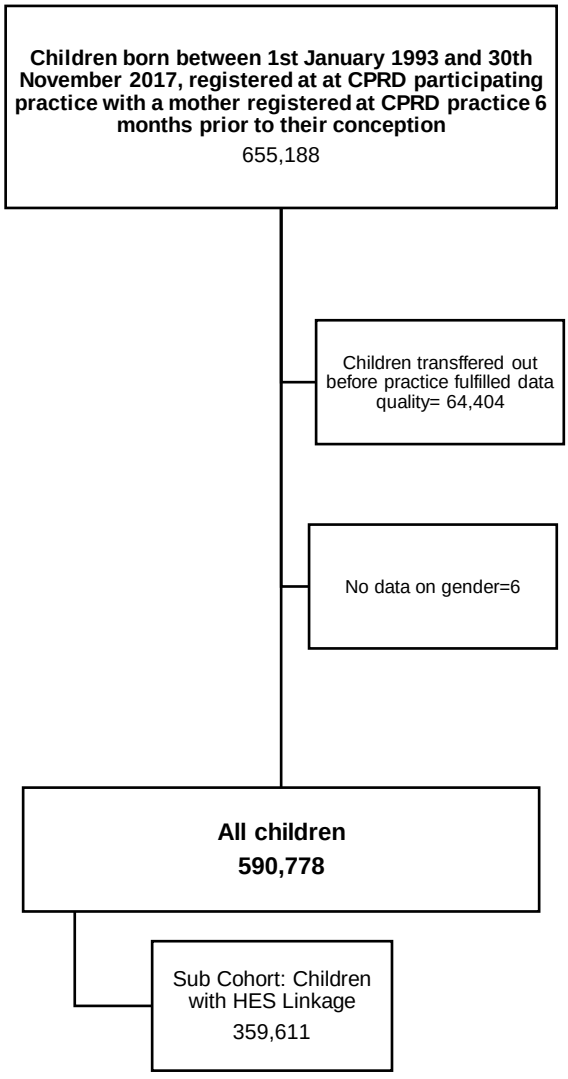

Figure 10 Atopy cohort selection process

Table 14 Characteristics of atopy mother-child cohort, children born between 1st January 1993 and 31st December 2015

	Frequency	%
Child Sex		
Female	287,682	48.7
Male	303,096	51.3
Child Ethnicity		
Asian/British Asian	18,980	3.2
Black/ Black British	8,891	1.5
Mixed	11,656	2.0
Other	5,334	0.9
White	363,226	61.5
Unknown	182,691	30.9
Child Atopy		
Any	217,568	36.8
Asthma	49,893	8.5
Eczema	180,933	30.6
Allergic rhinitis	33,097	5.6
Food allergies	9,753	1.7
Maternal Age at delivery (year)		
<20	21,488	3.6
20-29	232,765	39.4
30-39	308,106	52.2
>40	28,419	4.8
Maternal Mental Illness		
Common Mental Illness	227,832	38.6
Serious Mental Illness	4,432	0.8
Addiction	7,745	1.3
Other	6,188	1.1
Maternal Smoking*		
Never	292,312	49.5
Former	60,542	10.3
Current	212,295	35.9
Missing	25,629	4.3
Smoking during pregnancy		
No	504,128	85.3
Smoker	61,021	10.3
Missing	25,629	4.3
Deprivation quintile of general practice area		
1 least deprived	104,166	17.6
2	94,699	16.0
3	110,142	18.6
4	124,141	21.1
5 most deprived	157,630	26.7
Region		
North East	11,230	1.9
North West	71,945	12.2
Yorkshire & The Humber	20,908	3.5
East Midlands	23,513	4.0
West Midlands	54,894	9.3
East of England	54,143	9.2
South West	52,368	8.9
South Central	67,521	11.4
London	56,796	9.6
South East Coast	56,388	9.5
Northern Ireland	21,181	3.6
Scotland	48,389	8.4
Wales	50,502	8.6

*During child's life

Child Atopy and Maternal Mental Illness

5.5.1 Asthma

The incidence of asthma diagnosis was higher among children exposed to other maternal mental illness (18.4 vs 12.8, HR 1.39, 95% CI=1.27–1.51) and CMI (HR 1.31, 95% CI=1.29–1.34) compared to unexposed children (Table 15).

Controlling for all potential confounders, except maternal smoking status, there was evidence of an increased risk of atopic asthma associated with maternal CMI (aHR 1.19, 95% Cl=1.16–1.22). When maternal smoking status was added to the model the risk remained elevated (aHR 1.17, 95% Cl=1.15–1.20).

5.5.2 Allergic rhinitis

Following similar patterns to that observed for asthma; children exposed to CMI were found to have an increased risk of allergic rhinitis (aHR 1.16, 95% CI=1.13–1.20) after adjusting for potential confounders. These associations persisted after adjusting for maternal smoking as well (aHR 1.17, 95% CI=1.15–1.20).

5.5.3 Eczema

There was little or no evidence that exposure to maternal CMI was associate with offspring risk of developing eczema (aHR 1.00, 95% CI= 0.99–1.01). However, children exposed to SMI showed 9% reduced risk of developing eczema compared to unexposed children (aHR 0.91, 95%CI= 0.83–1.00) and children exposed to maternal addiction also had significantly reduced risk of eczema (aHR 0.87, 95% CI=0.81–0.93).

5.5.4 Food allergies

Following similar patterns to that observed for eczema; children exposed to MMI showed lower rates of food allergies compared to unexposed children: children exposed to CMI had 5% reduced risk (HR 0.95, 95% CI=0.90–0.99) which was attenuated on adjustment (aHR 0.96, 95%CI=0.91–1.01) and for maternal addiction, the risk was reduced 35% (aHR 0.65, 95% CI= 0.45–0.93).

Table 15 Unadjusted and Adjusted Hazard Ratios showing the association between atopy and maternal mental illness (N= 590,778 children)

	Person-Years, 1,000	**Atopy Cases N**	**Atopy Rate (95%CI)** per 1,000 person-years	**Unadjusted HR**	***p***	**Adjusted HR Model 1 † (95%CI)**	***p***	**Adjusted HR Model 2 †† (95%CI)**	***p***
Asthma									
Unexposed	2352.68	30060	12.8 (12.6-12.9)	**REF**	**-**	**REF**	**-**	**REF**	**-**
Common Mental Illness	1213.67	19394	16.0 (15.8-16.2)	1.31 (1.29-1.34)	<0.0001	1.19 (1.16-1.22)	<0.0001	1.17 (1.15-1.20)	<0.0001
Serious Mental Illness	18.30	263	14.4 (12.7-16.2)	1.11 (0.98-1.25)	0.107	1.04 (0.90-1.21)	0.566	1.04 (0.90-1.20)	0.629
Addiction	34.65	498	14.4 (13.2-15.7)	1.12 (1.02-1.22)	0.015	1.01 (0.91-1.12)	0.883	0.98 (0.88-1.09)	0.713
Other MMI	29.24	537	18.4 (16.9-20.0)	1.39 (1.27-1.51)	<0.0001	1.08 (0.97-1.20)	0.163	1.08 (0.97-1.20)	0.176
Allergic Rhinitis									
Unexposed	2429.48	19070	7.9 (7.7-8.0)	**REF**	**-**	**REF**	**-**	**REF**	**-**
Common Mental Illness	1288.28	13659	10.6 (10.4-10.8)	1.22 (1.19-1.25)	<0.001	1.16 (1.13-1.20)	<0.001	1.17 (1.13-1.21)	<0.001
Serious Mental Illness	19.64	192	9.8 (8.5-11.3)	1.02 (0.88-1.18)	0.766	0.96 (0.80-1.14)	0.608	0.97 (0.81-1.15)	0.714
Addiction	37.10	338	9.1 (8.2-10.1)	0.95 (0.85-1.07)	0.404	0.91 (0.80-1.05)	0.188	0.92 (0.80-1.05)	0.222
Other MMI	31.67	356	11.2 (10.1-12.5)	1.19 (1.07-1.33)	0.001	1.04 (0.91-1.19)	0.570	1.05 (0.92-1.20)	0.490
Eczema									
Unexposed	1803.80	130512	72.4 (72.0-72.6)	**REF**	**-**	**REF**	**-**	**REF**	**-**
Common Mental Illness	922.01	49096	53.3 (52.8-53.7)	1.01 (1.00-1.02)	0.091	1 .00(0.99-1.01)	0.985	1.02 (1.00-1.03)	0.023
Serious Mental Illness	14.64	642	43.9 (40.6-47.4)	0.90 (0.84-0.98)	0.010	0.91 (0.83-1.00)	0.040	0.93 (0.85-1.01)	0.093
Addiction	28.04	1125	40.1 (37.8-42.5)	0.82 (0.78-0.87)	<0.001	0.87 (0.81-0.93)	<0.0001	0.91 (0.85-0.97)	0.007
Other MMI	22.32	1240	55.6 (52.6-58.7)	1.06 (1.00-1.12)	0.046	1.06 (0.99-1.13)	0.101	1.06 (0.99-1.14)	0.083
Food Allergies									
Unexposed	2493.37	6864	2.7 (2.6-2.8)	**REF**	**-**	**REF**	**-**	**REF**	**-**
Common Mental Illness	1359.41	2809	2.1 (2.0-2.1)	0.95 (0.90-0.99)	0.019	0.96 (0.91-1.01)	0.133	0.99 (0.94-1.05)	0.854
Serious Mental Illness	20.73	46	2.2 (1.7-3.0)	1.10 (0.83-1.47)	0.501	1.04 (0.75-1.46)	0.796	1.08 (0.78-1.51)	0.641
Addiction	39.27	40	1.0 (0.7-1.4)	0.51 (0.37-0.69)	<0.001	0.59 (0.41-0.84)	0.004	0.65 (0.45-0.93)	0.018
Other MMI	33.85	70	2.1 (1.6-2.6)	0.99 (0.78-1.25)	0.924	1.08 (0.82-1.43)	0.569	1.11 (0.84-1.47)	0.465

† Adjusted for maternal atopy history, antibiotic use during pregnancy, maternal age, child sex, child ethnicity, birth season, birth year practice IMD and practice region
†† Adjusted for all variables in model one, plus maternal smoking

5.5.5 Covariates

Overall, children in the lowest quintiles of socio-economic deprivation, those with maternal asthma, maternal antibiotic use during pregnancy, maternal smoking or male children had increased risk of asthma (Appendix G1). By contrast, overall, children from least deprived areas were at greater risk of developing eczema and food allergies than children from deprived areas. Moreover, maternal smoking appeared significantly to *reduce* eczema and food allergy risks. Overall, Asian and Black children had increased risks of developing all types of atopic disorder compared to White children (Appendix G2).

5.5.6 Sensitivity analysis

After repeating the analysis starting children at age three (therefore excluding infantile eczema) , the fully adjusted model found a small positive association between children exposed to maternal CMI and eczema (aHR 1.06, 95% CI=1.02–1.10). However, results for SMI, addiction and other MMI (Appendix G3) were inconclusive.

5.5.7 Hospitalisation for asthma

The risk of hospital inpatient admission for asthma among children exposed to maternal CMI was 26% (aHR 1.26, 95% CI=1.17–1.36) higher than for unexposed children. The relative hazard of asthma diagnosis among children exposed to maternal addiction was reduced in primary care, however there was limited evidence of a change in the risk of hospital admission for children exposed to maternal addiction (aHR 1.20, 95% CI=0.89–1.62, p=0.236, Table16).

Table 16 Unadjusted and Adjusted Hazard Ratios showing the association between hospital inpatient admission for asthma and maternal mental illness (N = 359,611 children)

	Person-Years, 1,000	**Atopy Cases N**	**Atopy Rate (95%CI)** per 1,000 person-years	**Unadjusted HR**	***p***	**Adjusted HR Model 1 † (95%CI)**	***p***	**Adjusted HR Model 2 †† (95%CI)**	***p***
Asthma Inpatient									
Unexposed	1538.59	2059	1.3 (1.3-1.4)	**REF**	**-**	**REF**	**-**	**REF**	**-**
Common Mental Illness	797.58	1412	1.8 (1.7-1.9)	1.46 (1.37-1.57)	<0.0001	1.29 (1.20-1.38)	<0.0001	1.26 (1.17-1.36)	<0.0001
Serious Mental Illness	11.70	15	1.3 (0.8-2.1)	0.98 (0.59-1.64)	0.951	0.76 (0.45-1.27)	0.296	0.77 (0.46-1.28)	0.315
Addiction	21.41	46	2.6 (1.6-2.9)	1.72 (1.29-2.30)	<0.0001	1.27 (0.95-1.71)	0.113	1.20 (0.89-1.62)	0.236
Other MMI	19.88	45	2.6 (1.7-3.0)	1.68 (1.25-2.25)	0.001	1.28 (0.95-1.72)	0.103	1.29 (0.96-1.74)	0.088

† Adjusted for maternal atopy history, antibiotic use during pregnancy, maternal age, child sex, child ethnicity, birth season, birth year practice IMD and practice region
†† Adjusted for all variables in model one, plus maternal smoking

5.6 DISCUSSION

5.6.1 Principal findings

To our knowledge, this is the first UK population-based study to examine the association between exposure to maternal mental illness and the risk of different atopic disorders in children. Our main findings were that risk of asthma, eczema, allergic rhinitis, but not food allergy was higher in children with mentally ill mothers compared to children of non-mentally ill mothers. However, this association did not hold for all maternal mental illness: maternal addiction was inversely associated both with offspring risk of food allergies and eczema diagnosed in primary care. Also, the risk of atopic disorders was not higher in children exposed to serious mental illness.

Eczema risk was marginally increased for children exposed to CMI, eating and personality disorders but children exposed to maternal SMI or addiction were significantly less likely to develop eczema. Allergic rhinitis was significantly more likely to occur in children exposed to maternal CMI but not other maternal diagnoses. Food allergies were significantly reduced in children with maternal addiction.

Male children, children of ethnic Asian heritage and children exposed to antibiotic use during pregnancy, or a maternal history of atopy were at greater risk of atopic disorders. By contrast, maternal smoking was only a risk factor for childhood asthma but was associated with reduced risk for eczema and food allergies in children. The influence of deprivation varied for different outcomes: while children from the most deprived households had the highest risk of asthma, their risk of eczema was lowest. This pattern was also apparent for children developing food allergies but less in allergic rhinitis. Finally, in a sub cohort of children with HES linkage, the risk of asthma related inpatient hospital admission was greater among children exposed to maternal CMI when compared to unexposed children.

5.6.2 Research in context

Some of our results are consistent with existing evidence. The increased risk of asthma in children exposed to maternal CMI was also reported by Brew *et* al [90] in a sample of 360,226 Swedish mother-baby pairs and by Magnus *et* al [247] in a Norwegian sample of 63,626 mother-baby pairs. Similarly, increased risk of allergic rhinitis among children exposed to CMI was reported by Li *et* al [251].

Unlike other smaller cohort/case-control studies [95,98,246], we do not report that children exposed to CMI have an excess risk of developing eczema compared to unexposed children. Exposure to maternal smoking and socioeconomic deprivation explained some of the risk associations with asthma in our study cohort. Eczema is very common in infancy (0-3 years). It could be that **mild** eczema cases are more likely to be presented to GPs in higher socioeconomic families, where mothers may be more health literate, non-smoking and living in less deprived circumstances [252].

The potential mechanism of the inverse relationship between maternal mental illness and some atopy disorders could be related to the fact that some mothers with CMI e.g. anxiety disorders are more vigilant about their child's health and more likely to have concerns about it. This could explain why there is more frequent reporting of symptoms in this group and a relatively reduced reporting in children in other groups. Eczema may also be more commonly undetected among children exposed to maternal mental illnesses and/or maternal smoking who live in more deprived areas; they may also be less likely to attend the GP if they have limited access to transport or to childcare support for other children. We do not see an inverse relationship between asthma and mental illness: asthma is more likely to be life-threating, symptoms such as wheeze may be less easy to miss and especially if the child experiences serious asthma attacks and is of school age. We were not able to capture the severity of eczema in our primary care data. This means we have limited capacity to investigate the complexity of the relationship between serious mental illness, maternal smoking, deprivation levels and eczema. More research is needed to understand whether

maternal/parental education, health literacy plays a role in lower rates of eczema presentation to primary care in the children exposed to maternal mental illness.

We also report that children exposed to maternal addiction are significantly less likely to develop food allergies. However, we observed a pattern in the main and sensitivity analysis results for eczema among children exposed to maternal addiction. In a post-hoc analysis, we further examined these data to rule out possible confounding in the results. In a sub sample of children with HES linkage and eczema diagnosis from primary care, we estimated the risk of hospital inpatient admission for any skin disorders using the Cox proportional hazard models. The results showed that children exposed to maternal addiction and eczema diagnosis in primary care had increased risk of admission to hospital for any skin disorders (aHR 1.47, 95% CI=0.98– 2.22, p=0.063*, Appendix G4*) when compared to unexposed children with eczema diagnosis.

Elbert *et* al [96] reported decreased risk of food allergies in children with mothers experiencing depression; in our cohort this group did not show significant reduction in food allergy risk. Overall, we report similar patterns related to deprivation levels for food allergy and eczema risks; this may indicate that these atopic disorders have particular associations with middle/higher social class although further studies are needed to understand these differences. Different atopic disorders are linked by a shared underlying problem with immune activation [77]; nevertheless, our observations suggest that socio-economic status of the mother contributes to the aetiology of these disorders. It is well-established that low-socioeconomic status is associated with generally poor health outcomes; however, our findings indicate that children from the most deprived areas have reduced risk of eczema/food allergies.

The so called ‘hygiene hypothesis’ is widely recognised as one the explanations of the inverse relationship between eczema/food allergies and deprivation [253]. According to this hypothesis, early life exposure to microorganisms in less hygienic environments, could protect the child from developing atopic disorders [254]. However, we report contradictory results for asthma and eczema

risk. If the hygiene hypothesis was relevant here, we should have seen a lower risk of asthma in deprived areas as we observed for eczema and food allergies.

Our post-hoc analysis results indicate that children exposed to maternal addiction are significantly less likely to be seen in primary care for eczema, but have increased risk of hospital admission for skin disorders. This supports the notion that mothers with addiction could be less vigilant about their child's eczema symptoms and seek help only when it worsens. There is convincing evidence that mothers with addiction tend to come from the most deprived areas; this is also the case in our study. Therefore, it is likely that deprivation levels play a significant role in this group but cannot be explained by the hygiene hypothesis.

5.6.3 Strengths and limitations

The use of electronic health care records in this study enables a large cohort to determine enough precision in estimates and allows us to investigate the possible link between individual maternal mental illnesses and offspring atopic disorders.

However, there are several limitations. First, we were unable to capture the severity of eczema in the primary care datasets; this is important if we are to explain the inverse relationship between serious mental illnesses and reduced risk of eczema. Secondly, we were unable to study the confounding effects of air pollution, which is an important risk factor for asthma [255], as this is not recorded in healthcare system. We could only look at geographical region and area level indices of deprivation. Thirdly, ethnicity is another important factor in atopic disorders [256]; and mental illness in non-white and migrant mothers may be underestimated in primary care because they are less likely to use primary care services for mental illness [213]. Fourthly, despite the fact deprivation levels based on the GP location were taken into consideration for all analyses, there are no data recording other deprivation indicators such as household income level, welfare receipt or employment status. Finally, a HES linkage was required to investigate atopy-related healthcare utilisation for children; this meant excluding a significant number of mother-baby pairs from the

general practice records because the data collection for HES is later than primary care; and it only includes hospitals in England. This means we did not have secondary care information for children from Scotland, Wales or Northern Ireland.

5.6.4 Clinical and policy implications

In the UK, the Healthy Child Programme [9] is a public health intervention which aims to provide parents with advice on child health. The Healthy Child Programme [9] does not link common mental illnesses with risk of developing asthma or allergic rhinitis.

Public health policies and practice guidelines including the Healthy Child Programme [9] should be modified to tailor support to mothers with mental illness whose health literacy may be compromised. For instance, children were at high risk of developing asthma if they were exposed to common maternal mental illnesses, but also if exposed to maternal smoking during their lifetime, or to antibiotics in-utero and lived in most deprived areas. Therefore, expanding preventive programmes to target groups of more vulnerable mothers and specifically tailoring information is a clear implication of our findings. Such tailored information is important because increasing evidence suggests that people with mental illness are less likely to adopt preventive health measures or be able to change behaviour following widespread public health campaigns [191]. This means that we are at risk of increasing health inequalities if those at greatest risk are unable to access the benefits of available healthcare. Preventable causes of risk, such as maternal smoking, are particularly important – far more needs to be done to improve smoking cessation in mothers with mental illness.

5.6.5 Conclusion

We found that maternal common mental disorders are associated with increased asthma and allergic rhinitis in offspring. Aetiological mechanisms in atopic disorders remain elusive, but this and other findings make it likely that maternal environment plays a role. Future research should

focus on as yet unmeasured risk factors and public health policy and intervention programmes should consider specifically tailored approaches which support families and are likely to provide less deprived and healthier environments for their children. Given the likely excess costs of atopic disorders in children, such an approach might have significant economic benefits.

Summary box

What is already known on this topic?

- Prior studies indicate that children of mothers with depression and anxiety disorders have increased risk specifically of developing asthma. However, results are mixed for children's risk of eczema. These studies are limited by small samples.
- To date, there are no UK studies that investigate the association between maternal mental illnesses and different childhood atopic disorders.
- Existing studies elsewhere had a narrower scope, generally examining only one type of atopic disorder and its association with maternal depression.

What this study adds?

- This is the first UK study to examine the impact of maternal mental illness on different types of atopic disorder.
- This is the largest study to-date and confirms the association between maternal common mental illnesses, asthma and allergic rhinitis.
- This is the first study to identify reduced risk of food allergy and eczema among children exposed to maternal serious mental illnesses and maternal addiction.
- These findings identify risk subsets within this risk cohort who policy makers and clinicians might target to prevent childhood atopic disorders.

CHAPTER 6- PERINATAL SMOKING: ITS PREVALENCE AND LINK WITH MATERNAL MENTAL ILLNESS

Brief Research Article

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Contributions: KMA conceived of the study, CSO wrote the study protocol, with input from KMA, MP, HH, and JPAI. CSO carried out the analysis with support from MP and HH and all authors interpreted the results. CSO wrote the initial draft of the manuscript and all authors contributed to and approved the final version.

6.1 DESCRIPTION OF STUDY IN CONTEXT OF THESIS

This chapter presents the fourth study of this thesis and examines the perinatal smoking status of women with and without mental illness in the UK. This study was developed during the atopy study (Chapter 5) as maternal smoking was one of the most important risk factors for children atopic disorders. Capturing smoking status recording in primary care was not straightforward, therefore an algorithm was developed (see subsection 2.3.2) to capture all available information meaningfully from the primary care records. This study shows the smoking status of women with and without mental illness during perinatal period as well as reports on how many of the women who smoked before pregnancy continued, stopped or restarted to smoking during pregnancy. This study is formatted as a short communication and currently under review at the *Addiction*.

6.2 ABSTRACT

This paper reports the perinatal smoking rates among women with and without mental illness in the UK using Clinical Practice Research Datalink (CPRD-GOLD). Perinatal smoking was significantly higher among women with mental illness than women without (37% vs 19%). Women with mental illness struggled to stop smoking once pregnant or in the postnatal period. Perinatal smoking remains a serious concern and should be proactively targeted in primary care. Tailored approaches to smoking cessation are essential for perinatal women with mental illness.

6.3 INTRODUCTION

Tobacco use during perinatal period is linked to many adverse infant and child outcomes such as risk of preterm delivery, low birth weight, stillbirth, sudden infant death syndrome (SIDS) and respiratory illnesses [257]. The tobacco smoking status of women at delivery was reported as 11% in England in 2018/19 by NHS Digital [258] which provides national population-based statistics and in a population-based study, 23% of women in Scotland (n=697,003) were smoking tobacco at their first antenatal booking [259].

Approximately 20% of women in the UK experience perinatal mental illness [260] and there is long-standing evidence that tobacco use is considerably higher among people with mental illness compared to general population and they are less likely to respond to smoking cessation messages [261]. For instance, Webb *et* al [191] reported that 41% of women with an admission to psychiatric units (n=61,748) in Sweden were current tobacco smokers at their primary antenatal booking.

However, currently in the UK, the perinatal tobacco smoking status among women with mental illness is not known. This analysis provides contemporary rates of perinatal tobacco smoking among women with and without mental illness in the UK using the Clinical Practice Research Datalink (CPRD-GOLD): a national UK primary care database representing 11.3 million patients.

6.4 METHODS

6.4.1 Data and cohort

This retrospective cohort study utilised data from CPRD-GOLD, which contains anonymised primary healthcare records representing 10% of UK general practices [143]. Clinical event data are collected on clinical consultations (including diagnosis), referrals and prescriptions.

The cohort involved women recorded in the CPRD's mother-baby link which matches mothers with their offspring registered at the same practice; if mother's delivery date is within 60 days of the offspring's birthday and if they share the same family identifier. This means that the mother-baby link only involves biological mother-baby pairs.

We selected women with first deliveries between 01/01/2005 and 31/12/2015 and had valid data for the 'perinatal period' (defined as one year before and after the baby's date of birth). These time points were specifically selected, the data recording in primary care post-2004 significantly improved following the introduction of the Quality Outcomes Framework (QoF) and the year 2015 was the latest time point that we would be able to identify women's pregnancies.

6.4.2 Measures

Mental illness during the perinatal period **(**depression, anxiety, non-affective and affective psychosis, alcohol and substance misuse or personality disorder) was mapped to ICD-10 defined psychiatric disorder and identified from clinical data using the algorithm created by Abel *et* al [17] combining psychiatric diagnoses, symptoms, prescriptions and service use. For analysis purposes mental illnesses were grouped into the following non-exclusive categories: common mental illnesses (anxiety/depression), serious mental illnesses (non-affective and affective psychosis), maternal addiction (alcohol and drug misuse), and other mental illness (eating and personality disorders).

Perinatal smoking was identified if general practitioners (GPs) recorded a woman as currently smoking or provided advice/treatment to help quit smoking. All tobacco smoking related Read codes were extracted from the mother's medical files however it is important to highlight that capturing tobacco smoking information in the CPRD is not always straightforward, because the information may not be always reliable as a result of unstandardised terminology, changing attitudes towards smoking and patient's changes in smoking behaviour [167,168]. Maternal non-smoking status was identified where GPs recorded a mother as an ex- or non-smoker. Absence of smoking records during the perinatal period was recorded as missing. Finally, because smoking information is gathered from clinical consultations, we lacked granular data on timing of maternal smoking and number of cigarettes smoked per day. Since missingness was low (~*3*%) and similar across mothers with and without mental illness groups, we excluded missing cases in analyses as the chi-square tests indicated there was no significant difference between these groups.

Additional data was used on the Index of Multiple Deprivation (IMD) linked to the GP practice postcode. The IMD is a rank score of area-level deprivation, divided into quintiles, derived from seven poverty indicators; income, employment, education, health and disability, crime, barriers to housing and services and the lived environment.

6.4.3 Statistical analysis

Statistical analyses involved describing the distribution of smoking by region and IMD and birth-year. In a sub-cohort of women who smoked prior to pregnancy we constructed a perinatal smoking variable (1) stopped in pregnancy & post-natal; (2) smoked in pregnancy/stopped post-natal; (3) stopped in pregnancy/restarted postnatal; (4) smoked in pregnancy & postnatal. We calculated the proportion of mothers with and without mental illness in each category of perinatal smoking, using an ordinal logistic regression analysis. Data were analysed using Stata SE 15.0.

6.5 RESULTS

Between 2005-2015, 23% (38,563/169,402) of women were recorded as smoking tobacco during the perinatal period. Among 35,735 women with any mental illness and 133,667 women without 37% and 19% smoked tobacco during the perinatal period, respectively ($p<0.0001$). Overall, in the UK, perinatal women in Wales (40.8%) and in the North East of England (a poor and deprived region, 39.6%) had the highest proportion of tobacco smoking. Between 2005 and 2015, tobacco smoking fell from 38% to 33% in women with mental illness and from 21% to 16% in women without mental illness (Table 17).

Of all women, 20% experienced common mental illness, 0.4% had a diagnosis of serious mental illness, 0.5% had an addiction diagnosis and 0.4 % had other mental illness diagnosis. Although there were few numbers of women with addiction and psychotic disorders, the highest smoking rates were observed among women specifically experiencing these mental illnesses (45% and 76%).

Overall, 17,291 women with any mental illness and 39,028 women without mental illness smoked tobacco before pregnancy. Of these, 32% versus 43%, stopped smoking tobacco during pregnancy, 19% versus 20% stopped smoking tobacco in the year after birth, 18% versus 16% restarted smoking tobacco postnatally and 31% versus 21% continued to smoke tobacco in pregnancy and the year after birth, respectively (Table 18).

When we examined records of GPs giving smoking cessation advice and referral to smoking cessation programmes to women with and without mental illness, we observed that women with mental illness who continued to smoke during pregnancy and postnatal period, 95% of them were provided advice on stopping smoking and 15% of them were referred to smoking cessation programme (Table 18).

Table 17 Perinatal smoking among mentally ill and not mentally ill mothers with information on smoking; by region, deprivation and year

	Mothers <u>with</u> any mental illness	**Actively Smoked in Perinatal Period**		***Mothers <u>without</u> any mental illness***	**Actively Smoked in Perinatal Period**	
	N	**N**	**%**	***N***	**N**	**%**
Total	*35,735*	13,131	36.80	*133,667*	25,432	19.0
Type of maternal mental illnesses*						
Common mental Illness	*35,117*	12,813	36.5			
Serious mental illness	*640*	281	43.9			
Addiction Disorders	*914*	698	76.4			
Other mental illness	*600*	254	42.3			
By region						
North East	*603*	239	39.6	*2,110*	530	25.1
North West	*4,446*	1,736	39.1	*14,338*	3,058	21.3
Yorkshire & The Humber	*733*	267	36.4	*2,795*	576	20.6
East Midlands	*954*	347	36.4	*3,146*	582	18.5
West Midlands	*3,171*	1,178	37.2	*12,050*	2,529	21.0
East of England	*2,603*	925	35.5	*10,593*	1,838	17.4
South West	*3,181*	1,193	37.5	*11,470*	2,395	20.9
South Central	*4,219*	1,370	32.5	*15,722*	2,521	16.0
London	*2,673*	825	30.9	*15,667*	2,240	14.3
South East Coast	*3,588*	1,231	34.3	*14,315*	2,574	18.0
Northern Ireland	*1,678*	664	39.6	*4,641*	1,001	21.6
Scotland	*4,221*	1,660	39.3	*14,100*	2,818	20.0
Wales	*3,665*	1,496	40.8	*12,726*	2,763	21.7
UK IMD quintile**						
1 *(least deprived)*	*5,307*	1,440	27.1	*23,594*	2,847	12.1
2	*5,520*	1,752	31.7	*22,071*	3,498	15.9
3	*6,891*	2,491	36.2	*26,201*	4,817	18.4
4	*7,755*	3,000	38.7	*29,117*	6,093	20.9
5 *(most deprived)*	*10,262*	4,448	43.3	*32,690*	8,170	25.0
By year						
2005	*3,488*	1,314	37.7	*12,935*	2,683	20.7
2006	*3,619*	1,409	38.9	*13,443*	2,773	20.6
2007	*3,608*	1,348	37.4	*13,731*	2,704	19.7
2008	*3,721*	1,401	37.7	*14,383*	2,846	19.8
2009	*3,644*	1,300	35.7	*13,918*	2,734	19.6
2010	*3,461*	1,273	36.8	*13,751*	2,566	18.7
2011	*3,493*	1,273	36.4	*13,040*	2,371	18.2
2012	*3,422*	1,266	37.0	*12,524*	2,293	18.3
2013	*2,895*	1,031	35.6	*10,609*	1,969	18.6
2014	*2,472*	883	35.7	*8,840*	1,456	16.5
2015	*1,912*	633	33.1	*6,499*	1,030	15.9

* Note that maternal illness categories are not mutually exclusive
**Based on the GP location postcode

Table 18 The number who smoked prior to pregnancy and their smoking status during pregnancy and postnatal periods

	Mothers with any mental illness *N=17,291*				**Mothers without any mental illness** *N= 39,028*				**Absolute Difference in smoking status % (95%CI)***
Smoking status	**N**	**% (95% CI)**	**Received Smoking Advice N (%)**	**Referred to Smoking Cessation Programme N (%)**	**N**	**% (95% CI)**	**Received Smoking Advice N (%)**	**Referred to Smoking Cessation Programme N (%)**	
Stopped smoking in pregnancy and postnatal	5,392	32 (31-33)	3,800 (70.5)	326 (6.0)	16,768	43 (42-43)	11,005 (65.6)	718 (4.3)	-10.6% (-9.7-11.3)
Continued smoking in pregnancy and stopped smoking in postnatal	3,571	19 (18-20)	3,143 (88.0)	361 (10.1)	7,434	20 (19-20)	6,396 (86.0)	587 (7.9)	-0.5% (-0.4 -0.6)
Stopped smoking pregnancy and restarted smoking in postnatal	3,087	18 (17-18)	2,853 (92.5)	345 (11.2)	6,185	16 (15-16)	5,646 (91.4)	637 (10.3)	2.4% (2.2-2.5)
Continued to smoke in pregnancy and postnatal	5,241	31 (30-31)	4,956 (94.5)	810 (15.5)	8,641	21 (21-22)	8,018 (92.7)	1,053 (12.2)	8.7% (8.0-9.4)

*Marginal estimate from an ordinal regression, corrected for multiple comparisons

6.6 DISCUSSION

The scale of perinatal maternal tobacco smoking remains a concern and significantly worse among mentally ill than non-mentally ill women. Not only is this pattern continuing over time, but mentally ill women are also substantially less likely to give up smoking once pregnant or in the first year of their child's life. It is also apparent that despite the fact GPs provide smoking cessation advice to mothers during perinatal period, very few of them are actually referred to smoking cessation programmes.

Globally, tobacco smoking is an important, well-known, modifiable risk factor for many serious child health problems but appears neglected compared to far less important lifestyle factors [262]. We replicate and add to evidence that generic public health programs are less effective for mentally ill individuals [259,261]. Moreover, we report the highest smoking rates in the most deprived regions and poorest areas in the UK.

While these findings are important towards understanding the smoking patterns in pregnant women, we recognise some limitations. We may have underestimated smoking during pregnancy for two reasons. First, smoking information during pregnancy is generally retrieved as self-report during the woman's first antenatal appointment which takes place in the first three months of pregnancy and quarter of active smokers do not declare their smoking behaviour. This may have led our smoking rates to be underestimated. Secondly, the Mother-Baby link only includes women with live births and rates of smoking may be elevated among pregnant women who experienced a still birth or spontaneous abortion [263], but we could not investigate this. Finally, in this study we provide crude rates and maternal age might be a potential confounder. In this study, we rather describe the scale of the problem in the UK and we cannot infer a causality.

Pregnancy represents an optimal time to attempt successful smoking cessation but ~20% of non-mentally ill women who smoke continue to do so during pregnancy and postnatal periods. Therefore, perinatal smoking remains a serious concern for offspring of both non and mentally ill

mothers. Our perinatal smoking rate is comparable to rates in Scotland calculated using electronic health records which was reported as 23% [259] and higher than the US survey which was reported as 7% [264]. These results highlight the need for urgent review of the access to, promotion and adequacy of existing smoking cessation interventions for women who are pregnant or planning pregnancy.

For example, Bérard *et* al [265] utilised medical records to identify a cohort of Canadian women without depression who smoked in pregnancy and reported that, after adjustment for potential confounders, compared to women who smoked throughout, women who started a pharmacological smoking cessation treatment in their first trimester were 8 times less likely to experience a preterm birth, and most continued to be non-smokers one year post-partum. Gilbody *et* al [261] demonstrated using a randomised controlled trial study design that women with serious mental illness have the desire but find it much harder to stop smoking and require a tailored approach that combines pharmaceutical and psychosocial support to commence and maintain smoking cessation during pregnancy [261]. Given the high rates of smoking we saw among women with mental illnesses and the fact that most were given smoking cessation advice from their GP such tailored approaches are necessary. Few women were referred to smoking cessation programmes and further research into possible barriers pregnant women or women with young children face accessing traditional programmes is a priority.

Despite changes to the law and increased awareness of the damage smoking does among the general population the proportion of women smoking during pregnancy has not markedly reduced in the past ten years: more needs to be done. Refocusing on reducing perinatal smoking would be a highly cost-effective strategy for improving the health of women, pregnancy outcomes, infant mortality and child health.

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CHAPTER 7- THE EFFECT OF MATERNAL MENTAL ILLNESS ON CHILDHOOD CANCER: A POOLED ANALYSIS OF ENGLAND AND SWEDEN NATIONAL COHORTS

Journal Article

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Contributions: KMA gained funding for the study and MP and KMA conceived of the study. CSO wrote the study protocol for the English cohort and AN for the Swedish cohort with input from KMA, MP and HH. CSO carried out the data processing and statistical analysis for the English cohort and AN for the Swedish cohort with support from MP, KK and HH. CSO conducted the meta-analysis and wrote the initial draft of the manuscript and all authors contributed to the final version.

7.1 DESCRIPTION OF STUDY IN CONTEXT OF THESIS

This chapter presents the fifth and final study of this thesis. In this study the effects of maternal mental illness on childhood cancers in two national cohorts of England and Sweden is investigated. This study was conceived of as a meta-analysis in order to have sufficient power to investigate this rare outcome. The analyses were done in parrallel at each site before being pooled. This involved close collaboration with colleauges at the Karolinska Instututet in order to co-ordinate methods across sites. In both national cohorts, Cox proportional hazard model (see subsection 2.4.3) was used to measure the risk of cancer among children exposed to maternal mental illness. Exposure to maternal mental illness was defined as time-varying (see subsection 2.4.3-time varying variable). Following the risk estimations from two national cohorts, a pooled analysis was conducted using meta-analysis method (see subsection 2.4.4) to increase the statistical power of the analysis as the outcome of interest is a rare childhood disorder.

7.2 ABSTRACT

Importance: There is limited knowledge about the effect of maternal mental illness (MMI) on childhood cancers.

Objective: To examine the effect of maternal mental illness on childhood cancer.

Design: Retrospective cohort study.

Setting: England and Sweden.

Participants: Mother-baby pairs from England and Sweden were included. Children were linked to Hospital Episodes Statistics database known as HES (England) and Swedish Cancer register (Sweden) to capture child's cancer diagnosis. Mother's mental illness was identified from mother's primary care records (England) and National Patient register and specialised outpatient care (Sweden).

Main Outcomes and Measure: The primary outcome was diagnosis of childhood cancer after the exposure to maternal mental illness. MMI included depression, anxiety, psychosis, eating disorder, personality disorder and alcohol and substance misuse disorders.

Crude and adjusted hazard ratios for the risk of cancer among children associated with MMI were calculated using Cox proportional hazard models separately in England and Sweden cohorts. In both cohorts, demographic characteristics were adjusted in regression models. A pooled analysis was then conducted to combine the results from both cohorts.

Results: Total sample included 2,897,916 mother-baby pairs and contributed to 36,734,049 person years. The cancer rate among children exposed to any maternal mental illness in England was 13.0, while in Sweden it was 17.6 per 100,000 person years. Children exposed to maternal alcohol and drug addiction had significantly increased childhood cancer risk compared to children unexposed to maternal mental illness (adjusted hazard ratio: 1.36, 95%CI=1.01-1.84, p=0.0404). Reduced cancer risk among children exposed to maternal psychotic disorders was observed, but not reached to statistically significance level (adjusted hazard ratio: 0.72, 95%CI 0.38-1.36, p=0.3059). No cancer risk was observed among children exposed to common maternal mental illnesses (depression /anxiety).

Conclusions: Our results indicate that maternal mental illness may have a role in childhood cancer. Child's cancer risk varies based on the mother's type of mental illness, however more international collaborations are essential to enable more robust conclusions. Children exposed to maternal addiction had the greatest risk of cancer compared to children exposed to other types of mental illnesses as well as unexposed children. Tailored approaches to vulnerable mothers and their families should be considered in public health policies and interventions.

7.3 INTRODUCTION

Although relatively rare, childhood cancers are the second most common cause of death in children in economically developed countries [109]. The cancer rates among individuals aged 0-24 in 2017 in England was 19 per 100,000 person years, while in Sweden it was 23 per 100,00 person years [266,267]. In both countries, incidence of childhood cancer has increased slightly over the last decade from 18 to 19 per 100,00 person years in England and from 20 to 23 per 100,000 person years in Sweden [266,267]. Leukaemia, and brain/intracranial tumours are the most common types of cancers observed in children.

The role of the mother in their child's life starts from conception and continues throughout adolescence. In the UK, it is estimated that one in four children aged between 0-16 lives with a mother experiencing mental illness [17]. Poor maternal mental health is a risk factor for congenital anomalies [1], premature birth and low birth weight [268], neurodevelopmental disorders [269–271], missing vital vaccinations [153] and injuries [272]. However, less is known about the possible effects of maternal mental illness on rare childhood diseases like cancer.

The relationship between cancer and mental illness is not straightforward [273]. For example, studies have reported that people with schizophrenia have reduced risk of developing cancer when compared with general population [122,274–276], while other studies reported no reduced risk in this population [277] or increased risk [278,279]. Other studies have reported reduced risk in first degree relatives of patients with schizophrenia [114,116,277] and increased cancer risk among children of mothers with addiction disorders [38,39,118,119].

However, no study to-date has specifically examined the risk of cancer among children under age 18 with mentally ill mothers. We investigated this outstanding knowledge gap in a large, contemporary and high-quality population-based cohorts of the England and Sweden. We hypothesised that there will be a lower risk of childhood cancer among children exposed to serious

maternal mental illness and an increased risk of cancer among children exposed to maternal common mental illnesses.

7.4 METHODS

7.4.1 Data sources

This retrospective cohort study was conducted using national cohorts from England and Sweden.

Data for the **English** cohort was extracted from the Clinical Research Practice Datalink (CPRD-GOLD), which is comprised of anonymised primary care health records from approximately 10% of the UK population [143]. CPRD contains data on patient's clinical consultations, immunisation records, prescriptions and external healthcare referrals. Study participants were identified from the CPRD's mother-baby link, which is an algorithm developed within CPRD to identify the mother-baby pairs [143] (see Osam *et* al [153] for further details on mother-baby link algorithm). In order to ascertain hospital inpatient records, children in this cohort were linked to Hospital Episodes Statistics (HES) dataset using a unique NHS identifier. Linkage to the HES dataset is only available on practices that consented to linkage (75% of English practices).

Children in the **Swedish** cohort were identified from the Total Population Register [171]. Each person resident in Sweden for at least 6 months is provided a unique personal identifier. This was used to link children to: the multi-generation register [280] to link parents, and their demographics information; the National Patient Register [281], which contains information on inpatient care and specialised outpatient care to identify the exposure of parental mental illness; the Swedish Cancer Register [282] to identify cancer outcomes; the Longitudinal integrated database for health insurance and labour market studies (LISA) [283] to obtain individual and family-level socioeconomic information; and the Medical Birth Register [284] which contained information on perinatal characteristics.

7.4.2 Cohort selection

For the English cohort, eligible children were selected from all those born between 1st January 1996 and 30th December 2017 and linked to HES. In order to have sufficient data to determine exposure status, we excluded those whose mother was registered at an up to standard general practice for less than six months prior to the child's birth (Figure 11A).

Children's follow-up started at the latest date of: child's date of birth; the date when the practice started collecting data that was deemed 'up-to-standard'; the date of the child's registration at that clinical practice; and the HES linkage start date (1st April 1997). Their follow up ended at the earliest date of: the date they transferred out of the general practice, their 18th birthday, their date of death, their mother's date of death, the practice data collection end date; and the study end date (31st July 2017). In total 591,092 children and 418,944 mothers were identified for analysis with an average follow-up time of 11.16 person years.

In the Swedish cohort, eligible children were selected if they were born in Sweden between 1991-2011; linked to their parents. Children's follow-up started from their date of birth until the first date of cancer diagnosis, either parent's emigration, child emigration, death of children, death of either parents, age 18, or 31st December 2016, whichever was earliest. The final cohort consisted of 2,192,476 children linked to 1,244,239 mothers and 1,207,810 fathers (Figure 11B).

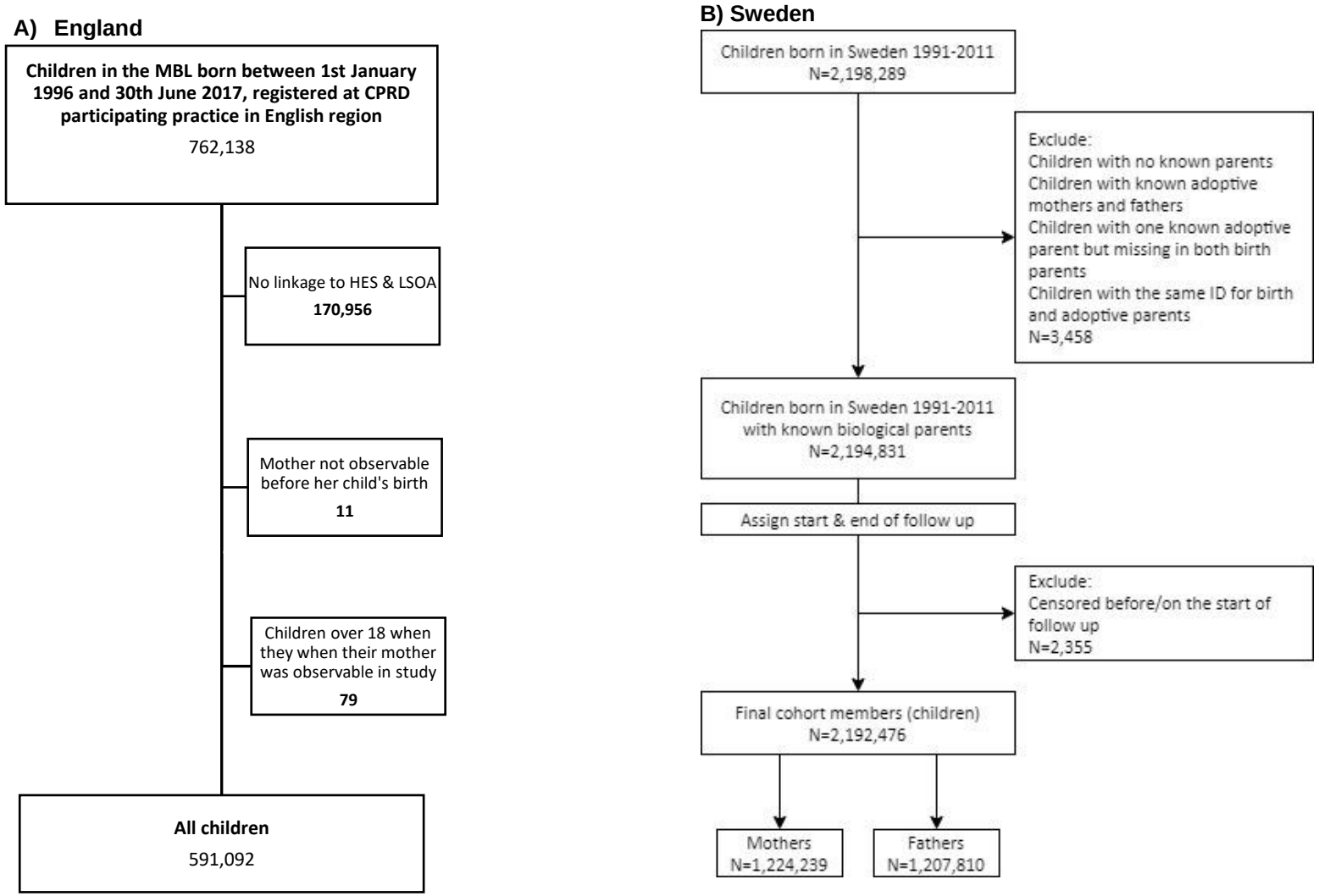


Figure 11 Cohort selection A) England, B) Sweden

7.4.3 Exposure: Maternal mental Illness (MMI)

Children in both cohorts were defined as exposed to MMI if their mother had any MI record one year prior to birth until the child' follow up. However, MMI was captured differently in both cohorts.

In the **English** cohort, MMI was identified using primary care data on each mother's recorded diagnoses, symptoms, prescription and referral to external services. Mental illness was determined by using four methods: diagnosis of a mental illness; a referral to psychiatric care services; a psychotropic medication or symptom if there was a related historical diagnosis; or a psychotropic medication and a related symptom within three months of each other. See Abel *et* al [17] for further details on the algorithm. Children were defined as exposed from the time of the first recorded event relating to depression, anxiety, non-affective and affective psychosis, alcohol and substance misuse, eating disorders and personality disorders between one year prior to birth and the end of the child's follow up.

In the Sweden cohort, MMI was captured from the National Patient register and specialised outpatient care using ICD-9 and 10 codes for the following mental illnesses: non-affective psychotic disorders, affective psychotic disorders, alcohol or drug misuse, depressive disorders excluding those with psychotic, anxiety and stress-related disorders, eating disorders and personality disorders.

In both cohorts, mental illnesses were grouped into following categories: common mental illnesses (CMI, anxiety or depression), psychotic disorders (non-affective or affective psychosis), maternal addiction (alcohol or substance misuse) and other MMI (eating or personality disorders).

7.4.4 Outcome: Childhood cancer

In the **English** cohort, childhood cancer diagnosis was captured from the child's inpatient admission records using ICD-10 codes (C00-C97; excluding D00-D09: in situ neoplasms, D10-D36 benign neoplasms and D37-D48 neoplasms of uncertain or unknown behaviour). For the Swedish cohort, childhood cancer was obtained from the Swedish Cancer Register using ICD-9 codes (140-208, 230-234, see Appendix *E*).

7.4.5 Other variables

In the English cohort, demographic and lifestyle related data were extracted on maternal age at birth, maternal smoking, maternal antibiotic use during pregnancy, child's sex, birth year and child's ethnicity. Also, an area-level measure of deprivation was extracted using the 2010 quintile of the Index of Multiple Deprivation, based on residential address [285]. Child's ethnicity was captured from both the HES dataset and the CPRD and categorised into: Asian, Black, Mixed, Other and White.

In the Swedish cohort, data were extracted on children's birth year, sex, parental country of birth (Sweden/other countries), and parental age at childbirth. Parental education and household disposable income in quintiles were also captured in Sweden cohort. Parental education was defined as the highest educational attainment of the parents (mothers or fathers) categorised into compulsory (≤9 years), secondary (10-12 years), and university education (≥13 years). Household disposable income was defined as the yearly sum of income and public benefits earned by all family members, adjusted for taxation, categorised into quintiles for each year. Data was also captured on parental history of cancer and paternal mental illness at birth.

7.4.6 Statistical methods

In both cohorts, crude and adjusted hazard ratios (HR and aHR) for association the association between MMI and childhood cancer were calculated using Cox proportional hazard models. For the

English cohort analysis, the adjusted model included: maternal age at birth, maternal smoking, maternal antibiotic use during pregnancy, deprivation, England region, child's sex and ethnicity. Similarly, in the Swedish analysis, demographic characteristics of the children (sex and birth year) as well as the parents (country of birth and age at childbirth), parental socioeconomic position (education and household disposable income), parental history of cancer, and parental comorbid mental illness were adjusted for. In both cohorts, clustering by maternal sibships was accounted for using the Hubber/White sandwich estimate of the standard error [209].

Once effect estimates (HRs) were obtained from both cohorts, a pooled analysis was conducted using the the Sidik-Jonkman random-effects meta-analysis model [177]. Heterogeneity of the study was evaluated by I^2 and Q Tau-squared statistics [286]. Hazard Ratios in both cohorts were estimated using Stata SE 15.0 and meta-analysis was carried out in R (Version 4.0.2) using 'meta' [287] and 'metafor' [288] packages.

7.5 RESULTS

7.5.1 Cohort characteristics

Across both cohort there were for 2,783,568 mother-baby pairs and children were followed up for 33,052,781 person years. Table 19 illustrates the characteristics of the samples from England and Sweden. In both cohorts, mean maternal age was 30 years (standard deviation= 5.8 for UK- 5.6 for Sweden) and 49% of children were female.

In the English cohort, overall children from most deprived areas were more common than children from least deprived areas (24% vs 16%). Similarly, in Sweden cohort, there were more children living in houses with lower family disposable income than children living in highest family disposable income (28% vs 13%).

In the English cohort, 35% of children (205,804/ 591,092) were exposed to maternal common mental disorders at some point over follow-up and less than one per cent was exposed to maternal psychotic disorders. In Sweden, only 12% of children (258,085/2,192,476) were identified as exposed to CMI and 2% (34,950/ 2,192,476) were exposed to psychotic disorders.

There were 950 children with cancer diagnosis in the English cohort and 33% of these children were exposed to CMI, 1% were exposed to maternal addiction disorders and less than 1% of children were exposed to psychotic and other maternal mental illnesses. In the Swedish cohort, there were 5,245 children with cancer diagnosis and 8% of them were exposed to CMI, 2% were exposed to maternal addiction disorders and 1% were exposed to psychotic and other maternal mental illnesses.

The prevalence of maternal smoking any time during child's life (from the beginning of pregnancy till child's end of follow up) was 30% however this number was even higher for mothers with mental illness (46%; Table 19). In Sweden, the maternal smoking information is captured at first antenatal visit and it was available for children born before 2010 (N=2,018,555) and among these, 12% of the children had mothers who reported to smoke during the first antenatal visit (missing 5%).

Table 19 England (N=591,092) and Sweden cohort demographics (N=2,192,476)

	ENGLAND				SWEDEN			
	Children exposed to any MMI *(N= 205,804)*		Children unexposed to any MMI *(N= 385,288)*		Children exposed to any MMI *(N= 421,887)*		Children unexposed to any MMI *(N=1,770,589)*	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Child sex								
Female	99,933	48.6	188,439	48.9	204,152	48.4	861,747	48.7
Male	105,871	51.4	196,849	51.1	217,735	51.6	908,842	51.3
Birth year								
1991-1995					100,835	23.9	477,537	27
1996-2000					99,762	23.7	355,470	20.1
2001-2005					104,977	24.9	388,106	21.9
2006-2011					116,313	27.6	549,476	31
Child ethnicity								
Asian/British Asian	4,980	2.4	26,382	6.9	-	-	-	-
Black/ black British	2,616	1.3	15,343	4	-	-	-	-
Mixed	5,642	2.7	13,110	3.4	-	-	-	-
Other	2,098	1	8,366	2.2	-	-	-	-
White	176,751	85.9	287,163	74.5	-	-	-	-
Unknown	10,282	5	24,178	6.3	-	-	-	-
Missing	3,435	1.7	10,746	2.8	-	-	-	-
Parental country of birth								
All known parents born outside Sweden	-	-	-	-	62,452	14.8	231,216	13.1
All known parents born in Sweden	-	-	-	-	299,591	71	1,337,130	75.5
One parent born outside, and one parent born inside Sweden	-	-	-	-	59,843	14.2	202,194	11.4
Missing	-	-	-	-	1	0	49	0
Maternal age at delivery (year)								
<20	10,636	5.2	13,791	3.6	-	-	-	-
20-29	94,213	45.8	148,481	38.5	-	-	-	-
30-39	92,633	45	204,938	53.2	-	-	-	-
>40	8,322	4	18,078	4.7	-	-	-	-
Maternal age at birth (years) Mean (SD)					29.4	5.6	30.2	5
Paternal age at birth (years) Mean (SD)					32.5	6.7	33.1	6
Maternal Mental Illness (MMI) †								
Any MMI	205,804	34.8		-	276,120	12.6		
Common	202,948	34.3		-	258,085	11.8		
Psychotic Disorders	4,095	0.7		-	34,950	1.6		
Addiction	6,854	1.2		-	27,912	1.3		
Other	6,105	1.0			32,032	1.5		
Maternal comorbid psychotic disorders								
No	-	-	-	-	421,648	98.3	1,758,995	99.8
Yes	-	-	-	-	7,081	1.7	2,328	0.1
Missing	-	-	-	-	309	0.1	2,115	0.1
Maternal comorbid common mental disorders								
No	-	-	-	-	379,097	88.4	1,730,105	98.1
Yes	-	-	-	-	49,632	11.6	31,218	1.8
Missing	-	-	-	-	309	0.1	2,115	0.1
Maternal comorbid other mental illness								
No	-	-	-	-	409,839	95.5	1,750,668	99.3
Yes	-	-	-	-	18,890	4.4	10,655	0.6
Missing	-	-	-	-	309	0.1	2,115	0.1
Child Cancer								
Any	314	0.1	637	0.1				
Leukaemia	126	40.1	254	39.8				
Eye, Brain & CNS	70	22.3	169	26.6				
Soft Tissue	9	2.9	40	6.3				
Thyroid	14	6.4	34	5.4				
Bone	20	6.4	22	3.5				
Other	75	23.9	118	18.6				

Table 19 Cont	ENGLAND				SWEDEN			
	Children exposed to any MMI *(N= 205,804)*		Children unexposed to any MMI *(N= 385,288)*		Children exposed to any MMI *(N= 421,887)*		Children unexposed to any MMI *(N=1,770,589)*	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Parental history of cancer								
No	-	-	-	-	407,978	96.7	1,715,155	96.9
Yes	-	-	-	-	13,909	3.3	55,434	3.1
Antibiotic use during pregnancy								
Used	74,641	36.3	93,130	24.2	-	-	-	-
Not Used	131,163	63.7	292,158	75.8	-	-	-	-
Maternal smoking††								
Never	77,195	37.5	201,257	52.2	-	-	-	-
Former	23,732	11.5	46,776	12.1	-	-	-	-
Current	96,185	46.7	90,891	23.6	-	-	-	-
Missing	8,692	4.2	46,364	12	-	-	-	-
Parental family disposable income in quintiles								
Q1 (lowest)	-	-	-	-	83,858	19.9	253,601	14.3
Q2	-	-	-	-	122,424	29	463,415	26.2
Q3	-	-	-	-	99,576	23.6	431,852	24.4
Q4	-	-	-	-	64,373	15.3	343,518	19.4
Q5 (highest)	-	-	-	-	47,142	11.2	261,235	14.8
Missing					4,514	1.1	16,968	1
Parental education								
Compulsory	-	-	-	-	46,533	11	88,860	5
Secondary	-	-	-	-	218,123	51.7	775,845	43.8
University	-	-	-	-	148,514	35.2	871,675	49.2
Missing	-	-	-	-	8,717	2.1	34,209	1.9
UK IMD quintile†††								
1 least deprived	29,024	14.1	66,745	17.3	-	-	-	-
2	37,535	18.2	76,654	19.9	-	-	-	-
3	39,272	19.1	73,084	19	-	-	-	-
4	42,984	20.9	81,628	21.2	-	-	-	-
5 most deprived	56,989	27.7	87,177	22.6	-	-	-	-
Region								
North East	5,672	2.8	6,979	1.8	-	-	-	-
North West	34,629	16.8	46,088	12	-	-	-	-
Yorkshire & The Humber	7,403	3.6	12,624	3.3	-	-	-	-
East Midlands	7,206	3.5	11,638	3	-	-	-	-
West Midlands	24,080	11.7	39,176	10.2	-	-	-	-
East of England	23,540	11.4	48,749	12.7	-	-	-	-
South West	27,936	13.6	43,730	11.4	-	-	-	-
South Central	29,550	14.4	50,981	13.2	-	-	-	-
London	20,142	9.8	75,957	19.7	-	-	-	-
South East Coast	25,646	12.5	49,366	12.8	-	-	-	-

† Note that maternal illness categories are not mutually exclusive
†† Any time during child's life
††† Based on GP location

7.5.2 Association between maternal mental illness and childhood cancer

Overall, 6,195 (England: 950; Sweden: 5,245) childhood cancers were observed. The mean age of cancer diagnosis in England cohort was 6.4 years (standard deviation= 5.3) and for Sweden it was 6.9 years (standard deviation=5.4). The cancer rate among children exposed to any MMI in England was 16.4, while in Sweden it was 17.6 per 100,000 person years.

Unadjusted and adjusted hazard ratios for the association between childhood cancer and MMI, in both cohorts, are presented in Table 20. The direction of the effect of different MMI on childhood cancer were similar in both cohorts, except the other MMI (personality and eating disorders) group. Children exposed to other MMI were observed to have reduced the cancer risk compared to unexposed children in English cohort however, this group was observed to have an increased cancer risk in Swedish cohort [aHR 0.85 (95% CI= 0.41–1.76) vs 1.28 (95% CI= 0.95–1.73].

Figure 12 illustrates the findings from the pooled analysis. Overall, in a pooled analysis, there was a little evidence of an association between common mental illness (depression/anxiety) and childhood cancers (aHR 1.05, 95% CI= 0.95–1.17). Children exposed to maternal psychotic disorders had reduced risk of developing cancer compared to children unexposed to maternal mental illness (aHR 0.72, 95% CI= 0.38–1.36). However confidence intervals crossing one indicate that there is no sufficient evidence to conclude with confidence that there is a reduction in the cancer risk in this group. Children exposed to maternal addiction disorders had 36% increased risk of developing childhood cancers (aHR 1.36, 95% CI= 1.01–1.84) and children exposed to other maternal mental illnesses (eating/ personality disorders) had 17% increased risk of childhood cancers (aHR 1.16, 95% CI= 0.79–1.72) however, confidence intervals crossing one warrants further evidence as it is not possible to conclude that this group has increased cancer risk. Finally, heterogeneity analysis for each type of maternal mental illness suggested a very low, non-significant level of heterogeneity in the pooled analysis (Table 21).

A post-hoc analysis was conducted for psychotic disorders to increase the statistical power. For this analysis, the Swedish cohort was extended to go back to those born from 1974. This increased the size of the Swedish sample from 2,190,052 to 3,090,672. The childhood cancer risk among children with maternal psychotic disorders was re-calculated in Swedish cohort (aHR 0.81, 95%CI= 0.61-1.08, Table 22) and meta-analysis was conducted again with new findings from Swedish cohort. The data from this post-hoc analysis was consistent with the primary finidngs and the meta-analysis increased statistical power, however it was still non-significant (p = 0.2836) indicating more data is needed to confirm this result (Figure 13).

7.5.3 Other risk factors for childhood cancer

In England cohort, maternal antibiotic use during pregnancy was significantly associated with increased risk of childhood cancer (aHR 1.15, 95% CI= 1.01–1.33). Also, older maternal age (i.e. 40≥) was a risk factor for childhood cancer, however further evidence is required as the confidence intervals crossed one (aHR 1.34, 95% CI= 0.87–2.07).

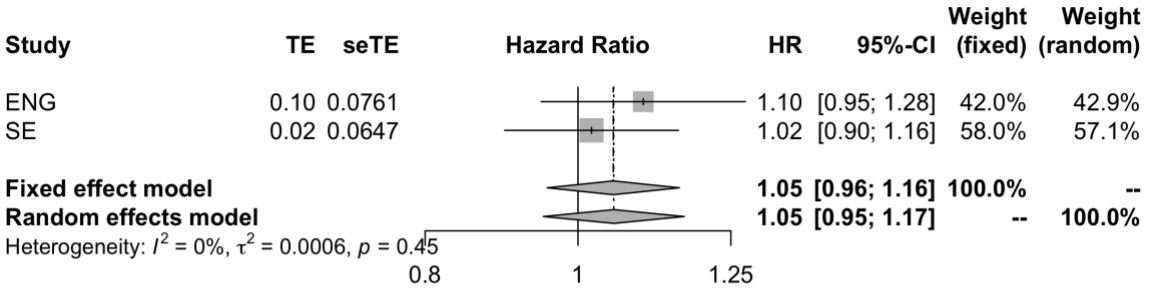
In Swedish cohort, parental history of cancer was associated with increased risk of childhood cancer (aHR 1.26, 95% CI= 1.09–1.45).

Table 20 Unadjusted and Adjusted hazard ratios showing the association between childhood cancer and *maternal mental illness in England and Sweden cohorts*

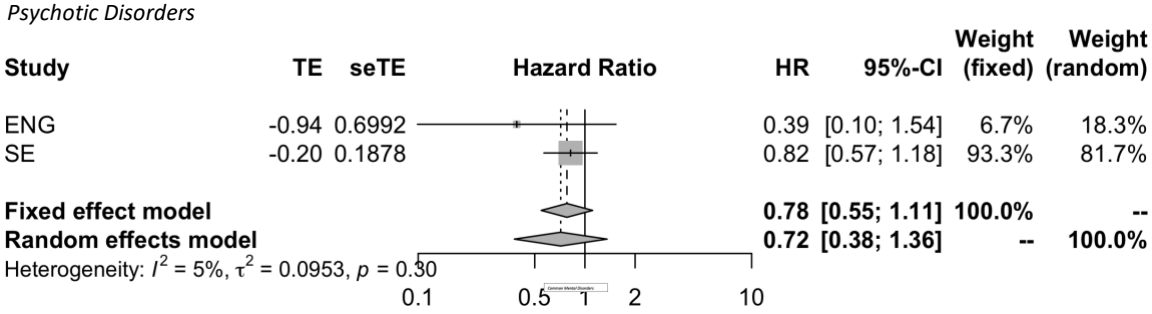
	Cohort	Person-Years	Cancer Cases	N	Cancer Rate (95%CI) *per 100,000 person-years*	Unadjusted HR (95%CI)	*p*	Adjusted HR† (95%CI)	*p*
Any MMI									
Unexposed	ENGLAND	4,187,574		637	15.2 (14.1-16.4)	REF	-	REF	-
Any Cancer		1,912,850		314	16.4 (14.7-18.3)	1.13 (0.99-1.30)	0.079	1.10 (0.95-1.28)	0.201
Unexposed	SWEDEN	27,053,054		4,926	18.2 (17.7-18.7)	REF	-	REF	-
Any Cancer		1,812,153		319	17.6 (15.8-19.6	1.04 (0.93-1.17)	0.490	1.02 (0.90-1.15)	0.765
Common MMI									
Unexposed	ENGLAND	4,215,125		642	15.2 (14.1-16.5)	REF	-	REF	-
Any Cancer		1,885,299		309	16.4 (14.7-18.3)	1.13 (0.99-1.30)	0.087	1.10 (0.95-1.28)	0.205
Unexposed	SWEDEN	27,217,961		4,956	18.2 (17.7-18.7)	REF	-	REF	-
Any Cancer		1,647,246		289	17.5 (15.6-19.7)	1.04 (0.92-1.17)	0.531	1.02 (0.90-1.16)	0.770
Psychotic Disorders									
Unexposed	ENGLAND	6,068,794		948	15.6 (14.7-16.7)	REF	-	REF	-
Any Cancer		31,631		2	6.3 (1.6-25.3)	0.42 (0.10-1.69)	0.223	0.39 (0.10-1.54)	0.182
Unexposed	SWEDEN	28,643,271		5,212	18.2 (17.7-18.7)	REF	-	REF	-
Any Cancer		221,936		33	14.9 (10.6-20.9)	0.87 (0.62-1.23)	0.436	0.82 (0.57-1.18)	0.301
Addiction									
Unexposed	ENGLAND	6,042,819		938	15,5(14.6-16.5)	REF	-	REF	-
Any Cancer		57,606		13	22.6 (13.1-38.8)	1.52 (0.88-2.64)	0.077	1.58 (0.91-2.75)	0.107
Unexposed	SWEDEN	28,698,245		5,207	18.1 (17.7-18.6)	REF	-	REF	-
Any Cancer		166,962		38	22.8 (16.6-31.3)	1.34 (0.97-1.84)	0.074	1.29 (0.93-1.79)	0.126
Other MMI									
Unexposed	ENGLAND	6,047,730		942	15.6 (14.6-16.6)	REF	-	REF	-
Any Cancer		52,694		8	15.2 (7.6-30.4)	1.00 (0.50-2.00)	0.999	0.85 (0.41-1.76)	0.659
Unexposed	SWEDEN	28,655,640		5,197	18.1 (17.6-18.6)	REF	-	REF	-
Any Cancer		209,567		48	22.9 (17.3-30.4)	1.34 (1.01-1.79)	0.046	1.28 (0.95-1.73)	0.103

† ENGLAND: Adjusted for child's sex, child's ethnicity, maternal age, maternal smoking during child's life, antibiotic use during pregnancy and region
† SWEDEN: Adjusted for child's sex, birth year, parental age at childbirth, parental country of birth, parental education, household disposable income in quintiles, parental history of cancer, maternal psychotic disorders at birth, maternal common mental disorders at birth, maternal other mental illness at birth, paternal psychotic disorders at birth, paternal common mental disorders at birth, paternal other mental illness at birth

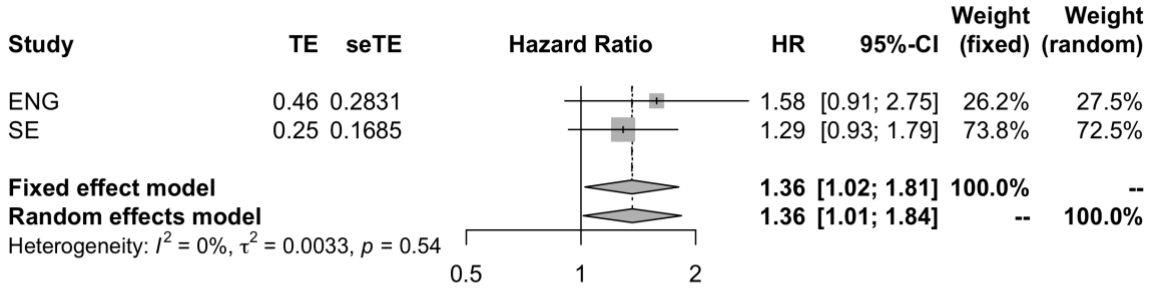
Common Mental Disorders



Psychotic Disorders



Addiction Disorders



Other Mental Illnesses

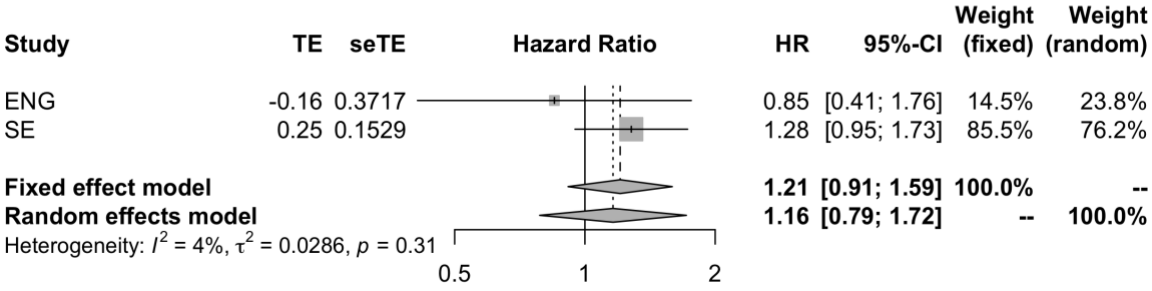


Figure 12 Forest plots of association between any MMI and any childhood cancer.

Table 21 Summary of meta-analysis results

	Effect size estimates- Fixed Effects model (FE) and Random Effects model (RE)	95% CI	Significance of model	Heterogeneity			
				τ^2	I^2 (%)	Cochran's Q	*p-value*
Any MMI	FE: 1.05	0.96- 1.16	0.2836	0.0007	0	0.61	0.436
	RE: 1.05	0.95- 1.16	0.3098				
Common MMI	FE: 1.05	0.96- 1.16	0.2960	0.0006	0	0.57	0.4497
	RE: 1.05	0.95- 1.17	0.3199				
Psychotic Disorders	FE: 0.78	0.55- 1.11	0.1707	0.0953	5.1	1.05	0.3047
	RE: 0.72	0.38- 1.36	0.3063				
Addiction	FE: 1.36	1.02- 1.81	0.0336	0.0033	0	0.38	0.5381
	RE: 1.36	1.01- 1.84	0.0404				
Other MMI	FE: 1.21	0.91- 1.59	0.1847	0.0286	3.6	1.04	0.3084
	RE: 1.16	0.79- 1.72	0.4526				

Table 22 Post Hoc Analysis- Swedish cohort

Cohort	Maternal mental illness		n cancer cases	Person-years	Cancer rate per 100,000 person-years (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
1974-2011	Psychotic disorders	No	10,297	57,763,365.6	17.8 (17.5-18.1)	**REF**	**REF**
		Yes	56	387,779.6	14.4 (11.1-18.8)	0.83 (0.64-1.09)	0.81 (0.61-1.08)
1991-2011	Psychotic disorders	No	5,212	28,643,270.9	18.2 (17.7-18.7)	**REF**	**REF**
		Yes	33	221,936.1	14.9 (10.6-20.9)	0.87 (0.62-1.23)	0.82 (0.57-1.19)

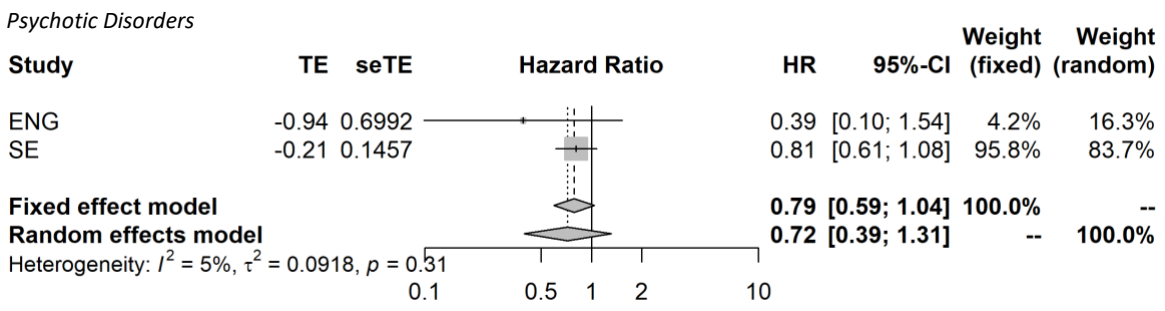


Figure 13 Post Hoc Analysis - Forest Plot for Psychotic Disorders

7.6 DISCUSSION

7.6.1 Main findings

This is the first large study to investigate the effects of different types of maternal mental illnesses on childhood cancer. Performing a meta-analysis in two national cohorts, we report that children exposed to maternal addiction disorders had an increased cancer risk compared to unexposed children. There was some evidence that children exposed to maternal psychotic disorders may have reduced cancer risk compared to children with non-mentally ill mothers, however wide confidence intervals indicated a low precision of this estimate therefore it is not possible to say with confidence that there is a decrease. There was little evidence that children with maternal common mental illness had a different risk compared to unexposed children.

The English cohort's cancer rate was lower when compared to England's national cancer registry rate for 2017 (15 vs 19 per 100,000 person years) [110]. There might be several reasons for this. Firstly, we only relied on cancer diagnosis from HES hospital inpatient dataset, whereas England's national cancer registry defines cancer from multiple sources [289] including as pathology reports, molecular testing which means that in our cohort there could be number of children awaiting cancer diagnosis defined as having no cancer. Moreover, our cancer rates cover for children aged between 0 to 18 while English cancer registry age range is 0 to 24 years old. Also, it is possible that there are some cancer cases diagnosed and treated in private hospitals which are not recorded in HES. Finally, some cases of cancer may be missed if codes relating to cancer diagnosis or surgery was not used.

7.6.2 Research in context

This is the most comprehensive study of the link between maternal mental illness and childhood cancers to-date. Previous studies have focused on the impact of maternal addiction disorders on childhood cancers [38,39,118,119], however we are not aware of any studies that have investigated the link between maternal common mental illness (depression/ anxiety) or maternal eating and personality disorders and childhood cancers.

Our results are consistent with those of previous studies investigating the effect of maternal addiction on childhood cancer. Using data on 785,438 children aged 0 to 5 in Canada, Auger *et* al [39] reported increased risk of leukaemia among children exposed to maternal illicit drug use before or during pregnancy, albeit with confidence intervals that cross one (HR 1.63, 95% CI=0.79–3.36). In a much smaller sample case-control study (N=1,042), Bluhm *et* al [38] found an increased risk of neuroblastoma among children with mothers who reported use of illicit drug use around their pregnancy period (OR 1.82, 95% CI=1.13–3.00). Although our pooled analysis was not able to identify different types of cancer due to small cell counts, we found that there is a significant increase in cancer risk among children exposed to maternal addiction disorders (HR 1.32, 95% CI=1.10–1.59).

Currently, there is only one study that has investigated parental serious mental illnesses (schizophrenia, bipolar disorder, and unipolar depression) and offspring cancer risk and they reported no or a weak association (IRR 1.00, 95% CI=0.96–1.04) [290]. However, this study followed offspring into adulthood, whereas we only included children up to age 18. Moreover, authors included paternal as well as maternal mental illness, which may have diluted the effect of maternal mental illness. Finally, authors included depression in their exposure definition which may weakened the effect of serious mental illness on child cancer risk. Apart from this study, there are no other studies that examined the role of different types of maternal mental illness on child cancer risk.

Our results regarding maternal psychotic disorders and child cancer risk indicate that children with mothers experiencing psychotic disorders may have reduced risk of cancer, although more data is needed to confirm this result (HR 0.72, 95% CI=0.38–1.36). A post-hoc analysis used more children to increase the statistical power for those exposed to maternal psychotic disorders, and it showed a poor evidence of a reduced risk of cancer. However, there are studies that report reduced risk of cancer among first degree relatives of people with schizophrenia. In a retrospective population based registry study, Levav *et* al [114] reported that parents and siblings of people with schizophrenia were found have reduced risk of cancer compared to general population in a sample

of 30,788. Mothers and fathers roughly had similar reductions in the cancer risk [Standardised Incident Ratio (SIR) 0.86, 95% CI=0.79–0.94 for mothers; SIR 0.84 95% CI=0.76–0.91 for fathers]. The greatest risk reduction was observed among siblings (SIR 0.74, 95% CI=0.63–0.86). In a similar study by Ji *et* al [115], significant reduction was reported in the cancer risk among parents (SIR 0.96, 95% CI=0.94–0.98) and siblings (SIR 0.92, 95% CI=0.89–0.96) of people diagnosed with schizophrenia in Sweden. Our findings among children with maternal psychotic disorders are in line with these studies which have consistently reported reduced cancer risk among first degree relatives of people with psychotic dioserders.

Furthermore, people with schizophrenia have been found to have a reduced lung cancer risk despite the fact they smoke twice more than general population [122]. As a result, GWAS studies have been conducted to find potential genetic markers for both schizophrenia and reduced cancer risk [291–293]. From these studies, gene P53 has been found to be associated with both schizophrenia and reduced cancer risk. Gene P53 is a tumour suppressor gene, which controls the cell divisions that are happening too fast, but this gene is also strongly associated with the schizophrenia [124]. Increased levels of P53 gene are found among people with schizophrenia as this gene is argued to elevate the cell death in vital areas in the central nervous system, which is thought to have a role in aetiology of schizophrenia [294].

The increased risk of childhood cancer among children exposed to maternal addiction disorders could be explained by the teratogenic effects of alcohol, smoking and illicit drugs. Exposure to alcohol, smoking and illicit drugs in utero can cause DNA damage and alter the immune system, which may play a role in development of childhood cancers [126].

To better understand the mechanisms between maternal mental illness and childhood cancers, future research should investigate mothers during pre-conception and pregnancy periods because the risk of childhood cancer is highest during the first few years of life, which means maternal exposures during pre-conception and in utero may be linked to childhood cancers [295].

Nevertheless, the rarity of childhood cancers in general makes it very difficult to investigate the possible mechanisms.

7.6.3 Strengths and weaknesses

One of the biggest strengths of this study is that we conducted a pooled analysis which allowed us to investigate a rare disorder, like childhood cancers because, individual studies are often yield inconclusive results. Also, by investigating two distinct populations with different data collection methods, the conclusions that could be drawn from any one population are strengthened.

This collaboration study uses electronic health records from England and Sweden. Electronic health records significantly minimise the biases associated with prospective cohort studies which are usually in small sample sizes, and with selection biases due to loss to follow-up, as well as recall or self-reporting biases.

However, there are a number of limitations that can be associated with this study. Firstly, in both cohorts it is likely that some mental illnesses may have remained undetected because they did not seek help for their mental illness. This misclassification will result in underestimated effects of maternal mental illness on childhood cancer.

Secondly, in the UK, cancer diagnosis was retrieved from hospital inpatient data which was only available for England, because remaining nations (i.e. Scotland, Wales and Northern Ireland) have different hospital data recording systems and these are not linked with CPRD. As a result, the cohort's statistical power was reduced as there were no hospital data from Scotland, Wales and Northern Ireland. Despite the fact that approximately 85% of all UK residents reside in England, the number of English GP practices contributing to the CPRD is decreasing over time while the number of Scottish GP contributing is increaing. Therefore, not having access to hospital data from Scotland as well as Wales and Northern Ireland was one of the limitations of this study. Also,

English cohort was restricted in the number of children to link with HES dataset, which may have led missing children with cancer.

A further limitation in this study was in the definition of common mental illnesses in two different national datasets. In the English cohort, primary care was used to identify mental illness, whilst in the Swedish cohort the majority were identified in secondary care. Therefore, the severity of mental illness is likely to be less in English data, where the threshold for accessing services is lower. This would mean that any effect that common mental illness has on childhood cancer might be more evident in Swedish data, as most effects show a dose-response relationship [296]. However, we did not see any evidence for a dose-response relationship and both results were consistent with each other and consistent with the finding of no, or small effect.

Another limitation that the English cohort faced was around potential confounders that are not captured in primary and secondary care. Some of these confounders were maternal education, employment status, social support and household income, all of which were available in Swedish cohort. However, in both cohorts, maternal exposure to pesticide, radiation and environmental pollution were not possible to capture. The Swedish cohort did not include mental illness diagnoses from primary care which may have led them to miss certain cases, especially the more common mental illness diagnoses.

Finally, despite creating the largest cohort to date to investigate the risk of childhood cancer among children with MMI, our findings still lacked statistical power. This means the evidence provided in this study is not conclusive and more data would be needed to make more robust conclusions. This study revealed the rarity of childhood cancer; more international collaborations are vital to provide more robust evidence with greater statistical power.

7.6.4 Public health implications

Families and their children are provided support to access healthcare services by the Healthy Child Programme [9], which is one of the public health interventions targeting families in England. However, this programme does not link maternal mental illnesses and childhood diseases. Our study highlights that children exposed to maternal addiction have significantly increased risk of developing cancer, a significant driver of childhood mortality.

In more general terms, public health policies and intervention programmes would be more effective if they are modified to provide additional support for mothers with addiction disorders. Tailored information is important for this group because people with mental illness are less likely to adopt preventative health measures or benefit from public health campaigns [191]. If mothers at greatest risk are not able to access the available healthcare services, then it would be very difficult to reduce the health inequalities.

This study also reports that in England, antibiotic use during pregnancy increases the child's risk of cancer. In 2019, the English government published a five-year action plan to tackle the antimicrobial resistance, with an aim to reduce the antibiotic use 10% by 2024 [297]. Our study recommends that women during their pregnancies should be acknowledged in future antibiotic related prevention programmes.

7.6.5 Conclusion

Aetiological mechanisms in childhood cancer remain obscure; however, this study shows that maternal addiction is a risk factor for childhood cancer in offspring while maternal psychotic disorders may have a protective effect. Future research should focus on conducting more collaboration studies in this area and identifying unmeasured risk factors which may shed a light on aetiological mechanisms. Public health policy and intervention programmes should consider specifically tailored approaches to vulnerable mothers and their families.

CHAPTER 8- GENERAL DISCUSSION

This chapter summarises the key findings from five research papers which have been submitted or published. Strengths and weaknesses of the thesis will be described before considering the implications of the findings and suggestions for future research.

8.1 SUMMARY OF RESULTS

This thesis investigates the effects of maternal mental illness on their offspring's physical health outcomes in the UK. It presents analyses on three main, separate outcomes for children with maternal mental illness: vaccination, atopy and cancer; and two smaller analyses on childhood obesity as an outcome and of perinatal smoking as an additional exposure. The analyses focus on data from a large UK primary care cohort. The results presented here highlight the importance and limitations of utilising routinely collected health data to explore how maternal mental illness affects the childhood health.

Chapter 3 describes how children exposed to maternal mental illnesses are less likely to complete their vaccination schedules in the UK by age two and five. Specifically, children exposed to common maternal mental illness (i.e., depression/anxiety) were found to be 14% less likely to have completed their essential vaccination schedule in both age groups (aOR 0·86, 95% Cl=0·84–0.88). The lowest uptake of vaccination was observed among children exposed to maternal alcohol and drug misuse disorder who were 50% less likely to complete recommended vaccination schedules in both age groups (aOR 0·50, 95% Cl=0·44–0·58). Moreover, for the first time, we were able to examine the effect of the Lancet's Andrew Wakefield MMR vaccine scandal in a large cohort study; we observed that uptake of MMR vaccination significantly reduced post-1998 (i.e. after the MMR scandal) among children with mentally well mothers and that the relative risk between the two groups decreased. Also, there were some evidence that the MMR vaccine uptake reduction was slower amongst children with maternal mental illness than with healthy mothers, and that the recovery was also slower for this group**.** Finally, this study estimated that if children with MMI had

the same vaccination rates as children without maternal mental illness, approximately five thousand more children per year would be vaccinated in the UK.

Chapter 4 examined the feasibility of investigating the effect of maternal mental illness on child's overweight/obesity. The results of indicated that more than half of the cohort children did not have weight or height recorded and 43% of those who had BMI data were overweight or obese, far higher than national prevalence rates. This feasibility study, therefore, suggests that it is not possible to conduct an analysis to investigate the maternal mental illness effects on child's physical health outcomes because the available sample is biased. This highlights an urgent need for consistent data recording of child weight and height measures across the primary care cohorts in all children. New public health and department of education legislation has since instituted primary school recording of weight, height and BMI for all children aged 5, 6, 10 and 11 through the National Child Measurement Programme [233]. Linkage to this data has not been established from primary care but would be a vital resource for public health research.

Chapter 5 shows that children's risk of atopic disorders differs based on the type of maternal mental illness to which they are exposed. Specifically, children exposed to maternal common mental illnesses had a 17% increased risk of developing asthma and allergic rhinitis (aHR 1.17, 95% CI= 1.13–1.21) and a 26% increased risk of hospital inpatient admission for asthma (aHR 1.26, 95% CI= 1.17–1.36). However, children exposed to maternal substance and alcohol misuse disorders were 9% less likely to present with eczema (aHR 0.91, 95% CI=0.85–0.97) and 35% less likely to develop food allergies (aHR 0.65, 95% CI=0.45–0.93).

Maternal smoking is a very important risk factor for many childhood disorders, especially for asthma. Therefore, it was vital to capture maternal smoking status for the atopy study in Chapter 5. Once an algorithm for capturing maternal smoking had been developed, it was a good opportunity to explore smoking during the perinatal period. Thus, **Chapter 6** presents a comparison of perinatal smoking among mentally ill and non-ill mothers. The results show that 37% of women with mental

illness and 19% of women without mental illness smoked during perinatal period. Amongst those who smoked prior to pregnancy, 32% of women with mental illness versus 43% of women without mental illness, stopped smoking during pregnancy.

Finally, **Chapter 7** illustrates the risk of cancers among children exposed to maternal mental illness compared to children unexposed to maternal mental illness in the two national cohorts of England and Sweden. The pooled analysis results revealed that children exposed to maternal addiction disorder had a 36% increased risk of childhood cancer (HR 1.36, 95% CI=1.01–1.84), children exposed to other maternal mental illnesses (i.e. personality and eating disorders) had a 16% increased cancer risk (HR 1.16, 95% CI=0.79–1.72) and children exposed to common maternal mental illnesses (i.e. depression and anxiety) had a 5% increased risk of cancer (HR 1.05, 95% CI= 0.95–1.17). Surprisingly, we report that across both country cohorts, children exposed to maternal psychotic disorders showed nearly a third reduced risk of any cancer diagnosis by the age of 18 (HR 0.72, 95% CI=0.39–1.34). These findings need to be confirmed using larger datasets and longer term follow up so we can distinguish whether these effects pertain for all cancers or are driven by particular types; or whether or not factors such as maternal and paternal age influence these risks; or offspring gender/sex. Only maternal addiction disorder had enough numbers to provide robust narrow confidence intervals. Further investigation is needed for common mental illnesses, psychotic disorders and other mental disorders because, here, the wide confidence intervals as well as confidence intervals that cross one indicated a lack of statistical evidence to confirm these observations.

8.2 STRENGTHS

The use of data from CPRD, which is one of the world's largest anonymised primary care databases, as described in Chapter 2, allowed this thesis to assess extensively the effects of maternal mental illness on different child physical health outcomes in far more detail than previously.

The results presented in this thesis have good generalisability, because the CPRD dataset has been shown to be representative of the general UK population in terms of age, sex and ethnicity [143]. This is a major advantage when compared to other epidemiological cohorts in this area, where issues like selection bias and the healthy-cohort effect means the study sample is healthier than general population where they are drawn from [298]. This may lead to an over or under-estimation of associations thus, poor generalisability was observed in various studies that examined maternal depression effect on childhood vaccination uptake [54], childhood obesity [139] where the study samples of these studies were skewed towards educated mothers from middle/high socio-economic class. Furthermore, CPRD data are derived from clinical events, and therefore reflects real health-care. Therefore, results from this thesis have high reliability and relevance to health service planning, decisionmakers and public health policy.

The recall errors or recall bias which are associated with self-reported data are less likely to be an issue in CPRD because most of the data in CPRD is recorded by healthcare providers as a part of their routine healthcare service recording. Observer bias (when the outcome assessment is influenced based on observer's conscious or unconscious predispositions) and Hawthorne effect (change in behaviour when participant knows s/he being observed) are also less likely to be a problem in CPRD data, because, as mentioned in Chapter 2, data is not collected for research purposes and neither practitioner nor patient are in a situation where these type of bias could occur. However, these bias exist in the studies examined effects of maternal mental illness on childhood vaccination uptake [54,299] childhood atopic disorders [89,91–93,95,97–99], child obesity [64,65,67,139] and childhood cancers specifically among children exposed to maternal alcohol and illicit drugs [38,118,300].

Cohorts were included only if their GP practices met the CPRD's quality criteria based on practice and patient level (refer to Chapter 2). This ensures reliability and validity of the studies presented in this thesis as it heavily depends on the quality and completeness of the data utilised for research.

Linkage to external datasets like HES and IMD creates an opportunity to follow patients in secondary care while gathering important demographic information. This allowed for specific questions to be addressed. For instance, in the atopy study (Chapter 5) linkage to HES data allowed for the investigation of the inpatient admission related to childhood asthma among children exposed and unexposed to maternal mental illness, which has not been examined before. Similarly, in the cancer study (Chapter 7), a linkage to inpatient admission was essential because when a GP suspects the patient may have a cancer, s/he refers the patient to the secondary care to be seen by a specialist and for a diagnosis to be made.

8.3 LIMITATIONS

It is important to acknowledge a number of limitations that arise because the data are not collected for research purposes. Completeness and accuracy of the electronic health care data is influenced by a number of factors that are not in control of the researchers. For example whether patient's present to their clinician, limited time of the GPs to record patient's data [301] or financial incentives for data recording [302], which may affected some of the results of the studies presented in this thesis. For instance, we were not able to investigate the association between maternal mental illness and child obesity, because child's weight is only partially recorded in primary care (see Chapter 4) and quality of the existing data on child's weight was not sufficient enough to conduct a research. Smoking status of mothers was another lifestyle variable that was complicated to work with. In the UK, smoking status of the patients are generally assessed when they register to a new GP practice and also recommended to be assessed every 12 months, for which GPs receive a financial reward [303]. Yet, it was shown that GPs can significantly vary in their smoking status recording as the it was found that GP practices did not record one quarter of newly registered patient's smoking status [23]. Such results may reflect the problems with inadequate terminology, guilt associated with this behaviour and frequent changes in the smoking behaviour. Moreover, it was not possible to retrieve smoking status of the mother from one source as the missingness was over 50%, thus we had to develop a complex algorithm to capture the maternal smoking from various data sources (see subsection 2.3.2).

In CPRD-GOLD, the UTS date is a practice-level quality indicator (see subsection 2.1.2) that leads to left-censoring. Any recorded data before the UTS date of GP practice is accepted as not reliable and should be not used, which means left-censoring (see Methods subsection 2.2). However, left-censoring as a result of UTS date was not a serious limitation for patients registered from 2000 and onwards, because we observed that the difference between the UTS date and patient registration date consistently dropped. This shows that the GP practices started to use electronic healthcare system more proficiently and fulfilled the CPRD's data quality criteria for research. This means that from 2000, the number of GP practices contributing research quality clinical data to the CPRD increased.

Left censoring also existed in the studies that utilised HES linkage. Even if linkage to HES is a big advantage, it does not cover exactly the same period of primary care data. Inpatient hospital admission, A&E and outpatient services are all secondary care units and they have different data collection start dates. In this thesis, mainly inpatient hospital admission data was used, and first data collection for this unit started in in April 1997, which means data prior to this date is not available in HES. Data collection in other units started even later; for instance, outpatient care data was collected for the first time in April 2003 and A&E care in April 2007. Moreover, HES data was only available for English region. In other words, no data was available from Scotland, Wales and Northern Ireland, and this caused a significant drop in the sample size and affects the generalisability of the results, which is another weakness in studies linking to HES.

Identifying mental illness in primary care data was another difficulty I experienced during this thesis. Mental health data in primary care is complex; it varies depending on the GP's coding reliability and behaviour. A coding for a mental illness diagnosis was sufficient to identify mothers with mental illness; however, Rait *et* al [161] reported that, from 1996, there was a systematic reduction in mental illness diagnosis codings in the record; and an increase in mental illness symptom records in the UK general practices. Also, since the introduction of the QoF in 2004, common mental illnesses, such as depression and anxiety, are less likely to be recorded as a diagnosis but, instead, are recorded as symptoms [162,305]. One of the reasons for reporting

mental illness symptoms instead of recording a diagnosis in primary care is that standard diagnostic interviews are not routinely used by GPs [306]. Rather, mental illness and particularly common mental disorders presented in primary care are described as ‘stress’ or ‘sadness’, ‘inability to cope’, ‘low mood’ [307]. Also, GPs also may prefer to record symptoms of mental illness, rather than a diagnosis as they would like to avoid labelling people if they are presenting for the first time or with only mild mental health symptoms [308]. This meant that it was not going to be enough to use mental illness diagnosis alone to identify mothers with mental illness and their exposed children. Therefore, I worked with our CAPRI research team and developed a sophisticated algorithm to capture mental illness using four different clinical data fields (see subsection 2.3.1). This highlights how identification of mental illness in primary care for research purposes is not straightforward and that it requires a group of experts in the fields of psychiatry, primary care and epidemiology.

Although the UK primary care coding system changed to SNOMED-CT in 2018, Read codes were utilised in this thesis to identify exposure and outcomes. This involved number of challenges. First, one condition could be recorded in many different ways, solely depending on the GP’s decision. This meant that different Read codes could define one condition (e.g. E107.11 and Eu25211 for cylic schizophrenia). This resulted in the timeconsuming and laborious task of identifying Read code lists for each condition. This was done either by collating already contsructed lists of codes (e.g. from clinilalcodes.org) or by hand searching the list of read codes.

Another limitation of the CPRD data was the lack of adequate recording of ethnicity. Ethnicity was missing for 39% of children. Furthermore, people with mental illness from Black,Asian and Minority Ethnic (BAME) groups are less likely to be detected and treated despite the fact they may be more likely to have higher burden of mental illnesses compared to White ethnic individuals [309]. Therefore, the studies presented in this thesis may have systematically underreported the effects of mental illness in mothers with ethnic minority background. It is important to acknowledge that BAME people in the UK face multiple barriers accessing healthcare [212,213]. There is substantial evidence that these barriers involve lack of consideration of the social, cultural and linguistic needs

of patients from ethnic minorities within healthcare and mental healthcare services [310,311], as well as cultural-related stigma [312], fear [313], language barriers [314] and a lack of awareness by clinicians about mental illness among people from BAME communities [315]. Therefore, having unrepresentative or inadequate ethnicity data in CPRD may reflect the fact that barriers to health care access in BAME women needs to be addressed urgently. If successful, then we may see an improvement in ethnicity recording in primary care among this group of women. If we had representative ethnicity data, we could have examined the possibility of an interaction between genetic and environmental factors. We also may have had the chance to conceptualise risk factors that may vary based on ethnicity, so that intervention and prevention programmes could have been tailored based on this information.

Although, CPRD provides linkage between mothers and their babies, there remains no linkage between children and fathers. This is an important aspect to be considered when investigating the children's physical health outcomes and our colleagues in Sweden were able to investigate both maternal and paternal mental illness effects on childhood injuries [272]. They reported that paternal mental illness also influenced risk of childhood injuries. If we had information on fathers, then maybe we could have developed a better understanding about the risk factors and, thereby, possible mechanisms.

Finally, some important potential confounders were not available in the CPRD. These particulary included social determinants of health such as maternal education, household income, parental employment, housing, social support, social class, social relationships, cultural beliefs and parenting practices. These factors may play an important role in the physical health outcomes that were investigated in this thesis. For instance, if we had had information on these social determinants, we would have been able to investigate possible reasons for the inverse relationship between maternal addictions, childhood eczema and food allergies (Chapter 5). We should also have had greater insight into the mechanisms between common maternal mental diorders and childhood atopic disorders.

8.4 IMPLICATIONS OF FINDINGS

This thesis presents findings that maternal mental illness is associated with reduced vaccination uptake in exposed children; as well as different types of childhood physical health inequalities for exposed children including atopic disorders and cancers.

Chapter 3 reports how, in the first five years of life, children exposed to maternal mental illness in the UK have reduced vaccination uptake compared with children of well mothers. Also, roughly 5,000 children per year would have been vaccinated if children exposed to maternal mental illness had the same vaccination rates as the unexposed children.

This study provides robust evidence that there is an urgent need to tailor public health campaigns to mothers with mental illness about vaccinations so that these mulitply disadvantaged children can at least benefit from freely available preventive health measures. These results are particularly prescient in the context of COVID-19 [316]; and reports of a 20% reduction in childhood vaccination in England since the peak of the pandemic in March 2020 compared with March 2019 [222]. We also know that 'lockdown', following COVID-19, has been associated with a significant increase in mental distress in women; and in parents with pre-school aged children in the UK [224]; the group of children who need to receive vaccinations. Therefore, our results suggest we should anticipate further reductions in vaccination uptake among children below five years of age because of the COVID-19 pandemic. Public health policies and campaigns need to consider mothers with mental illness when developing policies to target children at risk of not receiving preschool vaccinations. It is also prudent to consider that access to other preventive public health messages and interventions may also be reduced in children exposed to parental mental illness.

Chapter 4 suggested that, currently, it is not feasible to conduct research examining the effects of maternal mental illness on childhood obesity using CPRD. A large amount of child weight data are missing and the sample with weight/BMI data recording in primary care is biased towards overweight and obese children. While childhood obesity is one of the biggest public health

concerns currently in the UK, unfortunately, weight and BMI has not been recorded routinely in primary care. One of the reasons for this lack of routine data collection might be that the UK National Screening Committee (NSC) does not recommend obesity screening among children aged under 11 years old [317]. The committee's reasoning behind this advice is that they believe there is not enough evidence that child obesity would lead to other health problems in later life. However, there is clear evidence that children with obesity or problems of over eating are at high risk of developing type-II diabetics and cardiovascular disorders [318–320]. They may also be at greater risk of developing mental illness in adulthood. Also, according to the National Child Measurement Programme report published in 2017, there was a significant increase in children with type-II diabetes treatments as a result of obesity in England [321]. Another reason that the committee provided was that they are concerned about the reliability of screening tools to identify childhood obesity. The complexity of identifying childhood obesity using BMI as a measure is acknowledged; however, despite this complexity, there are reliable tools such as the British 1990 (UK90) growth chart and UK-WHO growth chart to identify child obesity. These growth charts can be used for children from birth until the age 18 and are recommended by the Royal College of Paediatrics and Child Health (RCPCH) [322,323]. Yet another reason worth mentioning is that there is no financial incentive for GP practitioners routinely to record the child's BMI [324] which may influence data recording. Of note, this gap in information is now being addressed within primary school aged children who are being monitored routinely for weight and height at aged 5-6 and 10-11 years through National Child Measurement Programme in England only [233].

According to the UK NICE guidance, cooperation should exist between NHS and health care practitioners including GPs, local authorities, nurseries and care-centres to prevent childhood obesity [325]. In this guidance, it states that children identified as obese or overweight should be offered support by an appropriately trained healthcare practitioner. However, this recommendation lacks detail about the content and timing of the support. Also, there is no information on the level of knowledge of the healthcare practitioners about the health risks of childhood obesity, which may explain why primary care settings are not utilised for childhood obesity interventions [326].

There are clearly important information gaps in health care organisations about childhood obesity. If child screening and recording of obesity/overweight is not recommended or encouraged, then tackling childhood obesity is challenging. There is strong evidence that early intervention is key in tackling childhood obesity especially for children from ethnic minority groups [327]; routinely collected data would allow monitoring children's development and assessment of the effectiveness of intervention and prevention programmes.

Routinely collected data would not only be effective in tackling child obesity through intervention and prevention programmes but also play a key role in management of other conditions in primary care such as food intolerance, drug dose calculations, self-harm assessment, child neglect, eating disorders/disordered eating behaviours; and precocious or delayed puberty, as a child's history of height and weight records are often important to diagnose and manage these conditions.

In the light of the feasibility study results, we recommend that child weight, height and BMI data should be regularly recorded in primary care; this would reduce stigmatisation and allow normalisation of weight and height recordings in routine care; it would also develop useful future linkages between NCMP and primary care. Primary care is the common place for the four nations of the UK routinely to record child's height and weight; such data would allow us to see the wider picture of childhood obesity in the UK and, thus, more efficiently monitor it; explore risk factors including the maternal mental illness and evaluate prevention programmes.

Finally, concerns have been expressed about mothers being blamed for childhood obesity. Clearly, there is a great deal of stigma involved and weight in young women especially remains a sensitive topic. In addition to improvements in data recording, supportive, clear and collaborative language is vital to use when discussing healthy child weight with families; even if child measurement becomes a routine check in primary care, many families may be reluctant to engage because of guilt, shame and blaming attached to childhood overweight and obesity. Recognising disorderd eating as a potential early marker of poor mental health may be an important way to raise awareness.

Atopic disorders are very common in childhood. **Chapter 5** illustrates that exposure to maternal common mental disorder increases the child's risk of developing asthma and allergic rhinitis. Also, children with asthma who are exposed to common maternal mental illness had increased risk of being admitted to hospital because of their asthma when compared to children with asthma but unexposed to maternal mental illness.

Per contra, children exposed to mothers with addiction disorders had *reduced* risk of presenting with an eczema diagnosis in primary care; but an increased risk of being admitted to hospital for skin disorders. This finding should be taken into consideration in public health policies and practice guidelines: mothers with addiction disorders may be less observant about their child's eczema symptoms and seek help only when their eczema worsens.

There is clear evidence and, in our view, an urgent need to expand current preventative programmes and to tailor them for, and target vulnerable mothers and their children. It is a fact that mothers suffering from mental illness and their children experience health inequalities; Marmot's [328] proposal to tackle health inequalities should be adopted in preventative programmes. Tailored information with support should be provided to this group because there is clear evidence that people with mental illness struggle to adopt preventative health measures through existing, widely available public health information and interventions e.g. smoking cessation [191]. As a result of this failure to make use of public health messages, the paradoxical result of which may be an *increase* in health inequalities for the groups most in need.

Maternal smoking during pregnancy (as well as during child's life) is a clear causal risk factor for a wide range of childhood disorders, including premature mortality from sudden infant death syndrome or SIDS. Atopy study in Chapter 5 reports that maternal smoking remains a risk factor for childhood asthma. In **Chapter 6,** rather than a specific childhood outcome, a very important risk factor for childhood disorders was investigated in detail. The overall aim of this study was to report perinatal smoking rates of women with and without mental illness in the UK using primary health

care records. Results from this study indicated that, overall, smoking rates among women during the perinatal period were high but, they were significantly worse among women with mental illness. Moreover, it was observed that women with mental illness were significantly less likely to stop smoking during pregnancy when compared to women without mental illness. Conception and early pregnancy represent the most successful times for smoking cessation overall. Therefore, this means that the infants of women with mental illness remain exposed to a wholly modifiable risk factor for childhood disorders as well as to the potentially less modifiable factor i.e. maternal mental illness itself. These results indicate that smoking cessation/or information about the harms of smoking may be relatively underprioritised by the public, by clinicans and by services compared to information, perhaps, about far less well evidenced or important lifestyle factors such as dietary/minor nutritional components or caffiene intake in pregnancy [e.g. 20].

Smoking cessation programmes require urgent attention in order to target women with mental illness. Although in the UK, smoking cessation services are provided for free by the NHS, people with mental illness have difficulties to access these services [261]. Specifically, women with mental illness who smoke would benefit from a tailored smoking cessation programme where she would receive mental health interventions along with smoking cessation programmes which included personal in-home supports shown to be more likley to lead to successful smoking cessation in people with mental illness; the cost-effectiveness of such approaches is well recognised to improve child, obstetric and mental health outcomes [329]. For instance, Gilbody *et* al's [261] smoking cessation for people with severe mental illness (SCIMITAR+) could be adapted to all women of reproductive age but especially focussed on pregnant women with mental illness.

Finally, **Chapter 7** suggests that exposure to maternal addiction disorders significantly increases a child's risk of cancer. These results were obtained from two national cohorts in England and Sweden; and indicate that, in both countries, a specific emphasis should be given to mothers who are experiencing addiction disorders who are also likely to experience other comorbid mental (and physical) illnesses. This infomration should usefully enrich the knowledge base of healthcare practitioners such as midwifes, GPs, health visitors - that the risk of cancer is increased for

offspring of mothers with addiction disorders. Also, the provision of comprehensive social and mental health supports for a mother with addiction disorders has increasingly been shown to be cost-effective [330]. The family drug and addiction courts (FDAC) are very effective ways to improve family outcomes among this group because FDACs play an important role in diverting parents to rehabilitation and detox programmes and support them during this process; this has resulted in significant success with rehabilitation and return of their children from social services [330]. Models that build on the FDAC collaborative approaches might be an interesting future consideration for services and researchers alike.

Current prevention strategies for childhood cancers generally include physical activity, healthy weight, good nutrition. Mothers with addiction disorders may be likely to struggle to adopt such changes either for their children or themselves. Therefore, additional support is clearly needed for this group of women. There are also other risk factors that are not under 'the control' of the mother, such as deprivation, exposure to maternal medication in utero, or other well-recognised factors such as environmental pollution. As a risk factor for many cancer types, air pollution is specifically highlighted in the UK government's "Clean Air Strategy 2019"; it is acknowledged that people living in more deprived areas are exposed to more air pollution as they live closer to busy roads with no access to green space. Stricter emissions regulations and fiscal incentives make up part of the UK government's strategy to tackle air pollution; it also aims to ban petrol and diesel cars by 2040 and all cars in the UK to be zero-emission by 2050 [331]; this would remove one of the important risk factors associated with excess cancer risks in those living in urban more deprived circumstances.

This thesis not only discovered that different types of maternal mental illness affect offspring physical health outcomes, but it also showed the importance of electronic healthcare record use in epidemiological research in a vulnerable population that is, otherwise, hard to investigate using traditional techniques. In the new 'era of pandemic', epidemiological research using electronic health records has evolved significantly in terms of speed as researchers started to work more collaboratively and data became more rapidly available to researchers. This means it would be possible to translate basic science into applicable public health policies in a rapid, life changing and

timely way if the quality of routinely collected health data continued to improve; and if more linkages became possible across data sources nationally and internationally.

8.5 FUTURE RESEARCH

An important step in reducing the adverse effects of maternal mental illness on childhood physical health outcomes is understanding **how** and **when** maternal mental illness affects the child's physical health. This thesis provides a valuable evidence base with which to address such questions; replication of the findings, using other healthcare data sources nationally and internationally, increases the strength of the findings. Moreover, international replications of findings allows comparison and exploration of differences in the health systems between countries. Evidence on maternal mental illness effects on childhood outcomes in low-middle income countries is limited; therefore, replicating these findings in LMICs would lead to a more robust and detailed picture of maternal mental illness and its universal as opposed to 'setting-specific' effects.

Moreover, the findings presented in this thesis have pointed out a number of important implications that warrant further exploration:

- **Vaccination uptake beyond five years and pre- and post-pandemic vaccination uptake**

The study in **Chapter 3** looked at vaccination uptake among children exposed to maternal mental illness and found reduced vaccination uptake in this group. Future studies should look at vaccination uptake beyond age five, specifically the Human Papilloma Virus (HPV) vaccine among female children. Another study examining vaccination uptake among children pre and post COVID-19 pandemic would also be important: a recent study showed that the COVID-19 pandemic has had a negative impact on the mental health of women and of parents living with preschool aged children [224]. Therefore, we might expect to see further reductions in vaccination uptake among pre-schoolers post-pandemic. Such future studies would contribute significantly to the effectiveness of public health policies and enable greater preparedness for future uncertainty or pandemic.

- **Socioeconomic disparities in atopic disorders**

The study in **Chapter 4** illustrated that children from most deprived areas were at high risk of developing asthma and allergic rhinitis; however, they had significantly reduced risk of developing eczema and food allergies. In this study, it was not possible to go beyond their IMD information as an indicator of level of deprivation. These findings require further investigation using more detailed socioeconomic indicators, including housing, income, education level of mother and occupation, in order to understand the mechanisms behind the inverse relationship between deprivation levels and child's risk of asthma, eczema and food allergies.

- **The role of gene P53 and its relationship with maternal psychotic disorders and childhood cancer**

In **Chapter 7** study, an inverse relationship between maternal psychotic disorders and childhood cancer in both cohorts from England and Sweden was observed. These findings warrant further international research as the confidence intervals from the pooled analysis crossed one. It would be particularly interesting to conduct a collaborative multidisciplinary research in genetics as it is vital to test the hypothesis about whether gene P53 has a protective effect in children exposed to maternal psychotic disorders. The current evidence suggests that parents and siblings of people with schizophrenia have reduced cancer risk because of gene P53 [114]; yet, there is no study that confirms this among children exposed to maternal psychotic disorders. A study in this area would contribute to our knowledge on the mechanisms of childhood cancer and possible role of maternal psychotic disorders.

- **COVID-19 effects on maternal psychotic and addiction disorders**

As previously mentioned, COVID-19 pandemic has negatively affected the mental health of women and parents with pre-school aged children [224]. Nevertheless, we do not have information on how the extent of this effect in mothers with psychotic and addiction disorders. This is very important because the vaccination study (Chapter 3) showed that children exposed to maternal addiction are 50% less likely to receive vital vaccination in the first five years of life and they have increased risk

of childhood cancers (Chapter 7). Mothers with psychotic disorders are also important to investigate, as their children are at the risk of missing necessary vaccinations. Future studies should examine whether these trends continue or change over time post pandemic and, hopefully, provide necessary evidence for public health policies and intervention programmes that target vulnerable mothers and their children.

8.6 FINAL CONCLUSIONS

Findings from this thesis extend our limited knowledge about the effects of maternal mental illness on child physical health using data from the UK. In particular, children exposed to maternal addiction disorders can be defined as the most vulnerable group as they have increased utilisation of A&E and hospital inpatient admission services than primary care services as we have shown in our healthcare utilisation research (Hope *et* al); and they have the highest risk of missing necessary vaccinations as well as of risk developing cancer in childhood.

This thesis also raises awareness about the importance of routinely recorded health factors such as height and weight among children in primary care by pointing out the insufficient data recording which did not allow for an epidemiological study of childhood obesity. Unfortunately, there are limited guidelines and standardisation of processes for data recording in primary care; this creates inevitable complexity about how patient data should be managed and processed. Improvements in this area will allow for better and stronger health care systems, as well as high quality research to be conducted.

This thesis has brought us one step closer to understanding when and how maternal mental health may influence child physical health. Our research showed that children with maternal mental illness represents a very large percentage of our population [17] and findings of this thesis clearly indicate that the disbenefit associated with this group of children and their families is very amenable by just knowing the risks and adapting this information to the existing interventions. Specifically, it is important to make sure that the risk associated with children with maternal mental illness is

acknowledged by the people who come in contact with these families and their children, because the key point is to share information across different agencies as well as key people within these agencies such as, primary care, schools, adult mental health services.

Another very important point that this thesis makes is that some of the findings reported here are very important in relation to COVID-19. Specifically, vaccination study findings on the effects of maternal mental illness on reduced childhood vaccination uptake may be even more important because, the rates of mental illness among parents from March 2020 is anticipated to increase as we know that lockdown to stop spread of COVID-19 in the UK has caused a sginificant mental distress to parents with young children.

Moreover, poverty is exponentially increasing as a result of COVID-19. Latest estimates indicate that globally more than 10 million people are being pushed into poverty and the health inequality gap is getting bigger [332]. There is a clear evidence that poverty is strongly linked with maternal mental illness and child health outcomes. Thus, increasing poverty means that adversity among this group is also going to increase. This may mean that some of the main risk factors for child physical illnesses we observed could increase, such as maternal smoking. Results of the perinatal smoking study (Chapter 6) have shown that mothers with mental illness are more likely to smoke and they are more live in the most deprived areas. Based on these findings, as a result of COVID-19, we could see increasing numbers of mothers smoking as the poverty increases and, because of this, we may see increasing rates of atopic disorders among children.

This thesis has provided a deeper insight into effects of maternal mental illness on physical health outcomes in children and highlighted a particular aspect of vulnerability that has not been considered before in the public health interventions and polices. Findings of this thesis are even more important following the COVID-19 pandemic. It also makes a strong case for public health policies such as the Healthy Child Programme, as well as intervention programmes to urgently to recognise the effects of maternal mental illness on child's physical health.

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APPENDICES

Appendix A1- List of ICD-10 mental disorder diagnosis and relevant read codes

Type of mental disorder	ICD-10 categories	Read codes
Mental and behavioural disorders due to alcohol misuse	F10	Eu10600, 1462,E23z.00, E012.00, E230300, E250100, E011000, Eu10512, 1B1c.00, , E011200, E011.00., Eu10400, Eu10y00, 136T.00, Eu10200, Eu10712, E01y000, E015.00, E01y.00, 136S.00, E231300, E230z00, Eu10514, E250.00, E230.11, Eu10011, E231000, E014.00, Z191.00, E011z00, E231z00, Eu10611, E250z00, E01z.00, E230000, E250200, Eu10.00, E230200, Eu10511, ZV11300, Eu10411, Eu10z00, E23..11, E230100, E231100, E011100, Eu10513, Eu10100, E250300, Eu10212, Eu10800, Eu10500, Eu10300, E231200, Eu10711, E012.11, E250000, E013.00, E01..00, Eu10000, E230.00, E231.00, E010.00, E012000, Eu10700
Mental and behavioural disorders due to substance misuse	F11	Z1Q6214, 146C.00, E248z00, E248000, E240z00, Eu11700, 1TD..00 , E240100, Eu11600, Eu11000, E240.12, 1V0A.00, E240.14, Eu11311, E255000, E240200, E240000, 1TD0.00, 1TD1.00, ZV11500, Z1Q6212, E255200, Eu11211, 1T E..00, 1T0..00, Eu11z00, Eu11100, Eu11400, 8B2P.00, Z1Q6200, 8B2N.00 , E248.00, 1TD2.00, E248200, Eu11y00, Eu11300, Eu11212, E255z00, 1TD3.00, 8B2R.00, 1T02.00, 8B2Q.00 , E240.11, 1T00.00, E255.00, Eu11200, 1T01.00, 13c1.00, 8B23.11, E240.00, E255100, 1T03.00, E255300, 1V65.00, Eu11500, Eu11.00, E248100,
	F12	Eu12600, E243.00, Eu12.00, E252.00, Eu12y00, Eu12000, E243300, E252200, Eu12100, Eu12z00, E252z00, Eu12300, Eu12700, Eu12211, E243000, E243200, E243z00, Eu12200, 13cE.00, E252100, E252000, E243.11, E243.13, Eu12500, E243100,
	F13	E241200
	F14	Eu14500, Eu1A.00, E256300, Eu14300, 1T61.00, 1T62.00, 1T50.00, 1T60.00, 1T6..00, 1T51.00, Eu1A200, Eu1A300, E256200, Eu14211, 1T40.00, Eu14100, Eu1A500, E242z00, 1T52.00, Eu1A000, 1T63.00, E242200, E256.00, E242100, Eu14700, E256z00, IT5..00, E256000, Eu14.00, Eu1A100, Eu14200, 1T53.00, E242.00, E242000, E256100, Eu14000, Eu1Az00,
	F15	1T43.00, E257100, E244000, E257200, E24A.00, E244011, 1V66.00, E257z00, SL97000, E257.00, 1T4..00, Eu15z00, 1T41.00, Eu15211, E257.11, E257.12, E244100, E257000, E244200, E244.11, E244300, E244z11, E244.00, 1T42.00, E244z00, E257300, E244.12,
	F16	E245000, Eu16500, Eu16100, Eu16700, E253.12, Eu19400, E245.00, E245200, E245.12, E245.11, Eu16.00, E253z00, Eu16211, E253000, E253100, Eu16200, Eu16z00, E253.00, Eu16000, Eu16711, E245z00, E253200, E245100, Eu16300, E253300, Eu18100, Eu18500, IT91.00, Eu18200,
	F18	Eu18.00, E246100, 1T92.00, 1T90.00, E246.00, Eu18z00, 1T9..00, E246200, Eu18000, E246000, 1T93.00, Eu18400, Eu18211, E246z00,

	F19	E259300, E247200, E247100, 13cF.00, Eu19211, 13cM000, ZV11400, E02z.00, E02..00, L183100, L183.11, E25yz00, 1V0 , E.00, 1V0..00, 1TG..00, Eu19700, E25y000, 1V3..00, E258.00, E249100, 1V23.00, 1V0C.00, E249200, Eu19200, E25y300, E24..00, E24..11, 1463, E259z00, Eu19000, Eu19600, 13cH.00, E25..00, 13c6.00, 9G2Z.00, Eu19500, E259000, 1V2..00, 13cB.00, 1V64.00, E247000, E247.00, 13c7.00, Eu19300, 1V...00, E25y.00, 13c..00, 13c8.00, E249000, Eu1..00, 1T...00, 13cD.00, E249z00, E249.00, 146F.00, E02y400, E259100, E02yz00, E02y.00, 1V02.00, 13cM.00, Eu19.00, E258z00, 13c5.00, E259.00, Eu19z00, L183300, 1283, L183z00, 1V01.00, E259200, E24z.00, Eu19100, E25y200, L183.00, E25z.00, E247z00, F464400, 9G2..00, E25y100, Eu19y00
Non-affective psychoses	F20	Eu20212, E103200, E101400, E102500, E102400, E10..00, E101500, E102000, Eu25012, E100z00, 1464, E102100, E10z.00, E100000, Eu20200, E103000, E103.00, E103100, E100200, E101000, Eu20y12, Eu20000, Eu20100, Eu20500, Eu20600, E101z00, E103z00, Eu25112, E103400, E100.00, ZV11000, E10y.11, E104.00, Eu20511, Eu20y00, Eu20211, 212W.00, E103500, Eu20111, E100500, E100100, Eu20.00, E10yz00, Eu20214, E10y.00, Eu20311, Eu20y13, E102z00, Eu2..00, E100.11, E102.00, E101.00, E106.00, E10y000, E10y100, Eu20213, Eu20300, E103300, Eu20z00, E100300, Eu20011, E100400
	F21	Eu21.15, E105.00, E105200, E105z00, Eu21.16, E105500, Eu21.11, Eu21.13, E105000, Eu21.14, Eu21.00, Eu21.17, Eu21.12
	F22	Eu22014, 1BH..11, Eu22y13, Eu22100, E121.00, 1BH1.00, E12y000, 1BH3.00, 225F.00, E12yz00, Eu22012, 1BH2.00, 225E.00, E123.11, Eu22111, 1BH..00, Eu22013, Eu22.00, Eu22y12, Eu22y00, Eu22000, Eu22200, Eu22y11, Eu22300, 1BH0.00, E122.00, E12..00, E120.00, E12y.00, Eu22015, Eu22z00, Eu22011
	F23	Eu23300, Eu23z12, E133.00, Eu23012, E12z.00, Eu23y00, Eu23z11, E13y100, E13yz00, E133.11, Eu23212, E134.00, Eu23000, E13y.00, E132.00, E104.11, Eu23211, E13..11, Eu23214, Eu23.00, Eu23112, Eu23100, Eu23312, Eu23z00, Eu23200, Eu23011
	F24	Eu24.12, E123.00, Eu24.11, Eu24.13, Eu24.00
	F28-9	E13z.00, Eu2y.00, E1z..00, E1y..00, Eu2y.11, E1...00, E13..00, 285..11, 286..11, Eu2z.00, Eu2z.11, E13z.11, 146H.00, Eu26.00, 212X.00
Affective Psychoses	F20	Eu20400
	F25	Eu25111, E107.11, E107.00, Eu25200, Eu25z00, Eu25100, E107300, Eu25.00, E107200, Eu25011, E107z00, E107000, E107500, Eu25y00, Eu25211, Eu25000, Eu25212, E107100, Eu25z11
	F30	Eu30z11, E110300, E111300, E110600, E110400, Eu30.11, Eu30200, Eu30y00, E111z00, Eu30000, E110100, Eu30z00, E111600, 1S42.00, E111.00, E110200, E11..13, E110z00, E110.00, E111000, Eu30.00, E11y100, E110500, Eu30212, E110.11, E111100, E111500, E110000, E111200, Eu30100, Eu31y12, E111400, Eu30211
	F31	E11y000, E114100, E117000, Eu31.13, E116.00, E116500, E11y.00, Eu31900, E115.00, Eu31100, E116200, Eu33213, Eu31400, Eu31700, E117200, E117600, E116z00, E114200, E115400, Eu31.12, E117300, E116100, ZV11111, E115.11, ZV11112, E117400, E114000, E115200, E11..11, E114500, Eu31.00, E117500, E114600, E115300, E117100, E116300, E116400, E114400, E115600, E115z00, Eu31600, Eu31000, E117.00, Eu31y00, E114z00, E11yz00, Eu31500, E116000, Eu31z00, E114300, E115000, Eu31800, E115100, E115500, Eu31.11, E117z00, E114.11, Eu31300, 146D.00, E114.00, E11y300, Eu31200, E116600, Eu33312, Eu31y11, Eu31911, 212V.00
	F32.3	E130.11, Eu32312, E11..12, Eu32800, Eu33311, Eu32314, Eu32900, Eu32313, Eu32300, Eu33313, E130.00, Eu32311, E112400, Eu33314
	F33.3	Eu32A00, Eu33300, Eu33315, Eu33316, E113400

	F39	E11z000, E11z.00, E11zz00, E11..00
Mood disorders	F32	E2B1.00, 212S.00, Eu32.11, Eu32z12, Eu32500, E112200, Eu32600, 1B17.00, Eu33z11, Eu32y00, E112z00, Eu32211, E291.00, E11z200, E112.00, Eu32100, E112000, Eu32z00, Eu32212, Eu32200, Eu32400, 1465, E112500, Eu33211, Eu32.00, Eu33214, Eu34111, Eu32z13, E112100, Eu34113, E112300, E11y200, Eu32y11, Eu32z14, Eu32000, Eu32700, Eu32z11, E204.00, Eu32y12, E2B..00, Eu32.13, Eu32213, E112600, E2B0.00, E135.00, E112.11
	F33	E118.00, Eu33.15, E113200, E113.00, E113z00, Eu33.00, Eu33.12, E112.12, Eu3y100, Eu33z00, Eu32.12, E113100, Eu33100, Eu33.13, E113300, Eu33200, Eu33.14, Eu33000, E113000, E113.11, E113500, Eu3y111, E113600, Eu33400, E112.14, E113700, Eu33.11, E112.13 Eu33y00
	F34	Eu34.00, Eu34000, E211200, Eu34y00, Eu34100, Eu34z00
	F38	Eu3y000, Eu3z.00, Eu3yy00, Eu3y011, E290z00, E290.00, Eu3..00, Eu3y.00
	F53	E204.11, Eu32B00, Eu53011, 62T1.00, Eu53012, E03y300, Eu53111
	F92	Eu92000
Neurotic disorders	F40	E202500, Eu40211, E202900, Eu40011, Eu40012, E202400, Eu40213, E202A00, Eu40y00, Eu40112, E202700, Eu40214, Eu40300, Eu40z12, Eu40.00, Eu40212, E202B00, Eu40z11, E202.11, E202000, E202.00, E28z.11, Eu40200, E202800, 8G52.00, E202E00, Eu40z00, E202200, E202.12, Eu40100, E202300, E202600, E202C00, Eu40000, E202100, 146G.00, E202z00, E28z.12, E202D00
	F41	Eu41000, Eu41100, Eu41y11, Eu41113, E200100, 225J.00, E200z00, E20z.00, E200200, E200111, E200400, E200000, E200500, Eu41z11, Eu41.00, Eu41112, Eu41012, E200300, Eu41111, Eu41z00, Eu41011, Eu41300, Eu41211, Eu41y00, E200.00
	F42	Eu42000, Eu42.12, E203.00, Eu42z00, Eu42100, E203000, Eu42.11, E203.11, Eu42200, E203z00, Eu42y00, Eu42.00, E203100
	F43	E290011, E29y000, Eu43012, E293.00, E28z.00, E293100, E29y300, E284.00, Eu43000, E29..00, E293200, Eu43011, E293000, E29y.00, E292400, Eu43211, E293z00, E29y400, E290000, E281.00, E28..00, E29y200, Eu43z00, Eu43212, Eu43014, E292.00, E292200, E28..11, E29z.00, E283.00, E29y500, E292z00, E280.00, Eu43y00, E283000, Eu43200, E29yz00, E294.00, E292y00, Eu43013, Eu43.00, E282.00, E292500, E283z00, E030000, Eu43400, E031000, Eu43111, Eu43300, E29y100, ZS7C700, Eu43100, E283100
	F44	Eu44000, E201z12, E201611, Eu44z00, Eu44y12, Eu44100, E201100, E201400, Eu44.00, E201z00, E201.00, E201600, E201700, E201z11, E201000, E201511, E201800, Eu45011, E131.00, E201900, Eu44.11, E201A00, Eu44600, E201200, E201300, Eu44300, Eu44200, Eu44.14, Eu44400, Eu44700, E13y000, Eu44.12, Eu44y11, E201500, E201z13, Eu44.13, Eu44y00, Eu44500
	F45	Eu46y14, E264300, Eu45324, Eu45z00, Eu45200, Eu44411, Eu45111, Eu46y11, E262z00, E260100, Eu45320, E264500, E264z00, Eu45316, E264011, E265z00, Eu45012, E263.00, Eu45318, E201612, E261.00, E261300, Eu45412, Eu45322, Eu44y14, E265200, Eu45100, E262200, E264311, E261z00, Eu44412, Eu45y00, E263000, Eu45313, E267.00, Eu44611, E265100, Eu45311, Eu45213, Eu45400, E265300, E20y000, Eu45511, E261100, Eu45312, E20y011, E261000, E263z00, Eu45411, Eu45323, Eu43015, E278200, Eu45317, E264.11, Eu45325, E26y.00, E262000, E201C00, Eu46000, Eu45y11, E262300, Eu45212, E265.00, E260000, E262.00, Eu45z11, E278.00, Eu4..00, E26..00, Eu45214, Eu45y15, Eu45413, E20y300, Eu45y14, E26yz00, Eu45500, Eu44511, E26y000, Eu45414, E261500, E278000, E207.00, Eu45y12, E260z00, Eu44y13, Eu45000, Eu45y13, E26z.00, E261200, Eu45215, Eu45314, Eu45321, E264400, E264000, Eu45319, E264.00, E261400, Eu45.00, Eu46y16, Eu45211, Eu45300, E278z00, E260.00, Eu46y15

	F48	E206.00, Eu46.00, E20y200, Eu46y00, Eu46y13, Eu46z00, E28z.13, E292311, E202z11, Eu46z11, Eu46y12, E292300, E2y..00, E20y.00, E292312, E2...00, E205.00, Eu46100, E20y100, E20z.11, E20yz00, E2z..00, E20..00, Eu46011, E201B00
Eating disorders	F50	1467, Eu50y11, Eu50y12, E275111, Eu50211, Eu50300, E275100, E275000, E275200, Eu50411, Eu50y00, Eu50.00, E275.00, R036011, E275y00, R030z00, E271.00, E275z00, Eu50200, Eu50z00, Eu50400, 1FF..00, Eu50000, Eu50100, Fy05.00, Eu50212, R030.00
Personality disorders		
	F60	Eu60212, Eu60014, E21..00, Eu60y12, Eu60y00, Eu60712, Eu60z11, E215200, Eu60511, Eu60211, E21y500, E212200, Eu60200, E213.11, Eu34013, Eu60713, E214000, E211100, E216.00, Eu60z12, E21y000, E212.00, Eu6..00, Eu60700, E21yz00, Eu60412, Eu60311, E21z.00, Eu60013, Eu60600, E216.13, Eu60y11, E21y100, E21z.11, Eu60011, Eu61.00, Eu60300, Eu6yy00, E21y600, E215.00, E21..11, Eu60513, E216.12, E215000, E216.11, Eu60213, E21y400, Eu60.00, E211.00, E211000, E214z00, E21y700, Eu34011, Eu60100, E214.11, Eu60z00, Eu60215, E211z00, Eu60y13, E215z00, Eu6y.00, E214100, E217.00, Eu60313, E21y200, Eu60500, Eu60y16, Eu60400, Eu60000, Eu34112, E214.00, E211300, E210.00, Eu21.18, E217.11, Eu60312, Eu6z.00, E212z00, E213.00, Eu60711, Eu60411, E21y711, E212000, E21y.00, E21y300, Eu60214, E215.11, Eu60y14, Eu60714, Eu60512
	F62	Eu62013, Eu62011, Eu62z00, Eu62015, Eu62100, Eu62014, Eu62y00, Eu62.00, Eu62000, Eu62012
	F63	Eu60800, Eu63000, Eu63z00, Eu63011, Eu63100, Eu63200, Eu63300, Eu63y00, Eu63.00
	F68	Eu6y100, Eu62y11, Eu6y300, Eu6y200, Eu6y111, E215100, Eu6y000
General	NA	9H6..00, 9H8..00, 146Z.00, 146..00

Appendix A2- Read codes of illness related to alcohol and substance misuse

Read code	Medcode	CPRD Read code description	Type of mental disorder
C150500	65754	Alcohol-induced pseudo-Cushing's syndrome	Alcohol misuse
F11x011	36748	Alcoholic encephalopathy	Alcohol misuse
F144000	33839	Cerebellar ataxia due to alcoholism	Alcohol misuse
F11x000	47555	Cerebral degeneration due to alcoholism	Alcohol misuse
F25B.00	30604	Alcohol-induced epilepsy	Alcohol misuse
F375.00	2925	Alcoholic polyneuropathy	Alcohol misuse
F394100	31742	Alcoholic myopathy	Alcohol misuse
G555.00	4915	Alcoholic cardiomyopathy	Alcohol misuse
J153.00	4506	Alcoholic gastritis	Alcohol misuse
J617.00	7943	Alcoholic hepatitis	Alcohol misuse
J610.00	10691	Alcoholic fatty liver	Alcohol misuse
J611.00	3216	Acute alcoholic hepatitis	Alcohol misuse
J617000	7602	Chronic alcoholic hepatitis	Alcohol misuse
J612000	21713	Alcoholic fibrosis and sclerosis of liver	Alcohol misuse
J613000	17330	Alcoholic hepatic failure	Alcohol misuse
J612.00	4743	Alcoholic cirrhosis of liver	Alcohol misuse
J613.00	7885	Alcoholic liver damage unspecified	Alcohol misuse
G852300	8363	Oesophageal varices in alcoholic cirrhosis of the liver	Alcohol misuse
J671000	24984	Alcohol-induced chronic pancreatitis	Alcohol misuse
TJ85000	40852	Adverse reaction to cocaine	Substance misuse
U204z00	66118	[X]Intent self poison psychotropic drug unspecif place	Substance misuse
E021z00	26481	Drug-induced paranoia or hallucinatory state NOS	Substance misuse
TJ96000	33876	Adverse reaction to cannabis	Substance misuse
SL85000	10859	Cocaine poisoning	Substance misuse
E02y300	46244	Drug-induced depressive state	Substance misuse
SL50.12	32760	Opiate poisoning	Substance misuse
E021100	20026	Drug-induced hallucinosis	Substance misuse
U204100	99011	[X]Intent self poison psychotropic drug at res institut	Substance misuse
SL97200	37544	Ecstasy poisoning	Substance misuse
U60A100	55611	[X]Opioid recept antag causing adverse effect in therap use	Substance misuse
U204y00	96687	[X]Int self poison psychotropic drug other spec place	Substance misuse
SL50500	37056	Morphine poisoning	Substance misuse
E021.00	45997	Drug-induced paranoia or hallucinatory states	Substance misuse
SL97011	102176	Amphetamine poisoning	Substance misuse
E02y000	29783	Drug-induced delirium	Substance misuse
U606312	109871	[X] Adverse reaction to cocaine	Substance misuse
E021000	12628	Drug-induced paranoid state	Substance misuse
SL50.00	61673	Opiate and narcotic poisoning	Substance misuse
SL96000	36231	Cannabis poisoning	Substance misuse
F2W..00	10502	Drug-induced headache, not elsewhere classified	Substance misuse

Appendix A3- List of symptom read codes indicating mental disorder

Read code	Medcode	CPRD Read code description	Type of mental disorder
1369	12976	Suspect alcohol abuse - denied	Alcohol misuse
136W.00	94670	Alcohol misuse	Alcohol misuse
2577.11	10161	O/E - alcoholic breath	Alcohol misuse
1V32.00	107780	Neck injector	Substance misuse
1V30.00	109558	Injects drugs subcutaneously	Substance misuse
13c4.00	42257	Intranasal drug user	Substance misuse
1V08.00	105999	Smokes drugs in cigarette form	Substance misuse
1V09.00	107593	Smokes drugs through a pipe	Substance misuse
13c0.00	22079	Injecting drug user	Substance misuse
1J10.00	6107	Suspected abuse soft drugs	Substance misuse
1V6..00	97245	Drug-related offending behaviour	Substance misuse
13r2.00	111927	Abstinent from drug misuse in protected environment	Substance misuse
13r0.00	63285	Abstinent from drug misuse	Substance misuse
1V63.00	97071	Possession of drugs	Substance misuse
13r1.00	73294	Abstinent from drug misuse in normal environment	Substance misuse
1J11.00	7234	Suspected abuse hard drugs	Substance misuse
1J1..00	3565	Suspected drug abuse	Substance misuse
1V00.00	97648	Occasional drug user	Substance misuse
E253.11	60048	'Bad trips'	Substance misuse
1V62.00	98169	Buying drugs	Substance misuse
1V35.00	103726	Shares drug equipment	Substance misuse
U205.11	28710	[X]Overdose - heroin	Substance misuse
R10B200	102044	[D]Finding of psychotropic drug in blood	Substance misuse
1V07.00	101697	Notified addict	Substance misuse
1V0B.00	103844	Sniffs drugs	Substance misuse
1V22.00	101892	Age at starting drug misuse	Substance misuse
U1A5.11	51334	[X]Accidental poisoning with heroin	Non-affective psychoses
Eu0z.12	8766	[x]symptomatic psychosis nos	Non-affective psychoses
R001.00	2455	[d]hallucinations	Non-affective psychoses
Ryu5300	53761	[x]other hallucinations	Non-affective psychoses
R001400	12064	[d]visual hallucinations	Non-affective psychoses
R001000	12120	[d]hallucinations, auditory	Non-affective psychoses
1B1E.00	1914	Hallucinations	Non-affective psychoses
R001100	53990	[d]hallucinations, gustatory	Non-affective psychoses
R001200	25283	[d]hallucinations, olfactory	Non-affective psychoses
R001300	64131	[d]hallucinations, tactile	Non-affective psychoses
R001z00	19916	[d]hallucinations nos	Affective psychoses
225C.00	32585	O/E - elated	Mood disorders
1B1U.11	10438	Depressive symptoms	Mood disorders
1B1U.00	9796	Symptoms of depression	Mood disorders
1BQ..00	25435	Loss of capacity for enjoyment	Mood disorders
1BU..00	53148	Loss of hope for the future	Mood disorders
2257	1908	o/e - depressed	Mood disorders
1B17.11	4824	C/O - feeling depressed	Mood disorders

1B17.12	2930	C/O - feeling unhappy	Mood disorders
1BT..11	8928	Low mood	Mood disorders
1BT..00	10015	Depressed mood	Mood disorders
1BT..12	26028	Sad mood	Mood disorders
2259	8725	O/E - nervous	Neurotic disorders
Z4I7100	62935	Recognising anxiety	Neurotic disorders
1468	50083	H/O: psychological trauma	Neurotic disorders
1B13.00	131	Anxiousness	Neurotic disorders
1B12.11	3586	'Nerves'	Neurotic disorders
Z7CG400	11267	Flashbacks	Neurotic disorders
1B12.12	514	Tension - nervous	Neurotic disorders
1B1V.00	11890	C/O - panic attack	Neurotic disorders
1B12.00	29608	'Nerves' - nervousness	Neurotic disorders
1B13.12	93401	Anxious	Neurotic disorders
Z4I7211	26295	Reducing anxiety	Neurotic disorders
Z4I7.00	22159	Acknowledging anxiety	Neurotic disorders
R2y2.00	2509	[D]Nervousness	Neurotic disorders
2258	13124	o/e - anxious	Neurotic disorders
1B13.11	5902	Anxiousness - symptom	Neurotic disorders
Z4I7200	28381	Alleviating anxiety	Neurotic disorders
R2y2.11	17853	[D]Nerves	Neurotic disorders
1466	3407	H/O: anxiety state	Neurotic disorders
Z7CG500	53526	Reliving traumatic memories	Neurotic disorders
ZV15400	32668	[V]Personal history of psychological trauma	Neurotic disorders
E205.12	7235	tired all the time	Neurotic disorders
E205.11	1582	nervous exhaustion	Neurotic disorders
R2y2.12	10723	[D]Nervous tension	Eating disorders
ZC18.00	38949	Attempts to counteract effects of bingeing	Eating disorders
ZV4K300	17643	[V]Inappropriate diet and eating habits	Eating disorders
R036000	17642	[D]Excessive eating	Eating disorders
1612.12	6607	Loss of appetite - symptom	Eating disorders
1614	35490	Excessive eating - polyphagia	Eating disorders
R07z.11	2868	[D]Trouble eating	Eating disorders
R036z00	72870	[D]Polyphagia NOS	Eating disorders
R036.00	15235	[D]Polyphagia	Eating disorders
1612	7608	appetite loss - anorexia	Eating disorders
1612.11	7744	anorexia symptom	Eating disorders
R036100	98900	[d]hyperalimentation	Eating disorders
1614.12	31227	Polyphagia symptom	Eating disorders
1614.11	60373	hyperalimentation - symptom	Eating disorders
SN42z00	14950	Effects of hunger NOS	Personality disorders
E21yz11	20033	Manipulative personality	Personality disorders
E212100	39011	Introverted personality	Personality disorders
E213.12	36043	Quarrelsome personality	Personality disorders

Appendix A4- List of read codes indicating referrals to and use of psychological services or therapies

Read code	Medcode	CPRD Read code description	Type of mental disorder
ZC22200	97163	Advice to change alcoholic drink intake	Alcohol misuse
8G32.00	29691	Aversion therapy - alcoholism	Alcohol misuse
9k12.00	63529	Alcohol misuse - enhanced service completed	Alcohol misuse
ZV6D600	8030	[V]Alcohol abuse counselling and surveillance	Alcohol misuse
66e0.00	32964	Alcohol abuse monitoring	Alcohol misuse
8W2..00	109105	Refer to MH services deferred until alcohol misuse resolved	Alcohol misuse
Z4B1.00	30460	Alcoholism counselling	Alcohol misuse
66e..00	12442	Alcohol disorder monitoring	Alcohol misuse
13Y8.00	18156	Alcoholics anonymous	Alcohol misuse
	11740	Alcohol misuse - enhanced services administration	Alcohol misuse
7P22000	30750	Delivery of rehabilitation for drug addiction	Substance misuse
9HCC.00	110232	On substance misuse programme	Substance misuse
9k51.00	97586	Shared care drug misuse treatment - enhanced services admin	Substance misuse
Z192.00	25522	Dependent drug detoxification	Substance misuse
9HC..00	31213	Substance misuse monitoring	Substance misuse
9No5.00	98221	Seen in substance misuse clinic	Substance misuse
9kS..00	98362	Drug misuse assessment declined - enhanced services administ	Substance misuse
13r4.00	94693	Abstinent from drug misuse when receiving blocking therapy	Substance misuse
9k53.00	98566	Pharmacy attended for drug misuse - enhanced services admin	Substance misuse
13r5.00	94554	Abstinent from substance misuse	Substance misuse
9HC6.00	96009	Substance misuse treatment declined	Substance misuse
8Hq..00	100178	Admission to substance misuse detoxification centre	Substance misuse
9HC0.00	22530	Initial substance misuse assessment	Substance misuse
9HC9.00	111886	Substnce misse treatmnt pgme del other healththcare provider	Substance misuse
9G21.00	24849	Drug addict notific to CMO	Substance misuse
8I2N.00	60985	Drug dependence home detoxification contraindicated	Substance misuse
8BE0.00	90198	Reinduction to methadone maintenance therapy	Substance misuse
9s...00	106802	Drug misuse clinic administration	Substance misuse
9N1yJ00	107355	Seen in drug misuse clinic	Substance misuse
ZV6D700	8463	[V]Drug abuse counselling and surveillance	Substance misuse
8HHL.00	11842	Referral to community drug dependency team	Substance misuse
9k52.11	111007	Drug misuse treatment in primary care	Substance misuse
1TF..00	85953	Does not use heroin on top of substitution therapy	Substance misuse
9G22.00	69963	Drug addict re-notific due	Substance misuse
9k51.11	103241	Shared care drug misuse treatment	Substance misuse
8BAW.00	32653	Drug dependence self detoxification	Substance misuse
9G24.00	65927	Drug addict-notify local SMR22	Substance misuse
Z416.00	9273	Substance abuse counselling	Substance misuse
9N4i.00	30465	DNA - Did not attend substance misuse clinic	Substance misuse
8H7x.00	12856	Referral to drug abuse counsellor	Substance misuse
9HC2.00	45550	Substance misuse clinical management plan agreed	Substance misuse
9HC3.00	72663	Substance misuse clinical management plan reviewed	Substance misuse

67H3.00	34115	Lifestyle advice regarding drug misuse	Substance misuse
8B2T.00	93979	Opioid antagonist therapy	Substance misuse
9HC5.00	91277	Substance misuse treatment programme completed	Substance misuse
9NX2.00	108288	In-house substance misuse treatment	Substance misuse
9G2..11	21623	Drug addict notific admin	Substance misuse
9HC4.00	91939	Substance misuse treatment withdrawn	Substance misuse
8Hh1.00	94686	Self referral to substance misuse service	Substance misuse
8B2S.00	93980	Opioid agonist substitution therapy	Substance misuse
8BAX.00	30679	Drug dependence home detoxification	Substance misuse
9k53.11	111460	Pharmacy attended for drug misuse	Substance misuse
9k52.00	97676	Drug misuse treatment primary care - enhanced services admin	Substance misuse
9G23.00	60372	Drug addict re-notif to CMO	Substance misuse
677W.00	111914	Substance abuse counselling	Substance misuse
8AA..00	54356	Drug abuse monitoring	Substance misuse
9HCA.00	110260	Substance misuse monitoring 6 month review	Substance misuse
8B23.00	7496	Drug addiction therapy	Substance misuse
8B23.13	9024	Drug dependence therapy	Substance misuse
8HkF.00	93850	Referral to substance misuse service	Substance misuse
9HC1.00	58145	Follow up substance misuse assessment	Substance misuse
8BAc.00	42649	Substance misuse management stopped - self withdrawal	Substance misuse
9k5..00	34398	Drug misuse - enhanced services administration	Substance misuse
9k50.00	62490	Drug misuse - enhanced service completed	Substance misuse
677T.00	96049	Substance misuse structured counselling	Substance misuse
13r3.00	68327	Abstinent from drug misuse on maintenance replacement	Substance misuse
8HHs.00	26178	Referral to psychosis early intervention service	Substance misuse
9HA1.00	44936	Removed from depression register	Mood disorder
9H91.00	12122	Depression medication review	Mood disorder
9H90.00	12399	Depression annual review	Mood disorder
8CAa.00	30483	Patient given advice about management of depression	Mood disorder
9H92.00	30405	Depression interim review	Mood disorder
9HA0.00	42931	On depression register	Mood disorder
8HHq.00	32841	Referral for guided self-help for depression	Mood disorder
9kQ..00	96995	on full dose long term treatment depression - enh serv admin	Mood disorder
Z4L..00	21600	Psychological counselling	Mood disorder
8G94.00	9125	anxiety management training	Neurotic disorder
8HHp.00	28925	referral for guided self-help for anxiety	Neurotic disorder
Z4L1.00	7999	anxiety counselling	Neurotic disorder
Z481.00	25749	Phobia counselling	Neurotic disorder
Z4B5.00	12201	eating disorder counselling	Eating disorders
8HTN.00	11612	referral to eating disorders clinic	Eating disorders
ZC2CD00	67510	dietary advice for eating disorder	General
665A.00	21317	Psych.treatment stopped	General
6653	3648	Initial psych. assessment	General
9H...12	21359	Psych. health administration	General
6659	36007	Psych.treatment started	General
665..00	20460	Psych. disorder monitoring	General

6658	20535	Psych. treatment change	General
665Z.00	33486	Psych. disorder monitoring NOS	General
6654	27610	Follow-up psych. assessment	General
9H9..00	32589	Mental health annual physical examination done	General

Appendix A5- List of antipsychotics order by generation

Prodcode	Product Name	Gen
68152	Abilify Maintena 400mg powder and solvent for prolonged-release suspension for injection pre-filled syringes (Otsuka Pharmaceuticals (U.K.) Ltd)	2
61075	Abilify Maintena 400mg powder and solvent for suspension for injection vials (Otsuka Pharmaceuticals (U.K.) Ltd)	2
63598	Amisulpride 400mg tablets (Zentiva)	2
62202	Amisulpride 50mg tablets (A A H Pharmaceuticals Ltd)	2
65773	Aripiprazole 30mg tablets (Zentiva)	2
66479	Aripiprazole 400mg powder and solvent for suspension for injection pre-filled syringes	2
61650	Aripiprazole 400mg powder and solvent for suspension for injection vials	2
65671	Aripiprazole 5mg tablets (Zentiva)	2
66255	Atrolak XL 200mg tablets (Accord Healthcare Ltd)	2
62531	Atrolak XL 400mg tablets (Accord Healthcare Ltd)	2
69544	Atrolak XL 50mg tablets (Accord Healthcare Ltd)	2
63133	Biquelle XL 150mg tablets (Aspire Pharma Ltd)	2
63351	Biquelle XL 200mg tablets (Aspire Pharma Ltd)	2
63087	Biquelle XL 300mg tablets (Aspire Pharma Ltd)	2
62943	Biquelle XL 400mg tablets (Aspire Pharma Ltd)	2
63049	Biquelle XL 50mg tablets (Aspire Pharma Ltd)	2
61748	Ebesque XL 200mg tablets (DB Ashbourne Ltd)	2
61747	Ebesque XL 300mg tablets (DB Ashbourne Ltd)	2
61746	Ebesque XL 400mg tablets (DB Ashbourne Ltd)	2
61575	Ebesque XL 50mg tablets (DB Ashbourne Ltd)	2
67717	Latuda 18.5mg tablets (Sunovion Pharmaceuticals Europe Ltd)	2
62463	Latuda 37mg tablets (Sunovion Pharmaceuticals Europe Ltd)	2
64210	Latuda 74mg tablets (Sunovion Pharmaceuticals Europe Ltd)	2
62924	Lurasidone 18.5mg tablets	2
62387	Lurasidone 37mg tablets	2
62517	Lurasidone 74mg tablets	2
63818	Mintreleq XL 150mg tablets (Aristo Pharma Ltd)	2
69637	Mintreleq XL 200mg tablets (Aristo Pharma Ltd)	2
64639	Mintreleq XL 300mg tablets (Aristo Pharma Ltd)	2
69635	Mintreleq XL 400mg tablets (Aristo Pharma Ltd)	2
63925	Mintreleq XL 50mg tablets (Aristo Pharma Ltd)	2
70367	Olanzapine 10mg tablets (Alliance Healthcare (Distribution) Ltd)	2
69511	Olanzapine 10mg tablets (Teva UK Ltd)	2
61103	Olanzapine 15mg oral lyophilisates sugar free	2
70415	Olanzapine 15mg tablets (Teva UK Ltd)	2
63615	Olanzapine 2.5mg tablets (Dr Reddy's Laboratories (UK) Ltd)	2
65944	Olanzapine 2.5mg tablets (Mylan Ltd)	2
63833	Olanzapine 2.5mg tablets (Zentiva)	2
69674	Olanzapine 2.5mg/5ml oral solution	2
65707	Olanzapine 20mg orodispersible tablets sugar free (Actavis UK Ltd)	2
70219	Olanzapine 5mg orodispersible tablets (Teva UK Ltd)	2
70542	Olanzapine 5mg orodispersible tablets sugar free (Alliance Healthcare (Distribution) Ltd)	2

63155	Olanzapine 7.5mg tablets (Actavis UK Ltd)	2
69121	Olanzapine embonate 405mg powder and solvent for suspension for injection vials	2
60842	Quetiapine 100mg tablets (Alliance Healthcare (Distribution) Ltd)	2
70313	Quetiapine 100mg tablets (DE Pharmaceuticals)	2
70192	Quetiapine 100mg/5ml oral suspension sugar free	2
70312	Quetiapine 200mg tablets (A A H Pharmaceuticals Ltd)	2
64484	Quetiapine 200mg/5ml oral suspension	2
66427	Quetiapine 25mg tablets (Accord Healthcare Ltd)	2
65938	Quetiapine 25mg tablets (Ranbaxy (UK) Ltd)	2
68375	Quetiapine 25mg tablets (Teva UK Ltd)	2
65174	Quetiapine 300mg tablets (A A H Pharmaceuticals Ltd)	2
69836	Quetiapine 400mg/5ml oral suspension	2
8881	Remoxipride 150mg capsule	2
12445	Remoxipride 300mg capsule	2
23034	Remoxipride 75mg capsule	2
64493	Risperidone 1mg tablets (A A H Pharmaceuticals Ltd)	2
63255	Risperidone 1mg tablets (Accord Healthcare Ltd)	2
63511	Risperidone 1mg tablets (Actavis UK Ltd)	2
65493	Risperidone 1mg tablets (Wockhardt UK Ltd)	2
64957	Risperidone 1mg/ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)	2
65472	Risperidone 3mg orodispersible tablets sugar free (A A H Pharmaceuticals Ltd)	2
63494	Risperidone 500microgram orodispersible tablets sugar free (A A H Pharmaceuticals Ltd)	2
62916	Risperidone 500microgram orodispersible tablets sugar free (Teva UK Ltd)	2
65137	Risperidone 500microgram tablets (Dexcel-Pharma Ltd)	2
65321	Risperidone 500microgram tablets (Teva UK Ltd)	2
69328	Risperidone 500microgram tablets (Wockhardt UK Ltd)	2
19016	Roxiam 150mg Capsule (AstraZeneca UK Ltd)	2
16223	Roxiam 300mg Capsule (AstraZeneca UK Ltd)	2
48077	Roxiam ir 75mg Capsule (AstraZeneca UK Ltd)	2
67334	Seroquel XL 50mg tablets (Waymade Healthcare Plc)	2
64778	Sondate XL 150mg tablets (Teva UK Ltd)	2
59345	Sycrest 5mg sublingual tablets (Lundbeck Ltd)	2
69787	Tenprolide XL 300mg tablets (Actavis UK Ltd)	2
68297	Trevicta 263mg/1.315ml prolonged-release suspension for injection pre-filled syringes (Janssen-Cilag Ltd)	2
70433	Trevicta 350mg/1.75ml prolonged-release suspension for injection pre-filled syringes (Janssen-Cilag Ltd)	2
70122	Trevicta 525mg/2.625ml prolonged-release suspension for injection pre-filled syringes (Janssen-Cilag Ltd)	2
68346	Zalasta 20mg tablets (Consilient Health Ltd)	2
68347	Zalasta 5mg tablets (Consilient Health Ltd)	2
63797	Zaluron XL 150mg tablets (Fontus Health Ltd)	2
63364	Zaluron XL 200mg tablets (Fontus Health Ltd)	2
63359	Zaluron XL 300mg tablets (Fontus Health Ltd)	2
63363	Zaluron XL 400mg tablets (Fontus Health Ltd)	2
63389	Zaluron XL 50mg tablets (Fontus Health Ltd)	2
37606	abilify 10mg orodispersible tablets (otsuka pharmaceuticals (u.k.) ltd)	2

24358	abilify 10mg tablets (otsuka pharmaceuticals (u.k.) ltd)	2
38010	abilify 15mg orodispersible tablets (otsuka pharmaceuticals (u.k.) ltd)	2
14858	abilify 15mg tablets (otsuka pharmaceuticals (u.k.) ltd)	2
38080	abilify 1mg/ml oral solution (otsuka pharmaceuticals (u.k.) ltd)	2
29879	abilify 30mg tablets (otsuka pharmaceuticals (u.k.) ltd)	2
57114	abilify 5mg tablets (mawdsley-brooks & company ltd)	2
18132	abilify 5mg tablets (otsuka pharmaceuticals (u.k.) ltd)	2
49699	abilify 5mg tablets (sigma pharmaceuticals plc)	2
46705	abilify 9.75mg/1.3ml solution for injection vials (otsuka pharmaceuticals (u.k.) ltd)	2
6524	amisulpride 100mg tablets	2
41702	amisulpride 100mg tablets (zentiva)	2
6482	amisulpride 100mg/ml oral solution sugar free	2
52076	amisulpride 12.5mg/5ml oral solution	2
51558	amisulpride 12.5mg/5ml oral suspension	2
5071	amisulpride 200mg tablets	2
46969	amisulpride 200mg tablets (a a h pharmaceuticals ltd)	2
34927	amisulpride 200mg tablets (zentiva)	2
46889	amisulpride 25mg/5ml oral solution	2
11938	amisulpride 25mg/5ml oral suspension	2
5927	amisulpride 400mg tablets	2
4876	amisulpride 50mg tablets	2
41714	amisulpride 50mg tablets (zentiva)	2
55625	amisulpride 50mg/5ml oral suspension	2
32076	aripiprazole 10mg orodispersible tablets sugar free	2
6561	aripiprazole 10mg tablets	2
31098	aripiprazole 15mg orodispersible tablets sugar free	2
6573	aripiprazole 15mg tablets	2
16575	aripiprazole 1mg/ml oral solution	2
16561	aripiprazole 30mg tablets	2
14344	aripiprazole 5mg tablets	2
38375	aripiprazole 9.75mg/1.3ml solution for injection vials	2
47167	asenapine 10mg sublingual tablets sugar free	2
47280	asenapine 5mg sublingual tablets sugar free	2
8047	clozapine 100mg tablets	2
40587	clozapine 200mg tablets	2
8046	clozapine 25mg tablets	2
40586	clozapine 50mg tablets	2
42242	clozapine 50mg/ml oral suspension sugar free	2
14112	clozaril 100mg tablets (novartis pharmaceuticals uk ltd)	2
17958	clozaril 25mg tablets (novartis pharmaceuticals uk ltd)	2
21199	denzapine 100mg tablets (britannia pharmaceuticals ltd)	2
41428	denzapine 200mg tablets (britannia pharmaceuticals ltd)	2
30487	denzapine 25mg tablets (britannia pharmaceuticals ltd)	2
41070	denzapine 50mg tablets (britannia pharmaceuticals ltd)	2

45444	denzapine 50mg/ml oral suspension (britannia pharmaceuticals ltd)	2
36954	invega 6mg modified-release tablets (janssen-cilag ltd)	2
18658	olanzapine	2
53556	olanzapine 10mg oral lyophilisates sugar free	2
47304	olanzapine 10mg oral lyophilisates sugar free	2
6023	olanzapine 10mg orodispersible tablet	2
55622	olanzapine 10mg orodispersible tablets	2
47049	olanzapine 10mg orodispersible tablets	2
47063	olanzapine 10mg orodispersible tablets sugar free	2
23431	olanzapine 10mg powder for solution for injection vials	2
1249	olanzapine 10mg tablets	2
58854	olanzapine 10mg tablets (actavis uk ltd)	2
58147	olanzapine 10mg tablets (zentiva)	2
56577	olanzapine 15mg oral lyophilisates sugar free	2
47394	olanzapine 15mg oral lyophilisates sugar free	2
6838	olanzapine 15mg orodispersible tablet	2
47152	olanzapine 15mg orodispersible tablets	2
56143	olanzapine 15mg orodispersible tablets	2
47103	olanzapine 15mg orodispersible tablets sugar free	2
6850	olanzapine 15mg tablets	2
55667	olanzapine 15mg tablets (actavis uk ltd)	2
2656	olanzapine 2.5mg tablets	2
52001	olanzapine 2.5mg tablets (aspire pharma ltd)	2
59143	olanzapine 2.5mg tablets (teva uk ltd)	2
57270	olanzapine 2.5mg/5ml oral suspension	2
47498	olanzapine 20mg oral lyophilisates sugar free	2
56265	olanzapine 20mg oral lyophilisates sugar free	2
16103	olanzapine 20mg orodispersible tablet	2
56072	olanzapine 20mg orodispersible tablets	2
47083	olanzapine 20mg orodispersible tablets	2
47093	olanzapine 20mg orodispersible tablets sugar free	2
29540	olanzapine 20mg tablets	2
57616	olanzapine 20mg tablets (teva uk ltd)	2
56193	olanzapine 5mg oral lyophilisates sugar free	2
57160	olanzapine 5mg oral lyophilisates sugar free	2
47256	olanzapine 5mg oral lyophilisates sugar free	2
6412	olanzapine 5mg orodispersible tablet	2
50214	olanzapine 5mg orodispersible tablets	2
47055	olanzapine 5mg orodispersible tablets	2
47098	olanzapine 5mg orodispersible tablets sugar free	2
3281	olanzapine 5mg tablets	2
5653	olanzapine 7.5mg tablets	2
43914	olanzapine embonate 210mg powder and solvent for suspension for injection vials	2
46422	olanzapine embonate 300mg powder and solvent for suspension for injection vials	2

46447	paliperidone 100mg/1ml suspension for injection pre-filled syringes	2
46351	paliperidone 150mg/1.5ml suspension for injection pre-filled syringes	2
37717	paliperidone 3mg modified-release tablets	2
46224	paliperidone 50mg/0.5ml suspension for injection pre-filled syringes	2
36116	paliperidone 6mg modified-release tablets	2
46556	paliperidone 75mg/0.75ml suspension for injection pre-filled syringes	2
37501	paliperidone 9mg modified-release tablets	2
5039	quetiapine 100mg tablets	2
40779	quetiapine 100mg/5ml oral solution	2
40932	quetiapine 100mg/5ml oral suspension	2
46764	quetiapine 12.5mg/5ml oral solution	2
46871	quetiapine 12.5mg/5ml oral suspension	2
58067	quetiapine 125mg/5ml oral suspension	2
44024	quetiapine 150mg modified-release tablets	2
5040	quetiapine 150mg tablets	2
59215	quetiapine 150mg tablets (ranbaxy (uk) ltd)	2
38912	quetiapine 200mg modified-release tablets	2
9794	quetiapine 200mg tablets	2
5283	quetiapine 25mg tablets	2
58821	quetiapine 25mg tablets (dr reddy's laboratories (uk) ltd)	2
53552	quetiapine 25mg tablets (zentiva)	2
49696	quetiapine 25mg/5ml oral solution	2
45839	quetiapine 25mg/5ml oral suspension	2
38906	quetiapine 300mg modified-release tablets	2
7039	quetiapine 300mg tablets	2
56647	quetiapine 300mg tablets (arrow generics ltd)	2
38840	quetiapine 400mg modified-release tablets	2
38885	quetiapine 50mg modified-release tablets	2
56215	quetiapine 50mg/5ml oral solution	2
51178	quetiapine 50mg/5ml oral suspension	2
55870	quetiapine oral liquid	2
10107	quetiapine starter pack	2
4820	risperdal 1mg tablets (janssen-cilag ltd)	2
5262	risperdal 1mg/ml liquid (janssen-cilag ltd)	2
9659	risperdal 2mg tablets (janssen-cilag ltd)	2
9340	risperdal 3mg tablets (janssen-cilag ltd)	2
9475	risperdal 4mg tablets (janssen-cilag ltd)	2
631	risperdal 500microgram tablets (janssen-cilag ltd)	2
11799	risperdal 6mg tablets (janssen-cilag ltd)	2
16908	risperdal consta 25mg powder and solvent for suspension for injection vials (janssen-cilag ltd)	2
14789	risperdal consta 37.5mg powder and solvent for suspension for injection vials (janssen-cilag ltd)	2
14767	risperdal consta 50mg powder and solvent for suspension for injection vials (janssen-cilag ltd)	2
51444	risperdal consta 50mg powder and solvent for suspension for injection vials (waymade healthcare plc)	2
16986	risperdal quicklet 1mg orodispersible tablets (janssen-cilag ltd)	2

16006	risperdal quicklet 2mg orodispersible tablets (janssen-cilag ltd)	2
35548	risperdal quicklet 3mg orodispersible tablets (janssen-cilag ltd)	2
35953	risperdal quicklet 4mg orodispersible tablets (janssen-cilag ltd)	2
11821	risperdal quicklet 500microgram orodispersible tablets (janssen-cilag ltd)	2
12579	risperdal(3 mg) 3 mg tab	2
51240	risperidone 125micrograms/5ml oral solution	2
6373	risperidone 1mg orodispersible tablets sugar free	2
1320	risperidone 1mg tablets	2
57217	risperidone 1mg tablets (generics (uk) ltd)	2
55661	risperidone 1mg tablets (kent pharmaceuticals ltd)	2
54346	risperidone 1mg tablets (teva uk ltd)	2
302	risperidone 1mg/ml oral solution sugar free	2
56387	risperidone 1mg/ml oral solution sugar free (alliance healthcare (distribution) ltd)	2
16434	risperidone 25mg powder and solvent for suspension for injection vials	2
11828	risperidone 2mg orodispersible tablets sugar free	2
1321	risperidone 2mg tablets	2
59548	risperidone 2mg tablets (alliance healthcare (distribution) ltd)	2
16425	risperidone 37.5mg powder and solvent for suspension for injection vials	2
35141	risperidone 3mg orodispersible tablets sugar free	2
5219	risperidone 3mg tablets	2
59829	risperidone 3mg tablets (a a h pharmaceuticals ltd)	2
35589	risperidone 4mg orodispersible tablets sugar free	2
2787	risperidone 4mg tablets	2
58822	risperidone 4mg tablets (almus pharmaceuticals ltd)	2
7382	risperidone 500microgram orodispersible tablets sugar free	2
667	risperidone 500microgram tablets	2
47832	risperidone 500microgram tablets (a a h pharmaceuticals ltd)	2
46677	risperidone 500microgram tablets (actavis uk ltd)	2
16489	risperidone 50mg powder and solvent for suspension for injection vials	2
2786	risperidone 6mg tablets	2
31063	serdolect 12mg tablets (lundbeck ltd)	2
23162	serdolect 16mg tablets (lundbeck ltd)	2
25966	serdolect 4mg tablets (lundbeck ltd)	2
18013	seroquel 100mg tablets (astrazeneca uk ltd)	2
14813	seroquel 150mg tablets (astrazeneca uk ltd)	2
6864	seroquel 200mg tablets (astrazeneca uk ltd)	2
14859	seroquel 25mg tablets (astrazeneca uk ltd)	2
21709	seroquel 300mg tablets (astrazeneca uk ltd)	2
18023	seroquel tablets starter pack (astrazeneca uk ltd)	2
44326	seroquel xl 150mg tablets (astrazeneca uk ltd)	2
38914	seroquel xl 200mg tablets (astrazeneca uk ltd)	2
38937	seroquel xl 300mg tablets (astrazeneca uk ltd)	2
39237	seroquel xl 400mg tablets (astrazeneca uk ltd)	2
57612	seroquel xl 400mg tablets (lexon (uk) ltd)	2

38913	seroquel xl 50mg tablets (astrazeneca uk ltd)	2
58425	seroquel xl 50mg tablets (de pharmaceuticals)	2
57613	seroquel xl 50mg tablets (sigma pharmaceuticals plc)	2
16998	sertindole 12mg tablets	2
19900	sertindole 16mg tablets	2
17050	sertindole 20mg tablets	2
12666	sertindole 4mg tablets	2
26544	solian 100 tablets (sanofi)	2
31576	solian 100mg/ml oral solution (sanofi)	2
4992	solian 200 tablets (sanofi)	2
6109	solian 400 tablets (sanofi)	2
16768	solian 50 tablets (sanofi)	2
57034	sondate xl 200mg tablets (teva uk ltd)	2
54483	sondate xl 300mg tablets (teva uk ltd)	2
57412	sondate xl 400mg tablets (teva uk ltd)	2
52940	sondate xl 50mg tablets (teva uk ltd)	2
58935	tenprolide xl 400mg tablets (actavis uk ltd)	2
58936	tenprolide xl 50mg tablets (actavis uk ltd)	2
46434	xeplion 100mg/1ml suspension for injection pre-filled syringes (janssen-cilag ltd)	2
46435	xeplion 150mg/1.5ml suspension for injection pre-filled syringes (janssen-cilag ltd)	2
47162	xeplion 50mg/0.5ml suspension for injection pre-filled syringes (janssen-cilag ltd)	2
46436	xeplion 75mg/0.75ml suspension for injection pre-filled syringes (janssen-cilag ltd)	2
53848	zalasta 5mg orodispersible tablets (consilient health ltd)	2
47302	zaponex 100mg tablets (teva uk ltd)	2
47233	zaponex 25mg tablets (teva uk ltd)	2
30088	zoleptil 25 tablets (movianto uk ltd)	2
9515	zoleptil 50 tablets (movianto uk ltd)	2
28759	zotepine 100mg tablets	2
17504	zotepine 25mg tablets	2
25336	zotepine 50mg tablets	2
55268	zypadhera 300mg powder and solvent for suspension for injection vials (eli lilly and company ltd)	2
45953	zyprexa 10mg powder for solution for injection vials (eli lilly and company ltd)	2
13820	zyprexa 10mg tablets (eli lilly and company ltd)	2
13888	zyprexa 10mg velotabs (eli lilly and company ltd)	2
19976	zyprexa 15mg tablets (eli lilly and company ltd)	2
16407	zyprexa 15mg velotabs (eli lilly and company ltd)	2
18453	zyprexa 2.5mg tablets (eli lilly and company ltd)	2
36163	zyprexa 20mg tablets (eli lilly and company ltd)	2
33883	zyprexa 20mg velotabs (eli lilly and company ltd)	2
18024	zyprexa 5mg tablets (eli lilly and company ltd)	2
14717	zyprexa 5mg velotabs (eli lilly and company ltd)	2
21964	zyprexa 7.5mg tablets (eli lilly and company ltd)	2
1943	Avomine 25mg tablets (Manx Healthcare Ltd)	1
500	Buccastem 3mg Tablet (Reckitt Benckiser Healthcare (UK) Ltd)	1

42882	Buccastem 3mg tablets (Alliance Pharmaceuticals Ltd)	1
5971	Buccastem M 3mg tablets (Alliance Pharmaceuticals Ltd)	1
9202	CODEINE PHOS/EPHEDRINE HYD/PROMETHAZINE LIN	1
67820	Chlorpromazine 100mg/5ml oral suspension	1
60908	Chlorpromazine 10mg capsules	1
65246	Chlorpromazine 10mg/5ml oral suspension	1
67747	Chlorpromazine 25mg tablets (Almus Pharmaceuticals Ltd)	1
61153	Chlorpromazine 25mg tablets (Phoenix Healthcare Distribution Ltd)	1
25759	DROPERIDOL	1
13341	DROPERIDOL 5 MG/5ML ELI	1
66652	Decazate 25mg/ml Injection (Berk Pharmaceuticals Ltd)	1
40928	Droperidol 2.5mg/1ml solution for injection ampoules	1
57571	Droperidol 5mg/5ml oral solution	1
24457	Fentanyl with droperidol 500microgramwith2.5mg/ml Injection	1
600	Flupentixol 1mg tablets	1
2275	Flupentixol 500microgram tablets	1
69365	Haloperidol 1mg/ml sugar free Oral solution (Pinewood Healthcare)	1
70112	Haloperidol 200micrograms/ml oral solution sugar free	1
70584	Haloperidol 500micrograms/5ml oral solution	1
67364	Haloperidol 5mg tablets (Crescent Pharma Ltd)	1
60942	Haloperidol 5mg/5ml oral solution	1
12356	LARGACTIL 50 MG INJ	1
10689	LARGACTIL FORTE SYR	1
67247	Largactil 50mg tablets (Waymade Healthcare Plc)	1
64673	Levomepromazine 10mg/5ml oral suspension	1
61083	Levomepromazine 25mg/1ml solution for injection ampoules (A A H Pharmaceuticals Ltd)	1
60719	Levomepromazine 5mg/5ml oral solution	1
65865	Levomepromazine 6.25mg/5ml oral suspension	1
70515	Levomepromazine 6mg/5ml oral solution	1
65843	Levomepromazine 6mg/5ml oral suspension	1
20174	Loxapac 10mg capsules (Wyeth Pharmaceuticals)	1
12619	Loxapac 25mg capsules (Wyeth Pharmaceuticals)	1
26800	Loxapac 50mg capsules (Wyeth Pharmaceuticals)	1
12616	Loxapine 10mg capsules	1
12615	Loxapine 25mg capsules	1
12630	Loxapine 50mg capsules	1
68660	Loxapine 9.1mg/dose inhalation powder	1
26661	MELLERIL 100mg/5ml	1
19606	MELLERIL 25mg/5ml	1
23201	MELLERIL 25mg/5ml	1
19738	MORPHINE,COCAINE & CHLORPROMAZINE MIX	1
8774	Melleril 100mg tablets (Novartis Pharmaceuticals UK Ltd)	1
15157	Melleril 100mg/5ml oral suspension (Novartis Pharmaceuticals UK Ltd)	1
284	Melleril 10mg tablets (Novartis Pharmaceuticals UK Ltd)	1

1162	Melleril 25mg tablets (Novartis Pharmaceuticals UK Ltd)	1
3579	Melleril 25mg/5ml oral suspension (Novartis Pharmaceuticals UK Ltd)	1
4673	Melleril 25mg/5ml syrup (Novartis Pharmaceuticals UK Ltd)	1
2502	Melleril 50mg tablets (Novartis Pharmaceuticals UK Ltd)	1
29967	NEULACTIL FORTE	1
8922	Oxypertine 10mg capsules	1
18991	Oxypertine 40mg tablets	1
25629	PHENERGAN 2 % CRE	1
18986	PHENERGAN 50 MG INJ	1
25960	PHENERGAN comp EXPECT LIN	1
14373	PROMETHAZINE 50 MG INJ	1
21010	PROMETHAZINE HCl 2 % CRE	1
10901	Paracetamol with promethazine hydrochloride 120mg+1.5mg/5ml suspension	1
22236	Paracetamol with promethazine hydrochloride 120mg+1.5mg/5ml suspension sugar free colour free	1
24445	Paracetamol with promethazine hydrochloride tablet	1
67777	Pericyazine 2.5mg tablets (Zentiva)	1
19116	Pethidine 100mg/2ml / Promethazine 50mg/2ml solution for injection ampoules	1
918	Phenergan 10mg tablets (Sanofi)	1
49968	Phenergan 25mg tablets (DE Pharmaceuticals)	1
55838	Phenergan 25mg tablets (Lexon (UK) Ltd)	1
3582	Phenergan 25mg tablets (Sanofi)	1
35437	Phenergan 25mg/1ml solution for injection ampoules (Sanofi)	1
7438	Phenergan 25mg/ml Injection (Aventis Pharma)	1
1610	Phenergan 5mg/5ml elixir (Sanofi)	1
14955	Phenergan Nightime 25mg tablets (Sanofi)	1
18193	Pholcodine 1.5mg/5ml / Promethazine 1.5mg/5ml oral solution sugar free	1
27988	Pholcodine with promethazine hydrochloride linctus	1
64567	Pimozide 1mg tablets	1
4769	Prochlorperazine 3mg buccal tablets	1
60971	Prochlorperazine 3mg buccal tablets (A A H Pharmaceuticals Ltd)	1
66990	Prochlorperazine 3mg buccal tablets (Alliance Healthcare (Distribution) Ltd)	1
59008	Prochlorperazine 3mg buccal tablets (Focus Pharmaceuticals Ltd)	1
61592	Prochlorperazine 5mg tablets (Almus Pharmaceuticals Ltd)	1
68942	Prochlorperazine 5mg tablets (DE Pharmaceuticals)	1
62115	Prochlorperazine 5mg tablets (Genesis Pharmaceuticals Ltd)	1
65449	Promazine 25mg tablets (Teva UK Ltd)	1
63601	Promazine 25mg/5ml oral solution (A A H Pharmaceuticals Ltd)	1
67799	Promazine 50mg/5ml oral suspension	1
35846	Promethazine 25mg/1ml solution for injection ampoules	1
62980	Promethazine 25mg/5ml oral solution	1
62590	Promethazine 25mg/5ml oral suspension	1
47056	Promethazine 50mg/2ml solution for injection ampoules	1
1998	Promethazine 5mg/5ml oral solution sugar free	1
33230	Promethazine hydrochloride 1.5mg with paracetamol 120mg/5ml oral solution	1

23052	Promethazine hydrochloride 1.5mg with paracetamol 120mg/5ml oral solution colour free and sugar free	1
29732	Promethazine hydrochloride 1.5mg with pholcodine 1.5mg/5ml oral solution	1
5561	Promethazine hydrochloride 10mg tablets	1
11004	Promethazine hydrochloride 20mg tablets	1
3494	Promethazine hydrochloride 25mg tablets	1
12214	Promethazine hydrochloride 25mg/ml injection	1
33954	Promethazine hydrochloride 50mg with pethidine 100mg/2ml injection	1
989	Promethazine teoclate 25mg tablets	1
60782	Psytixol 20mg/1ml solution for injection ampoules (Generics (UK) Ltd)	1
24243	STEMETIL	1
19824	STEMETIL (1ML)	1
7985	STEMETIL 2.5 MG SUP	1
21359	Sominex 20mg tablets (Teva UK Ltd)	1
62182	Sominex Herbal tablets (Teva UK Ltd)	1
45064	Sominex herbal Tablet (Actavis UK Ltd)	1
8445	Stelabid Tablet (GlaxoSmithKline Consumer Healthcare)	1
23475	THALAMONAL (2ML)	1
28979	THIORIDAZINE 100mg/5ml	1
26082	THIORIDAZINE 25mg/5ml	1
20668	THIORIDAZINE 25mg/5ml	1
52143	THIORIDAZINE CONCENTRATE 750MG/5ML 750 MG ELI	1
10870	THIORIDAZINE S/F 50 MG/5ML SYR	1
17877	TRIFLUPERIDOL 2 MG TAB	1
10675	Thioridazine 100mg/5ml oral suspension	1
43424	Thioridazine 25mg tablets (A A H Pharmaceuticals Ltd)	1
67765	Thioridazine 25mg/5ml oral solution (A A H Pharmaceuticals Ltd)	1
47881	Thioridazine 25mg/5ml oral solution (Rosemont Pharmaceuticals Ltd)	1
9387	Thioridazine 25mg/5ml oral suspension	1
34902	Thioridazine 50mg tablets (A A H Pharmaceuticals Ltd)	1
23173	Tranquilyn 10mg tablets (Genesis Pharmaceuticals Ltd)	1
62584	Tranquilyn 20mg tablets (Genesis Pharmaceuticals Ltd)	1
23161	Tranquilyn 5mg tablets (Genesis Pharmaceuticals Ltd)	1
31889	Ziz 10mg tablets (Chatfield Laboratories)	1
3490	amitriptyline 10mg / perphenazine 2mg tablets	1
595	amitriptyline 25mg / perphenazine 2mg tablets	1
21744	anquil 250microgram tablet (concord pharmaceuticals ltd)	1
47365	anquil 250microgram tablets (archimedes pharma uk ltd)	1
2540	benperidol 250microgram tablets	1
31796	benquil 250microgram tablets (concord pharmaceuticals ltd)	1
28862	chloractil 100mg tablet (ddsa pharmaceuticals ltd)	1
17227	chloractil 25mg tablet (ddsa pharmaceuticals ltd)	1
25653	chloractil 50mg tablet (ddsa pharmaceuticals ltd)	1
8506	chlorpromazine 100mg suppository	1
2154	chlorpromazine 100mg tablets	1

46960	chlorpromazine 100mg tablets (ivax pharmaceuticals uk ltd)	1
34736	chlorpromazine 100mg tablets (teva uk ltd)	1
58492	chlorpromazine 100mg tablets (waymade healthcare plc)	1
8519	chlorpromazine 100mg/5ml oral solution	1
45281	chlorpromazine 100mg/5ml oral solution (rosemont pharmaceuticals ltd)	1
9965	chlorpromazine 100mg/5ml oral suspension sugar free	1
37705	chlorpromazine 100mg/5ml suspension	1
2474	chlorpromazine 10mg tablets	1
8045	chlorpromazine 200 mg tab	1
13479	chlorpromazine 25 mg sup	1
588	chlorpromazine 25mg tablets	1
31175	chlorpromazine 25mg tablets (a a h pharmaceuticals ltd)	1
31184	chlorpromazine 25mg tablets (ivax pharmaceuticals uk ltd)	1
34668	chlorpromazine 25mg tablets (teva uk ltd)	1
34693	chlorpromazine 25mg tablets (thornton & ross ltd)	1
22606	chlorpromazine 25mg/1ml solution for injection ampoules	1
3952	chlorpromazine 25mg/5ml oral solution	1
44186	chlorpromazine 25mg/5ml oral solution (a a h pharmaceuticals ltd)	1
37871	chlorpromazine 25mg/5ml oral solution (rosemont pharmaceuticals ltd)	1
9190	chlorpromazine 25mg/5ml oral solution sugar free	1
56862	chlorpromazine 25mg/5ml syrup (rosemont pharmaceuticals ltd)	1
8311	chlorpromazine 25mg/ml injection	1
41645	chlorpromazine 25mg/ml injection (antigen pharmaceuticals)	1
247	chlorpromazine 50 mg inj	1
3348	chlorpromazine 50mg tablets	1
31171	chlorpromazine 50mg tablets (a a h pharmaceuticals ltd)	1
31172	chlorpromazine 50mg tablets (teva uk ltd)	1
34630	chlorpromazine 50mg tablets (thornton & ross ltd)	1
35929	chlorpromazine 50mg/2ml solution for injection ampoules	1
4434	chlorpromazine 50mg/5ml oral solution	1
17221	chlorpromazine hcl 10 mg inj	1
12544	chlorpromazine hcl 100 mg mix	1
30346	chlorpromazine hcl 100 mg tab	1
12137	chlorpromazine hcl 25 mg tab	1
19033	chlorpromazine hcl 50 mg inj	1
10446	chlorpromazine hcl 50 mg tab	1
31747	chlorpromazine hydrochloride	1
30111	chlorprothixene 50mg tablets	1
1319	clopixol 10mg tablets (lundbeck ltd)	1
22049	clopixol 200mg/1ml solution for injection ampoules (lundbeck ltd)	1
3774	clopixol 200mg/ml oily injection (lundbeck ltd)	1
9347	clopixol 25mg tablets (lundbeck ltd)	1
13368	clopixol 2mg tablets (lundbeck ltd)	1
31538	clopixol acuphase 100mg/2ml solution for injection ampoules (lundbeck ltd)	1

36101	clopixol acuphase 50mg/1ml solution for injection ampoules (lundbeck ltd)	1
5762	clopixol acuphase 50mg/ml oily injection (lundbeck ltd)	1
12073	clopixol conc 500mg/1ml solution for injection ampoules (lundbeck ltd)	1
19752	depixol (10ml vial)	1
2155	depixol -conc 100mg/ml injection (lundbeck ltd)	1
19283	depixol 20mg/1ml solution for injection ampoules (lundbeck ltd)	1
2136	depixol 20mg/ml injection (lundbeck ltd)	1
5712	depixol 3mg tablets (lundbeck ltd)	1
2156	depixol 40mg/2ml solution for injection ampoules (lundbeck ltd)	1
14889	depixol conc 100mg/1ml solution for injection ampoules (lundbeck ltd)	1
18197	depixol conc 50mg/0.5ml solution for injection ampoules (lundbeck ltd)	1
14130	depixol low volume 200mg/1ml solution for injection ampoules (lundbeck ltd)	1
25015	depixol-conc (1ml amp)	1
10666	dolmatil 200mg tablets (sanofi)	1
24069	dolmatil 400mg tablets (sanofi)	1
28679	dozic 2mg/ml oral solution (rosemont pharmaceuticals ltd)	1
6134	dozic 5mg/5ml oral solution (rosemont pharmaceuticals ltd)	1
15171	droleptan 10mg tablet (janssen-cilag ltd)	1
13369	droleptan 1mg/ml oral solution (janssen-cilag ltd)	1
21125	droleptan 5mg/ml injection (janssen-cilag ltd)	1
3773	droperidol 10mg tablets	1
15128	droperidol 1mg/ml liquid	1
22609	droperidol 5mg/ml injection	1
53634	droperidol capsules	1
42229	droperidol oral liquid	1
840	fentazin 2mg tablets (amco)	1
7919	fentazin 4mg tablets (amco)	1
228	fentazin 5mg/ml injection (goldshield pharmaceuticals ltd)	1
24282	fentazin 8 mg tab	1
27565	fluanxol	1
3951	fluanxol 1mg tablets (lundbeck ltd)	1
50592	fluanxol 1mg tablets (sigma pharmaceuticals plc)	1
59593	fluanxol 500microgram tablets (lexon (uk) ltd)	1
3953	fluanxol 500microgram tablets (lundbeck ltd)	1
18175	flupentixol 100mg/1ml solution for injection ampoules	1
14839	flupentixol 200mg/1ml solution for injection ampoules	1
14966	flupentixol 20mg/1ml solution for injection ampoules	1
5707	flupentixol 3mg tablets	1
2276	flupentixol 40mg/2ml solution for injection ampoules	1
18155	flupentixol 50mg/0.5ml solution for injection ampoules	1
8712	flupentixol decanoate 100mg/ml injection	1
1733	flupentixol decanoate 20mg/ml injection	1
55620	flupentixol liquid	1
5212	fluphenazine 1mg tablets	1

8377	fluphenazine 2.5mg tablets	1
5298	fluphenazine 5mg tablets	1
35176	fluphenazine decanoate 100mg/1ml solution for injection ampoules	1
10514	fluphenazine decanoate 100mg/ml injection	1
16229	fluphenazine decanoate 12.5 mg inj	1
35530	fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules	1
35065	fluphenazine decanoate 25mg/1ml solution for injection ampoules	1
41970	fluphenazine decanoate 25mg/1ml solution for injection ampoules (hospira uk ltd)	1
9022	fluphenazine decanoate 25mg/ml injection	1
41971	fluphenazine decanoate 25mg/ml injection (antigen pharmaceuticals)	1
35391	fluphenazine decanoate 50mg/0.5ml solution for injection ampoules	1
35723	fluphenazine decanoate 50mg/2ml solution for injection ampoules	1
17190	fluphenazine enanthate 25mg/ml injection	1
24107	fluphenazine hcl eli	1
20571	fluphenazine with nortriptyline 500microgramswith10mg tablet	1
10827	fluspirilene 2mg/ml injection	1
30351	haldol 1.5 mg tab	1
23678	haldol 10mg tablets (janssen-cilag ltd)	1
24494	haldol 10mg/ml liquid (janssen-cilag ltd)	1
15645	haldol 20 mg tab	1
12921	haldol 2mg/ml oral solution (janssen-cilag ltd)	1
22660	haldol 5mg tablets (janssen-cilag ltd)	1
38540	haldol 5mg/1ml solution for injection ampoules (janssen-cilag ltd)	1
6523	haldol 5mg/ml injection (janssen-cilag ltd)	1
12386	haldol decanoate 100mg/1ml solution for injection ampoules (janssen-cilag ltd)	1
2094	haldol decanoate 50mg/1ml solution for injection ampoules (janssen-cilag ltd)	1
329	haloperidol 1.5mg tablets	1
34339	haloperidol 1.5mg tablets (a a h pharmaceuticals ltd)	1
32838	haloperidol 1.5mg tablets (ivax pharmaceuticals uk ltd)	1
43520	haloperidol 1.5mg tablets (teva uk ltd)	1
52050	haloperidol 1.5mg/5ml oral suspension	1
17379	haloperidol 1.5mg/5ml sugar free oral solution	1
25063	haloperidol 100mg/ml	1
12050	haloperidol 100mg/ml 100 mg inj	1
475	haloperidol 10mg tablets	1
45810	haloperidol 10mg/5ml oral solution sugar free	1
47808	haloperidol 10mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)	1
10435	haloperidol 10mg/ml oral solution	1
47149	haloperidol 1mg/5ml oral solution	1
47013	haloperidol 1mg/5ml oral suspension	1
5192	haloperidol 1mg/5ml sugar free oral solution	1
41546	haloperidol 1mg/ml liquid (hillcross pharmaceuticals ltd)	1
34039	haloperidol 1mg/ml liquid (rosemont pharmaceuticals ltd)	1
2620	haloperidol 1mg/ml oral solution	1

9975	haloperidol 1mg/ml sugar free oral solution	1
12387	haloperidol 20mg tablets	1
8129	haloperidol 20mg/2ml solution for injection ampoules	1
36771	haloperidol 250micrograms/5ml oral suspension	1
49207	haloperidol 2mg/5ml oral solution	1
53649	haloperidol 2mg/5ml oral suspension	1
11213	haloperidol 2mg/5ml sugar free oral solution	1
55871	haloperidol 2mg/ml liquid (hillcross pharmaceuticals ltd)	1
42000	haloperidol 2mg/ml liquid (rosemont pharmaceuticals ltd)	1
13105	haloperidol 2mg/ml oral solution	1
3233	haloperidol 2mg/ml sugar free liquid	1
8136	haloperidol 5 mg liq	1
2419	haloperidol 500microgram capsules	1
42807	haloperidol 500microgram tablet (lagap)	1
3671	haloperidol 500microgram tablets	1
43431	haloperidol 500microgram tablets (a a h pharmaceuticals ltd)	1
41420	haloperidol 500microgram tablets (sandoz ltd)	1
32051	haloperidol 5mg tablet (generics (uk) ltd)	1
2621	haloperidol 5mg tablets	1
34903	haloperidol 5mg tablets (ivax pharmaceuticals uk ltd)	1
42895	haloperidol 5mg tablets (teva uk ltd)	1
38262	haloperidol 5mg/1ml solution for injection ampoules	1
55848	haloperidol 5mg/1ml solution for injection ampoules (amco)	1
45880	haloperidol 5mg/5ml oral solution sugar free	1
4234	haloperidol 5mg/ml injection	1
34272	haloperidol 5mg/ml injection (antigen pharmaceuticals)	1
15814	haloperidol decanoate 100mg/1ml solution for injection ampoules	1
10565	haloperidol decanoate 50mg/1ml solution for injection ampoules	1
43020	haloperidol oral solution	1
8921	integrin 10mg capsule (sanofi-synthelabo ltd)	1
27211	integrin 40mg tablet (sanofi-synthelabo ltd)	1
19002	largactil 100mg suppository (rhone-poulenc rorer ltd)	1
7493	largactil 100mg tablet (hawgreen ltd)	1
58702	largactil 100mg tablets (sanofi)	1
8771	largactil 10mg tablet (hawgreen ltd)	1
55012	largactil 10mg tablets (sanofi)	1
2814	largactil 25mg tablet (hawgreen ltd)	1
55011	largactil 25mg tablets (sanofi)	1
10434	largactil 25mg/5ml oral solution (hawgreen ltd)	1
57550	largactil 25mg/5ml syrup (sanofi)	1
3772	largactil 50mg tablet (hawgreen ltd)	1
58703	largactil 50mg tablets (sanofi)	1
7514	largactil 50mg/2ml solution for injection ampoules (sanofi)	1
15418	largactil forte 100mg/5ml oral suspension (hawgreen ltd)	1

28231	levinan 6mg tablet (link pharmaceuticals ltd)	1
49606	levinan 6mg tablets (archimedes pharma uk ltd)	1
5014	levomepromazine 25mg tablets	1
6064	levomepromazine 25mg/1ml solution for injection ampoules	1
59938	levomepromazine 25mg/1ml solution for injection ampoules (wockhardt uk ltd)	1
60250	levomepromazine 3mg/5ml oral solution	1
53951	levomepromazine 6.25mg/5ml oral solution	1
40782	levomepromazine 6mg tablet	1
7390	levomepromazine 6mg tablets	1
22174	modecate	1
8043	modecate 12.5 mg inj	1
35122	modecate 12.5mg/0.5ml solution for injection ampoules (sanofi)	1
33780	modecate 25mg/1ml solution for injection ampoules (sanofi)	1
3926	modecate 25mg/ml injection (sanofi-synthelabo ltd)	1
35445	modecate 50mg/2ml solution for injection ampoules (sanofi)	1
23340	modecate conc	1
35455	modecate concentrate 100mg/1ml solution for injection ampoules (sanofi)	1
12128	modecate concentrate 100mg/ml injection (sanofi-synthelabo ltd)	1
35487	modecate concentrate 50mg/0.5ml solution for injection ampoules (sanofi)	1
26692	modecate disposable syringe	1
26684	modecate disposable syringe	1
5597	moditen 1mg tablets (sanofi)	1
7918	moditen 2.5mg tablets (sanofi)	1
20703	moditen 5mg tablets (sanofi-synthelabo ltd)	1
25835	moditen enanthate 25mg/ml injection (sanofi-synthelabo ltd)	1
8493	motipress tablets (sanofi-synthelabo ltd)	1
2936	motival 10mg/500microgram tablets (sanofi)	1
8031	neulactil 10mg tablet (jhc healthcare ltd)	1
40881	neulactil 10mg tablets (sanofi)	1
7833	neulactil 2.5mg tablet (jhc healthcare ltd)	1
39830	neulactil 2.5mg tablets (sanofi)	1
21064	neulactil 25mg tablet (jhc healthcare ltd)	1
13902	neulactil forte syrup (sanofi)	1
7780	nortriptyline 10mg / fluphenazine 500microgram tablets	1
14578	nortriptyline 30mg / fluphenazine 1.5mg tablets	1
4232	nozinan 25mg tablets (sanofi)	1
52846	nozinan 25mg/1ml solution for injection ampoules (lexon (uk) ltd)	1
4442	nozinan 25mg/1ml solution for injection ampoules (sanofi)	1
27148	orap 10mg tablet (janssen-cilag ltd)	1
4524	orap 2mg tablets (janssen-cilag ltd)	1
15047	orap 4mg tablets (janssen-cilag ltd)	1
3356	parstelin tablet (glaxosmithkline consumer healthcare)	1
29972	pericyazine	1
8032	pericyazine 10mg tablets	1

12195	pericyazine 10mg/5ml oral solution	1
22655	pericyazine 2.5 mg eli	1
7834	pericyazine 2.5mg tablets	1
15472	pericyazine 25mg tablet	1
609	perphenazine 2mg tablets	1
16323	perphenazine 2mg with amitriptyline 10mg tablet	1
6894	perphenazine 2mg with amitriptyline 25mg tablet	1
14987	perphenazine 2mg/5ml oral solution sugar free	1
2157	perphenazine 4mg tablets	1
25909	perphenazine 4mg/5ml oral solution sugar free	1
17087	perphenazine 5mg/ml injection	1
20061	perphenazine 8 mg tab	1
8637	pimozide 10mg tablet	1
2489	pimozide 2mg tablets	1
5821	pimozide 4mg tablets	1
12340	piportil 50mg/ml depot injection (jhc healthcare ltd)	1
35488	piportil depot 100mg/2ml solution for injection ampoules (sanofi)	1
35235	piportil depot 50mg/1ml solution for injection ampoules (sanofi)	1
36394	pipotiazine 100mg/2ml solution for injection ampoules	1
35684	pipotiazine 50mg/1ml solution for injection ampoules	1
10944	pipotiazine palmitate 50mg/ml depot injection	1
14364	prochlorperazine 12.5mg/1ml solution for injection ampoules	1
32122	prochlorperazine 12.5mg/1ml solution for injection ampoules (amco)	1
1990	prochlorperazine 25mg suppositories	1
3932	prochlorperazine 25mg tablets	1
237	prochlorperazine 5 mg eli	1
9590	prochlorperazine 5mg effervescent granules sachets sugar free	1
1434	prochlorperazine 5mg suppositories	1
54458	prochlorperazine 5mg tablet (teva uk ltd)	1
85	prochlorperazine 5mg tablets	1
34344	prochlorperazine 5mg tablets (a a h pharmaceuticals ltd)	1
32064	prochlorperazine 5mg tablets (actavis uk ltd)	1
43420	prochlorperazine 5mg tablets (dr reddy's laboratories (uk) ltd)	1
32772	prochlorperazine 5mg tablets (generics (uk) ltd)	1
32551	prochlorperazine 5mg tablets (ivax pharmaceuticals uk ltd)	1
55038	prochlorperazine 5mg tablets (sigma pharmaceuticals plc)	1
32876	prochlorperazine 5mg tablets (teva uk ltd)	1
6036	prochlorperazine 5mg/5ml oral solution	1
4401	prochlorperazine maleate 10mg modified release capsule	1
15438	prochlorperazine maleate 15mg modified release capsul	1
3024	prochlorperazine maleate 3 mg tab	1
5510	prochlorperazine mesilate 12.5mg/ml injection	1
3197	promazine 100mg tablet	1
15395	promazine 12.5mg/5ml oral solution	1

46945	promazine 25mg tablet (biorex laboratories ltd)	1
2972	promazine 25mg tablets	1
60450	promazine 25mg tablets (a a h pharmaceuticals ltd)	1
6443	promazine 25mg/5ml oral solution	1
40390	promazine 25mg/5ml syrup (rosemont pharmaceuticals ltd)	1
3228	promazine 50mg tablets	1
41732	promazine 50mg tablets (teva uk ltd)	1
55890	promazine 50mg/5ml liquid (rosemont pharmaceuticals ltd)	1
17634	promazine 50mg/5ml oral solution	1
10780	promazine 50mg/5ml oral solution	1
14610	promazine 50mg/5ml oral solution sugar free	1
38089	promazine 50mg/5ml syrup (rosemont pharmaceuticals ltd)	1
15161	promazine 50mg/ml injection	1
43654	promazine 50mg/ml injection	1
41995	promazine 50mg/ml injection (genus pharmaceuticals ltd)	1
8988	promazine hcl 25 mg tab	1
26660	promazine hydrochloride	1
13607	proziere 5mg tablets (ashbourne pharmaceuticals ltd)	1
57170	psytixol 100mg/1ml solution for injection ampoules (generics (uk) ltd)	1
57762	psytixol 40mg/2ml solution for injection ampoules (generics (uk) ltd)	1
59816	psytixol 50mg/0.5ml solution for injection ampoules (generics (uk) ltd)	1
8044	redeptin 2mg/ml injection (janssen-cilag ltd)	1
8979	serenace 1.5mg tablets (teva uk ltd)	1
13484	serenace 10mg tablets (teva uk ltd)	1
13391	serenace 20 mg inj	1
13483	serenace 20mg tablets (teva uk ltd)	1
28968	serenace 20mg/2ml solution for injection ampoules (ivax pharmaceuticals uk ltd)	1
8153	serenace 2mg/ml liquid (teva uk ltd)	1
5545	serenace 500microgram capsules (teva uk ltd)	1
13338	serenace 5mg tablets (teva uk ltd)	1
7436	serenace 5mg/1ml solution for injection ampoules (ivax pharmaceuticals uk ltd)	1
33493	sparine 100mg tablet (wyeth pharmaceuticals)	1
12193	sparine 25mg tablet (wyeth pharmaceuticals)	1
3226	sparine 50mg tablet (wyeth pharmaceuticals)	1
3227	sparine 50mg/5ml liquid (wyeth pharmaceuticals)	1
13311	sparine 50mg/ml injection (wyeth pharmaceuticals)	1
27582	stelazine	1
1735	stelazine 10mg spansules (mercury pharma group ltd)	1
18289	stelazine 10mg/ml concentrate (goldshield pharmaceuticals ltd)	1
8042	stelazine 15mg spansules (mercury pharma group ltd)	1
57605	stelazine 1mg tablets (lexon (uk) ltd)	1
1318	stelazine 1mg tablets (mercury pharma group ltd)	1
8985	stelazine 1mg/5ml syrup (mercury pharma group ltd)	1
7479	stelazine 1mg/ml injection (goldshield pharmaceuticals ltd)	1

2713	stelazine 2mg spansules (mercury pharma group ltd)	1
1316	stelazine 5mg tablets (mercury pharma group ltd)	1
29838	stelazine concentrate 10mg/ml	1
29948	stelazine forte 1mg/ml oral solution (mercury pharma group ltd)	1
8775	stelazine tab	1
14356	stemetil 12.5mg/1ml solution for injection ampoules (sanofi)	1
3246	stemetil 12.5mg/ml injection (castlemead healthcare ltd)	1
1234	stemetil 25mg suppositories (sanofi)	1
5497	stemetil 25mg tablets (sanofi)	1
227	stemetil 5mg suppositories (sanofi)	1
512	stemetil 5mg tablet (castlemead healthcare ltd)	1
50462	stemetil 5mg tablets (de pharmaceuticals)	1
49170	stemetil 5mg tablets (lexon (uk) ltd)	1
51551	stemetil 5mg tablets (mawdsley-brooks & company ltd)	1
39887	stemetil 5mg tablets (sanofi)	1
51579	stemetil 5mg tablets (sigma pharmaceuticals plc)	1
54429	stemetil 5mg tablets (waymade healthcare plc)	1
7593	stemetil 5mg/5ml oral solution (castlemead healthcare ltd)	1
40001	stemetil 5mg/5ml syrup (sanofi)	1
3738	stemetil eff 5mg sachets (sanofi)	1
24053	sulparex 200mg tablet (e r squibb and sons ltd)	1
2135	sulpiride 200mg tablets	1
43423	sulpiride 200mg tablets (a a h pharmaceuticals ltd)	1
41675	sulpiride 200mg tablets (ivax pharmaceuticals uk ltd)	1
43522	sulpiride 200mg tablets (teva uk ltd)	1
34810	sulpiride 200mg tablets (wockhardt uk ltd)	1
8903	sulpiride 200mg/5ml oral solution sugar free	1
9247	sulpiride 400mg tablets	1
13620	sulpiride 500 mg tab	1
18352	sulpitil 200mg tablets (pfizer ltd)	1
18181	sulpor 200mg/5ml oral solution (rosemont pharmaceuticals ltd)	1
28147	taractan 15mg tablet (roche products ltd)	1
45860	thioridazine 100mg tablet (ivax pharmaceuticals uk ltd)	1
3021	thioridazine 100mg tablets	1
15598	thioridazine 100mg/5ml sugar free oral solution	1
1192	thioridazine 10mg tablets	1
2801	thioridazine 10mg/5ml oral solution	1
47361	thioridazine 10mg/5ml oral solution (rosemont pharmaceuticals ltd)	1
34905	thioridazine 25mg tablet (ivax pharmaceuticals uk ltd)	1
1218	thioridazine 25mg tablets	1
3605	thioridazine 25mg/5ml oral solution	1
10405	thioridazine 25mg/5ml sugar free oral solution	1
35787	thioridazine 50mg tablet (ivax pharmaceuticals uk ltd)	1
1314	thioridazine 50mg tablets	1

17399	thioridazine 50mg/5ml oral solution	1
42816	thioridazine 50mg/5ml oral solution (rosemont pharmaceuticals ltd)	1
3955	tranylcypromine with trifluoperazine tablet	1
2714	trifluoperazine 10mg modified-release capsules	1
22245	trifluoperazine 10mg/ml	1
18668	trifluoperazine 10mg/ml concentrate	1
3937	trifluoperazine 15mg modified-release capsules	1
1857	trifluoperazine 1mg tablets	1
40162	trifluoperazine 1mg tablets (a a h pharmaceuticals ltd)	1
13145	trifluoperazine 1mg/5ml oral solution sugar free	1
55382	trifluoperazine 1mg/5ml oral solution sugar free (amco)	1
8537	trifluoperazine 1mg/ml injection	1
1159	trifluoperazine 2mg modified-release capsules	1
19645	trifluoperazine 5.00mg/ml	1
10535	trifluoperazine 5.00mg/ml 5 mg syr	1
1245	trifluoperazine 5mg tablets	1
41663	trifluoperazine 5mg tablets (a a h pharmaceuticals ltd)	1
11531	trifluoperazine 5mg/5ml oral solution sugar free	1
28965	trifluoperazine hcl/isoprop.iodide forte tab	1
10356	trifluoperazine tab	1
24890	trifluoperazine with tranylcypromine 1mg + 10mg tablet	1
23659	trifluperidol 0.5mg tablet	1
22814	trifluperidol 1mg tablet	1
21047	triperidol 0.5mg tablet (lagap)	1
21027	triperidol 1mg tablet (lagap)	1
1453	triptafen m 2mg+10mg tablet (goldshield pharmaceuticals ltd)	1
1208	triptafen tablets (amco)	1
38827	triptafen-m tablets (mercury pharma group ltd)	1
21339	veractil 25mg tablet (rhone-poulenc rorer ltd)	1
8689	vertigon spansule 10 10mg spansule (glaxosmithkline consumer healthcare)	1
17849	vertigon spansule 15 15mg spansule (glaxosmithkline consumer healthcare)	1
9686	zuclopenthixol 10mg tablets	1
13600	zuclopenthixol 25mg tablets	1
12707	zuclopenthixol 2mg tablets	1
31537	zuclopenthixol acetate 100mg/2ml solution for injection ampoules	1
24270	zuclopenthixol acetate 50mg/1ml solution for injection ampoules	1
14576	zuclopenthixol acetate 50mg/ml oily injection	1
28355	zuclopenthixol decanoate 200mg/1ml solution for injection ampoules	1
3775	zuclopenthixol decanoate 200mg/ml oily injection	1
12224	zuclopenthixol decanoate 500mg/1ml solution for injection ampoules	1
25635	zuclopenthixol dihydrochloride	1

Appendix A6- List of mood stabilisers

Prodcode	Product name
12402	Camcolit 250 tablets (Essential Pharma Ltd)
12403	Camcolit 400 modified-release tablets (Essential Pharma Ltd)
34958	Carbamazepine 100mg Tablet (Berk Pharmaceuticals Ltd)
41726	Carbamazepine 100mg Tablet (IVAX Pharmaceuticals UK Ltd)
46888	Carbamazepine 200mg Modified-release tablet (Generics (UK) Ltd)
37800	Carbamazepine 200mg Modified-release tablet (Lagap)
46972	Carbamazepine 200mg Tablet (IVAX Pharmaceuticals UK Ltd)
43451	Carbamazepine 400mg Modified-release tablet (Generics (UK) Ltd)
40403	Carbamazepine 400mg Modified-release tablet (Lagap)
53188	Carbamazepine 500mg/5ml Oral suspension (Martindale Pharmaceuticals Ltd)
32900	Carbamazepine sr 200mg Tablet (IVAX Pharmaceuticals UK Ltd)
47294	Carbamazepine sr 400mg Tablet (IVAX Pharmaceuticals UK Ltd)
7064	Depakote 250mg gastro-resistant tablets (Sanofi)
9759	Depakote 500mg gastro-resistant tablets (Sanofi)
4195	Epilim 100mg crushable tablets (Sanofi)
38939	Epilim 200 gastro-resistant tablets (Sanofi)
2082	Epilim 200mg/5ml liquid (Sanofi)
4495	Epilim 200mg/5ml syrup (Sanofi)
38949	Epilim 500 gastro-resistant tablets (Sanofi)
53195	Epilim Chrono 200 tablets (Doncaster Pharmaceuticals Ltd)
49923	Epilim Chrono 200 tablets (Lexon (UK) Ltd)
3734	Epilim Chrono 200 tablets (Sanofi)
53524	Epilim Chrono 300 tablets (Doncaster Pharmaceuticals Ltd)
3733	Epilim Chrono 300 tablets (Sanofi)
53501	Epilim Chrono 500 tablets (Lexon (UK) Ltd)
3107	Epilim Chrono 500 tablets (Sanofi)
42038	Epilim Chronosphere MR 1000mg granules sachets (Sanofi)
38507	Epilim Chronosphere MR 100mg granules sachets (Sanofi)
38508	Epilim Chronosphere MR 250mg granules sachets (Sanofi)
39279	Epilim Chronosphere MR 500mg granules sachets (Sanofi)
39930	Epilim Chronosphere MR 50mg granules sachets (Sanofi)
39550	Epilim Chronosphere MR 750mg granules sachets (Sanofi)
20004	Epilim Intravenous 400mg powder and solvent for solution for injection vials (Sanofi)
3731	Epilim ec 200mg Gastro-resistant tablet (Sanofi)
2822	Epilim ec 500mg Gastro-resistant tablet (Sanofi)
36634	Episenta 1000mg modified-release granules sachets (Desitin Pharma Ltd)
36633	Episenta 150mg modified-release capsules (Desitin Pharma Ltd)
35747	Episenta 300mg modified-release capsules (Desitin Pharma Ltd)
37584	Episenta 500mg modified-release granules sachets (Desitin Pharma Ltd)
37611	Epival CR 300mg tablets (Chanelle Medical UK Ltd)
33058	Epival CR 500mg tablets (Chanelle Medical UK Ltd)
15660	LITHIUM 10.8 MMOLS/5MLS LIQ

10292	LITHIUM 250 MG CAP
25396	LITHIUM CHLORIDE 400 MG SOL
25345	Li-Liquid 1.018g/5ml oral solution (Rosemont Pharmaceuticals Ltd)
22018	Li-Liquid 509mg/5ml oral solution (Rosemont Pharmaceuticals Ltd)
3352	Liskonum 450mg modified-release tablets (Teofarma)
13654	Litarex 564mg modified-release tablets (Actavis UK Ltd)
760	Lithium carbonate 200mg modified-release tablets
56435	Lithium carbonate 200mg/5ml oral suspension
8041	Lithium carbonate 250mg tablets
65296	Lithium carbonate 250mg tablets (A A H Pharmaceuticals Ltd)
65301	Lithium carbonate 250mg tablets (Essential Pharma Ltd)
8827	Lithium carbonate 300mg Modified-release tablet
25344	Lithium carbonate 400mg Modified-release tablet (Approved Prescription Services Ltd)
1447	Lithium carbonate 400mg modified-release tablets
68292	Lithium carbonate 400mg modified-release tablets (AM Distributions (Yorkshire) Ltd)
65838	Lithium carbonate 400mg modified-release tablets (DE Pharmaceuticals)
66248	Lithium carbonate 400mg modified-release tablets (Ennogen Healthcare Ltd)
63989	Lithium carbonate 400mg modified-release tablets (Niche Pharma Ltd)
14954	Lithium carbonate 450mg modified-release tablets
12648	Lithium citrate 1.018g/5ml oral solution
10937	Lithium citrate 509mg/5ml oral solution
56427	Lithium citrate 509mg/5ml oral solution (Cubic Pharmaceuticals Ltd)
11491	Lithium citrate 520mg/5ml oral solution sugar free
13601	Lithium citrate 564mg modified-release tablets
16250	Lithonate 400mg modified-release tablets (Teva UK Ltd)
17152	Orlept 200mg gastro-resistant tablets (Wockhardt UK Ltd)
8885	Orlept 500mg gastro-resistant tablets (Wockhardt UK Ltd)
24153	Orlept SF 200mg/5ml liquid (Wockhardt UK Ltd)
3358	PRIADEL 800 MG TAB
15388	Phasal 300mg Tablet (Lagap)
3359	Priadel 200mg modified-release tablets (Sanofi)
53459	Priadel 400mg modified-release tablets (DE Pharmaceuticals)
51401	Priadel 400mg modified-release tablets (Necessity Supplies Ltd)
872	Priadel 400mg modified-release tablets (Sanofi)
10809	Priadel 520mg/5ml liquid (Sanofi)
63481	Sertraline 50mg tablets (Aurobindo Pharma Ltd)
44472	Sodium valproate 100mg modified-release granules sachets sugar free
4502	Sodium valproate 100mg tablets
40395	Sodium valproate 100mg tablets (Generics (UK) Ltd)
35471	Sodium valproate 150mg modified-release capsules
36318	Sodium valproate 1g modified-release granules sachets sugar free
43742	Sodium valproate 1g/10ml solution for injection ampoules
34414	Sodium valproate 200mg Tablet (Sterwin Medicines)
584	Sodium valproate 200mg gastro-resistant tablets
34120	Sodium valproate 200mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)

34626	Sodium valproate 200mg gastro-resistant tablets (Generics (UK) Ltd)
34707	Sodium valproate 200mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)
34632	Sodium valproate 200mg gastro-resistant tablets (Teva UK Ltd)
51751	Sodium valproate 200mg gastro-resistant tablets (Wockhardt UK Ltd)
39039	Sodium valproate 200mg modified-release tablets
45344	Sodium valproate 200mg/5ml Oral solution (Hillcross Pharmaceuticals Ltd)
33106	Sodium valproate 200mg/5ml Oral solution (IVAX Pharmaceuticals UK Ltd)
37306	Sodium valproate 200mg/5ml Oral solution (Sterwin Medicines)
1550	Sodium valproate 200mg/5ml oral solution
3845	Sodium valproate 200mg/5ml oral solution sugar free
34883	Sodium valproate 200mg/5ml oral solution sugar free (A A H Pharmaceuticals Ltd)
42090	Sodium valproate 200mg/5ml oral solution sugar free (Zentiva)
45106	Sodium valproate 250mg modified-release granules sachets sugar free
35024	Sodium valproate 300mg modified-release capsules
6711	Sodium valproate 300mg modified-release tablets
53197	Sodium valproate 300mg modified-release tablets (Sigma Pharmaceuticals Plc)
40070	Sodium valproate 300mg/3ml solution for injection ampoules
16609	Sodium valproate 400mg powder and solvent for solution for injection vials
40400	Sodium valproate 500mg Gastro-resistant tablet (C P Pharmaceuticals Ltd)
3350	Sodium valproate 500mg gastro-resistant tablets
34178	Sodium valproate 500mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)
46774	Sodium valproate 500mg gastro-resistant tablets (Teva UK Ltd)
44903	Sodium valproate 500mg gastro-resistant tablets (Zentiva)
35755	Sodium valproate 500mg modified-release granules sachets sugar free
6560	Sodium valproate 500mg modified-release tablets
55006	Sodium valproate 500mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)
45419	Sodium valproate 50mg modified-release granules sachets sugar free
44718	Sodium valproate 750mg modified-release granules sachets sugar free
30081	Sodium valproate CR 500mg Tablet (Hillcross Pharmaceuticals Ltd)
43648	Sodium valproate oral solution
43178	Sodium valproate with valproic acid 1000mg modified release granules
41137	Sodium valproate with valproic acid 100mg modified release granules
9281	Sodium valproate with valproic acid 200mg modified release tablets
39276	Sodium valproate with valproic acid 250mg modified release granules
7011	Sodium valproate with valproic acid 300mg modified release tablets
39452	Sodium valproate with valproic acid 500mg modified release granules
11075	Sodium valproate with valproic acid 500mg modified release tablets
43387	Sodium valproate with valproic acid 50mg modified release granules
39427	Sodium valproate with valproic acid 750mg modified release granules
2077	TEGRETOL liq 100 MG/5ML LIQ
13524	Tegretol 100mg Chewtabs (Novartis Pharmaceuticals UK Ltd)
5977	Tegretol 100mg tablets (Novartis Pharmaceuticals UK Ltd)
4913	Tegretol 100mg/5ml liquid (Novartis Pharmaceuticals UK Ltd)
21441	Tegretol 125mg suppositories (Novartis Pharmaceuticals UK Ltd)

12880	Tegretol 200mg Chewtabs (Novartis Pharmaceuticals UK Ltd)
49833	Tegretol 200mg tablets (Lexon (UK) Ltd)
2085	Tegretol 200mg tablets (Novartis Pharmaceuticals UK Ltd)
15082	Tegretol 250mg suppositories (Novartis Pharmaceuticals UK Ltd)
51760	Tegretol 400mg tablets (Lexon (UK) Ltd)
4066	Tegretol 400mg tablets (Novartis Pharmaceuticals UK Ltd)
48397	Tegretol Prolonged Release 200mg tablets (Doncaster Pharmaceuticals Ltd)
45941	Tegretol Prolonged Release 200mg tablets (Novartis Pharmaceuticals UK Ltd)
53492	Tegretol Prolonged Release 200mg tablets (Sigma Pharmaceuticals Plc)
52840	Tegretol Prolonged Release 400mg tablets (Necessity Supplies Ltd)
45903	Tegretol Prolonged Release 400mg tablets (Novartis Pharmaceuticals UK Ltd)
53893	Tegretol Prolonged Release 400mg tablets (Stephar (U.K.) Ltd)
2823	Tegretol retard 200mg Modified-release tablet (Novartis Pharmaceuticals UK Ltd)
2824	Tegretol retard 400mg Modified-release tablet (Novartis Pharmaceuticals UK Ltd)
30509	Timonil retard 400mg Modified-release tablet (C P Pharmaceuticals Ltd)
34150	Valproate sodium 200mg Gastro-resistant tablet (IVAX Pharmaceuticals UK Ltd)
34151	Valproate sodium 500mg Gastro-resistant tablet (IVAX Pharmaceuticals UK Ltd)
18614	Valproic acid 150mg gastro-resistant capsules
5848	Valproic acid 250mg gastro-resistant tablets
15650	Valproic acid 300mg gastro-resistant capsules
16021	Valproic acid 500mg gastro-resistant capsules
6305	Valproic acid 500mg gastro-resistant tablets
53211	Valproic acid 500mg/5ml oral solution

Appendix A7- List of antidepressants

Prodcode	CPRD drug prodcode description
61835	Amitriptyline 10mg tablets (DE Pharmaceuticals)
65879	Amitriptyline 10mg tablets (Sigma Pharmaceuticals Plc)
65987	Amitriptyline 25mg tablets (Crescent Pharma Ltd)
64647	Amitriptyline 25mg tablets (DE Pharmaceuticals)
65439	Amitriptyline 25mg tablets (Sandoz Ltd)
64330	Amitriptyline 50mg tablets (Almus Pharmaceuticals Ltd)
63953	Cipramil 20mg tablets (DE Pharmaceuticals)
60839	Citalopram 40mg tablets (Almus Pharmaceuticals Ltd)
62950	Sertraline 100mg tablets (Accord Healthcare Ltd)
61503	Sertraline 100mg tablets (Actavis UK Ltd)
62692	Sertraline 100mg tablets (Bristol Laboratories Ltd)
62819	Sertraline 12.5mg/5ml oral suspension
65771	Sertraline 200mg/5ml oral suspension (Special Order)
63481	Sertraline 50mg tablets (Aurobindo Pharma Ltd)
62693	Sertraline 50mg tablets (Bristol Laboratories Ltd)
62927	Sertraline 50mg tablets (Wockhardt UK Ltd)
873	amitriptyline 100 mg tab
3490	amitriptyline 10mg / perphenazine 2mg tablets
34916	amitriptyline 10mg tablet (berk pharmaceuticals ltd)
45242	amitriptyline 10mg tablet (sussex pharmaceutical ltd)
83	amitriptyline 10mg tablets
33090	amitriptyline 10mg tablets (a a h pharmaceuticals ltd)
52867	amitriptyline 10mg tablets (accord healthcare ltd)
24141	amitriptyline 10mg tablets (actavis uk ltd)
57972	amitriptyline 10mg tablets (alliance healthcare (distribution) ltd)
55491	amitriptyline 10mg tablets (almus pharmaceuticals ltd)
45233	amitriptyline 10mg tablets (ivax pharmaceuticals uk ltd)
34731	amitriptyline 10mg tablets (kent pharmaceuticals ltd)
57107	amitriptyline 10mg tablets (phoenix healthcare distribution ltd)
24152	amitriptyline 10mg tablets (teva uk ltd)
59161	amitriptyline 10mg tablets (waymade healthcare plc)
34401	amitriptyline 10mg tablets (wockhardt uk ltd)
46801	amitriptyline 10mg/5ml oral solution
22070	amitriptyline 10mg/5ml oral solution (rosemont pharmaceuticals ltd)
46818	amitriptyline 10mg/5ml oral suspension
3777	amitriptyline 10mg/5ml sugar free oral solution
19779	amitriptyline 10mg/ml injection

21081	amitriptyline 12.5mg / chlordiazepoxide 5mg capsules
13496	amitriptyline 200 mg tab
18342	amitriptyline 25mg / chlordiazepoxide 10mg capsules
595	amitriptyline 25mg / perphenazine 2mg tablets
487	amitriptyline 25mg modified-release capsules
34197	amitriptyline 25mg tablet (berk pharmaceuticals ltd)
41729	amitriptyline 25mg tablet (celltech pharma europe ltd)
42394	amitriptyline 25mg tablet (crosspharma ltd)
34474	amitriptyline 25mg tablet (regent laboratories ltd)
32439	amitriptyline 25mg tablet (sussex pharmaceutical ltd)
49	amitriptyline 25mg tablets
34782	amitriptyline 25mg tablets (a a h pharmaceuticals ltd)
54877	amitriptyline 25mg tablets (accord healthcare ltd)
24145	amitriptyline 25mg tablets (actavis uk ltd)
55139	amitriptyline 25mg tablets (alliance healthcare (distribution) ltd)
42078	amitriptyline 25mg tablets (almus pharmaceuticals ltd)
34503	amitriptyline 25mg tablets (ivax pharmaceuticals uk ltd)
24134	amitriptyline 25mg tablets (kent pharmaceuticals ltd)
60355	amitriptyline 25mg tablets (phoenix healthcare distribution ltd)
24147	amitriptyline 25mg tablets (teva uk ltd)
34129	amitriptyline 25mg tablets (wockhardt uk ltd)
6312	amitriptyline 25mg/5ml oral solution sugar free
34224	amitriptyline 25mg/5ml oral solution sugar free (rosemont pharmaceuticals ltd)
60410	amitriptyline 25mg/5ml oral solution sugar free (wockhardt uk ltd)
23497	amitriptyline 300 mg tab
4682	amitriptyline 50mg modified-release capsules
40396	amitriptyline 50mg tablet (berk pharmaceuticals ltd)
1888	amitriptyline 50mg tablets
34274	amitriptyline 50mg tablets (a a h pharmaceuticals ltd)
34634	amitriptyline 50mg tablets (actavis uk ltd)
46970	amitriptyline 50mg tablets (ivax pharmaceuticals uk ltd)
34182	amitriptyline 50mg tablets (kent pharmaceuticals ltd)
33624	amitriptyline 50mg tablets (teva uk ltd)
34107	amitriptyline 50mg tablets (wockhardt uk ltd)
4690	amitriptyline 50mg/5ml oral solution sugar free
34251	amitriptyline 50mg/5ml oral solution sugar free (rosemont pharmaceuticals ltd)
59820	amitriptyline 50mg/5ml oral solution sugar free (wockhardt uk ltd)

3771	amitriptyline 75 mg tab
2525	amitriptyline 75mg modified-release capsules
48065	amitriptyline oral solution
8250	amitriptyline s/f 25 mg/5ml syr
1712	cipramil 20mg tablets (lundbeck ltd)
2408	cipramil 40mg tablets (lundbeck ltd)
815	cipramil 40mg/ml drops (lundbeck ltd)
34722	citalopram 20mg tablet (neo laboratories ltd)
67	citalopram 20mg tablets
34356	citalopram 20mg tablets (a a h pharmaceuticals ltd)
34871	citalopram 20mg tablets (actavis uk ltd)
53394	citalopram 20mg tablets (alliance healthcare (distribution) ltd)
48026	citalopram 20mg tablets (almus pharmaceuticals ltd)
56009	citalopram 20mg tablets (arrow generics ltd)
58476	citalopram 20mg tablets (aurobindo pharma ltd)
52607	citalopram 20mg tablets (bristol laboratories ltd)
52354	citalopram 20mg tablets (de pharmaceuticals)
34415	citalopram 20mg tablets (generics (uk) ltd)
34970	citalopram 20mg tablets (niche generics ltd)
26016	citalopram 20mg tablets (sandoz ltd)
34966	citalopram 20mg tablets (teva uk ltd)
60568	citalopram 20mg tablets (waymade healthcare plc)
34822	citalopram 20mg tablets (zentiva)
43519	citalopram 40mg tablet (neo laboratories ltd)
4770	citalopram 40mg tablets
36746	citalopram 40mg tablets (a a h pharmaceuticals ltd)
46977	citalopram 40mg tablets (actavis uk ltd)
55033	citalopram 40mg tablets (de pharmaceuticals)
34603	citalopram 40mg tablets (generics (uk) ltd)
45223	citalopram 40mg tablets (niche generics ltd)
34466	citalopram 40mg tablets (sandoz ltd)
45304	citalopram 40mg tablets (teva uk ltd)
46926	citalopram 40mg tablets (zentiva)
513	citalopram 40mg/ml oral drops sugar free
57936	citalopram 40mg/ml oral drops sugar free (a a h pharmaceuticals ltd)
56292	citalopram 40mg/ml oral drops sugar free (actavis uk ltd)
4352	lustral 100mg tablets (pfizer ltd)
1612	lustral 50mg tablets (pfizer ltd)
16323	perphenazine 2mg with amitriptyline 10mg tablet

6894	perphenazine 2mg with amitriptyline 25mg tablet
727	sertraline 100mg tablets
55146	sertraline 100mg tablets (a a h pharmaceuticals ltd)
59600	sertraline 100mg tablets (almus pharmaceuticals ltd)
54933	sertraline 100mg tablets (pliva pharma ltd)
44944	sertraline 100mg tablets (teva uk ltd)
49519	sertraline 100mg/5ml oral suspension
54826	sertraline 150mg/5ml oral suspension
488	sertraline 50mg tablets
32401	sertraline 50mg tablets (a a h pharmaceuticals ltd)
58723	sertraline 50mg tablets (accord healthcare ltd)
42387	sertraline 50mg tablets (actavis uk ltd)
45915	sertraline 50mg tablets (almus pharmaceuticals ltd)
58664	sertraline 50mg tablets (generics (uk) ltd)
55488	sertraline 50mg tablets (teva uk ltd)
7328	sertraline 50mg/5ml oral suspension
7751	tryptizol 25mg tablet (merck sharp & dohme ltd)
8332	tryptizol 50mg tablet (merck sharp & dohme ltd)
8831	tryptizol mr 75mg modified-release capsule (merck sharp & dohme ltd)
64141	Amitriptyline 5mg/5ml oral solution
64423	Citalopram 10mg tablets (Accord Healthcare Ltd)
63441	Citalopram 10mg tablets (Rivopharm (UK) Ltd)
60888	Citalopram 10mg tablets (Sigma Pharmaceuticals Plc)
62620	Clomipramine 10mg capsules (Mylan Ltd)
65762	Clomipramine 25mg capsules (Waymade Healthcare Plc)
64458	Clomipramine 25mg/5ml oral suspension
65804	Clomipramine 50mg capsules (Teva UK Ltd)
62681	Dosulepin 75mg tablets (Sandoz Ltd)
65618	Duloxetine 30mg gastro-resistant capsules (A A H Pharmaceuticals Ltd)
65809	Duloxetine 30mg gastro-resistant capsules (Actavis UK Ltd)
63370	Duloxetine 30mg gastro-resistant capsules (Mawdsley-Brooks & Company Ltd)
62688	Duloxetine 30mg gastro-resistant capsules (Sigma Pharmaceuticals Plc)
63763	Duloxetine 60mg gastro-resistant capsules (A A H Pharmaceuticals Ltd)
65888	Duloxetine 60mg gastro-resistant capsules (Actavis UK Ltd)
65892	Duloxetine 60mg gastro-resistant capsules (Mawdsley-Brooks & Company Ltd)
64442	Duloxetine 60mg gastro-resistant capsules (Teva UK Ltd)
65738	Efexor 37.5mg tablets (Sigma Pharmaceuticals Plc)

65899	Efexor XL 225mg capsules (Pfizer Ltd)
63916	Escitalopram 10mg tablets (Actavis UK Ltd)
60962	Fluoxetine 20mg capsules (Alliance Healthcare (Distribution) Ltd)
62155	Fluoxetine 20mg capsules (Phoenix Healthcare Distribution Ltd)
3353	L-TRYPTOPHAN 500 MG CAP
20715	LIMBITROL 5
64101	Mirtazapine 15mg orodispersible tablets (Actavis UK Ltd)
61856	Mirtazapine 15mg orodispersible tablets (Consilient Health Ltd)
65555	Mirtazapine 15mg orodispersible tablets (Sigma Pharmaceuticals Plc)
61547	Mirtazapine 15mg/ml oral solution sugar free (DE Pharmaceuticals)
63403	Mirtazapine 30mg tablets (Teva UK Ltd)
64139	Mirtazapine 45mg orodispersible tablets (Mylan Ltd)
64223	Mirtazapine 45mg tablets (Teva UK Ltd)
12194	NORTRIPTYLINE 10 MG ELI
65237	Nortriptyline 10mg tablets (A A H Pharmaceuticals Ltd)
63276	Nortriptyline 25mg tablets (Alliance Healthcare (Distribution) Ltd)
8845	OPTIMAX 6 GM POW
3954	OPTIMAX TAB
64785	Paroxetine 30mg tablets (Alliance Healthcare (Distribution) Ltd)
61335	Prozac 20mg capsules (Mawdsley-Brooks & Company Ltd)
14521	SINEQUAN 15 MG TAB
65152	Trazodone 100mg/5ml oral solution
61842	Trazodone 50mg/5ml oral solution
61657	Trazodone 75mg/5ml oral solution
65445	Trimipramine 50mg capsules (A A H Pharmaceuticals Ltd)
65213	Trimipramine 50mg/5ml oral solution
62734	Venlafaxine 150mg/5ml oral suspension
65666	Venlafaxine 225mg modified-release capsules
60895	Venlafaxine 37.5mg tablets (Teva UK Ltd)
63859	Venlafaxine 75mg tablets (Waymade Healthcare Plc)
63268	Venlafaxine 75mg/5ml oral suspension
40494	agomelatine 25mg tablets
7677	allegron 10mg tablets (king pharmaceuticals ltd)
8640	allegron 25mg tablets (king pharmaceuticals ltd)
52516	alventa xl 150mg capsules (consilient health ltd)
52074	alventa xl 75mg capsules (consilient health ltd)
27876	amitriptyline
30738	amitriptyline s/f
20712	amitriptyline s/r

4411	amoxapine 150mg tablets
17319	amoxapine 25mg tablets
7515	anafranil 10mg capsules (novartis pharmaceuticals uk ltd)
13318	anafranil 25 mg inj
3657	anafranil 25mg capsules (novartis pharmaceuticals uk ltd)
30375	anafranil 25mg/2ml solution for injection ampoules (novartis pharmaceuticals uk ltd)
8719	anafranil 25mg/5ml syrup (novartis pharmaceuticals uk ltd)
7693	anafranil 50mg capsules (novartis pharmaceuticals uk ltd)
7894	anafranil sr 75mg tablets (novartis pharmaceuticals uk ltd)
21357	asendis 100mg tablet (wyeth pharmaceuticals)
24723	asendis 150mg tablet (wyeth pharmaceuticals)
15380	asendis 25mg tablet (wyeth pharmaceuticals)
14398	asendis 50mg tablet (wyeth pharmaceuticals)
17183	aventyl 10mg capsule (eli lilly and company ltd)
12549	aventyl 10mg/5ml liquid (eli lilly and company ltd)
12353	aventyl 25mg capsule (eli lilly and company ltd)
7468	bolvidon 10mg tablet (organon laboratories ltd)
8144	bolvidon 20mg tablet (organon laboratories ltd)
8585	bolvidon 30mg tablet (organon laboratories ltd)
12227	butriptyline 25mg tablets
32457	butriptyline 50mg tablets
648	cipralex 10mg tablets (lundbeck ltd)
26056	cipralex 10mg/ml oral drops (lundbeck ltd)
6360	cipralex 20mg tablets (lundbeck ltd)
41062	cipralex 20mg/ml oral drops (lundbeck ltd)
785	cipralex 5mg tablets (lundbeck ltd)
3861	cipramil 10mg tablets (lundbeck ltd)
34498	citalopram 10mg tablet (neo laboratories ltd)
476	citalopram 10mg tablets
34586	citalopram 10mg tablets (a a h pharmaceuticals ltd)
32848	citalopram 10mg tablets (actavis uk ltd)
49165	citalopram 10mg tablets (alliance healthcare (distribution) ltd)
42660	citalopram 10mg tablets (almus pharmaceuticals ltd)
52100	citalopram 10mg tablets (arrow generics ltd)
59650	citalopram 10mg tablets (aurobindo pharma ltd)
53787	citalopram 10mg tablets (bristol laboratories ltd)
34436	citalopram 10mg tablets (generics (uk) ltd)
33720	citalopram 10mg tablets (ivax pharmaceuticals uk ltd)

52408	citalopram 10mg tablets (kent pharmaceuticals ltd)
45286	citalopram 10mg tablets (niche generics ltd)
52824	citalopram 10mg tablets (pliva pharma ltd)
59193	citalopram 10mg tablets (ranbaxy (uk) ltd)
34499	citalopram 10mg tablets (sandoz ltd)
41528	citalopram 10mg tablets (teva uk ltd)
56355	citalopram 10mg tablets (waymade healthcare plc)
34413	citalopram 10mg tablets (zentiva)
54827	citalopram 10mg/5ml oral suspension
3194	clomipramine 10mg capsules
34866	clomipramine 10mg capsules (a a h pharmaceuticals ltd)
41628	clomipramine 10mg capsules (ivax pharmaceuticals uk ltd)
43561	clomipramine 10mg capsules (teva uk ltd)
3195	clomipramine 25 mg tab
3670	clomipramine 25mg capsules
34245	clomipramine 25mg capsules (a a h pharmaceuticals ltd)
41563	clomipramine 25mg capsules (ivax pharmaceuticals uk ltd)
45350	clomipramine 25mg capsules (teva uk ltd)
26513	clomipramine 25mg/2ml solution for injection ampoules
8720	clomipramine 25mg/5ml oral solution
3925	clomipramine 50mg capsules
45318	clomipramine 50mg capsules (a a h pharmaceuticals ltd)
41597	clomipramine 50mg capsules (ivax pharmaceuticals uk ltd)
53187	clomipramine 50mg capsules (kent pharmaceuticals ltd)
53161	clomipramine 50mg/5ml oral solution
38274	clomipramine 50mg/5ml oral suspension
8661	clomipramine 75mg modified-release tablets
25036	clomipramine hydrochloride
7755	concordin 10 tablet (merck sharp & dohme ltd)
7816	concordin 5 tablet (merck sharp & dohme ltd)
13151	cymbalta 30mg gastro-resistant capsules (eli lilly and company ltd)
14849	cymbalta 60mg gastro-resistant capsules (eli lilly and company ltd)
45664	depefex xl 150mg capsules (chiesi ltd)
45959	depefex xl 75mg capsules (chiesi ltd)
7981	desipramine 25mg tablets
26213	domical 10mg tablet (berk pharmaceuticals ltd)
20026	domical 25mg tablet (berk pharmaceuticals ltd)
27008	domical 50mg tablet (berk pharmaceuticals ltd)
43024	dosulepin 100mg/5ml oral solution

84	dosulepin 25mg capsules
23426	dosulepin 25mg capsules (a a h pharmaceuticals ltd)
34745	dosulepin 25mg capsules (actavis uk ltd)
34643	dosulepin 25mg capsules (almus pharmaceuticals ltd)
29875	dosulepin 25mg capsules (generics (uk) ltd)
31824	dosulepin 25mg capsules (ivax pharmaceuticals uk ltd)
44853	dosulepin 25mg capsules (kent pharmaceuticals ltd)
33164	dosulepin 25mg capsules (sandoz ltd)
34641	dosulepin 25mg capsules (sovereign medical ltd)
34223	dosulepin 25mg capsules (teva uk ltd)
19168	dosulepin 25mg/5ml mixture
50722	dosulepin 25mg/5ml oral solution
45737	dosulepin 25mg/5ml oral solution (rosemont pharmaceuticals ltd)
6054	dosulepin 25mg/5ml oral solution sugar free
74	dosulepin 75mg tablets
32121	dosulepin 75mg tablets (a a h pharmaceuticals ltd)
19186	dosulepin 75mg tablets (actavis uk ltd)
42734	dosulepin 75mg tablets (almus pharmaceuticals ltd)
34525	dosulepin 75mg tablets (generics (uk) ltd)
31826	dosulepin 75mg tablets (ivax pharmaceuticals uk ltd)
34058	dosulepin 75mg tablets (teva uk ltd)
57926	dosulepin 75mg/5ml oral solution
10948	dosulepin 75mg/5ml oral solution sugar free
1940	dothapax 25 capsules (ashbourne pharmaceuticals ltd)
15632	dothapax 75 tablets (ashbourne pharmaceuticals ltd)
3842	doxepin 10mg capsules
3554	doxepin 25mg capsules
40777	doxepin 25mg/5ml oral suspension
5073	doxepin 50mg capsules
7059	doxepin 75mg capsules
22872	doxepin hcl
7122	duloxetine 30mg gastro-resistant capsules
6895	duloxetine 60mg gastro-resistant capsules
51383	duloxetine 60mg gastro-resistant capsules (sigma pharmaceuticals plc)
3391	dutonin 100mg tablets (bristol-myers squibb pharmaceuticals ltd)
4297	dutonin 200mg tablets (bristol-myers squibb pharmaceuticals ltd)
15163	edronax 4mg tablets (pfizer ltd)
623	efexor 37.5mg tablets (wyeth pharmaceuticals)
6274	efexor 50mg tablets (wyeth pharmaceuticals)

9182	efexor 75mg tablets (wyeth pharmaceuticals)
5710	efexor xl 150mg capsules (pfizer ltd)
51280	efexor xl 150mg capsules (waymade healthcare plc)
1474	efexor xl 75mg capsules (pfizer ltd)
24680	elavil 10mg tablet (ddsa pharmaceuticals ltd)
603	escitalopram 10mg tablets
20152	escitalopram 10mg/ml oral drops sugar free
6218	escitalopram 20mg tablets
40726	escitalopram 20mg/ml oral drops sugar free
6405	escitalopram 5mg tablets
18932	evadyne 25mg tablet (wyeth pharmaceuticals)
23334	faverin
12123	faverin 100mg tablets (abbott healthcare products ltd)
2897	faverin 50mg tablets (abbott healthcare products ltd)
33071	felicium 20mg capsules (opus pharmaceuticals ltd)
58450	feprapax 70mg tablets (ashbourne pharmaceuticals ltd)
42499	fluoxetine 10mg tablets
38890	fluoxetine 20mg capsule (milpharm ltd)
22	fluoxetine 20mg capsules
19183	fluoxetine 20mg capsules (a a h pharmaceuticals ltd)
45329	fluoxetine 20mg capsules (actavis uk ltd)
45247	fluoxetine 20mg capsules (fannin uk ltd)
34288	fluoxetine 20mg capsules (generics (uk) ltd)
34202	fluoxetine 20mg capsules (genus pharmaceuticals ltd)
34294	fluoxetine 20mg capsules (ivax pharmaceuticals uk ltd)
59358	fluoxetine 20mg capsules (milpharm ltd)
42107	fluoxetine 20mg capsules (niche generics ltd)
19470	fluoxetine 20mg capsules (ranbaxy (uk) ltd)
45224	fluoxetine 20mg capsules (sandoz ltd)
34456	fluoxetine 20mg capsules (teva uk ltd)
34849	fluoxetine 20mg capsules (tillomed laboratories ltd)
45316	fluoxetine 20mg capsules (wockhardt uk ltd)
33410	fluoxetine 20mg capsules (zentiva)
60534	fluoxetine 20mg dispersible tablets sugar free
60138	fluoxetine 20mg orodispersible tablets sugar free
2548	fluoxetine 20mg/5ml oral solution
34216	fluoxetine 20mg/5ml oral solution (a a h pharmaceuticals ltd)
42803	fluoxetine 20mg/5ml oral solution (ivax pharmaceuticals uk ltd)
60619	fluoxetine 20mg/5ml oral solution (kent pharmaceuticals ltd)

30258	fluoxetine 20mg/5ml oral solution (teva uk ltd)
36893	fluoxetine 20mg/5ml oral solution sugar free
4075	fluoxetine 60mg capsules
34856	fluoxetine 60mg capsules (generics (uk) ltd)
20571	fluphenazine with nortriptyline 500microgramswith10mg tablet
2290	fluvoxamine 100mg tablets
48045	fluvoxamine 100mg tablets (a a h pharmaceuticals ltd)
44861	fluvoxamine 100mg tablets (actavis uk ltd)
43518	fluvoxamine 100mg tablets (ivax pharmaceuticals uk ltd)
2880	fluvoxamine 50mg tablets
43968	foraven xl 75mg capsules (forum products ltd)
2093	gamanil 70mg tablets (merck serono ltd)
3668	imipramine 100 mg tab
1310	imipramine 10mg tablets
41681	imipramine 10mg tablets (a a h pharmaceuticals ltd)
34222	imipramine 10mg tablets (actavis uk ltd)
32863	imipramine 10mg tablets (teva uk ltd)
7573	imipramine 25 mg cap
34872	imipramine 25mg tablet (c p pharmaceuticals ltd)
1809	imipramine 25mg tablets
34813	imipramine 25mg tablets (a a h pharmaceuticals ltd)
34355	imipramine 25mg tablets (actavis uk ltd)
41408	imipramine 25mg tablets (teva uk ltd)
8055	imipramine 25mg/5ml oral solution
42247	imipramine 25mg/5ml oral solution sugar free
7784	imipramine 50 mg tab
10649	imipramine 75 mg tab
27476	iprindole hc 15mg
27733	iprindole hc 30mg
25945	iproniazid 25mg
41731	isocarboxazid 10mg tablet (cambridge laboratories ltd)
12207	isocarboxazid 10mg tablets
2486	lentizol 25mg modified-release capsules (pfizer ltd)
2985	lentizol 50mg modified-release capsules (pfizer ltd)
11963	limbitrol 10 capsule (roche products ltd)
14534	limbitrol 5 capsule (roche products ltd)
25070	lofepramine
41627	lofepramine 70mg tablet (teva uk ltd)
114	lofepramine 70mg tablets

34046	lofepramine 70mg tablets (a a h pharmaceuticals ltd)
34950	lofepramine 70mg tablets (actavis uk ltd)
34578	lofepramine 70mg tablets (ivax pharmaceuticals uk ltd)
56703	lofepramine 70mg tablets (sandoz ltd)
34672	lofepramine 70mg tablets (sterwin medicines)
60591	lofepramine 70mg tablets (teva uk ltd)
56229	lofepramine 70mg/5ml oral solution
43534	lofepramine 70mg/5ml oral suspension (rosemont pharmaceuticals ltd)
4218	lofepramine 70mg/5ml oral suspension sugar free
25444	lomont 70mg/5ml oral suspension (rosemont pharmaceuticals ltd)
9206	manerix 150mg tablets (meda pharmaceuticals ltd)
5832	manerix 300mg tablets (meda pharmaceuticals ltd)
12503	marplan 10mg tablet (cambridge laboratories ltd)
3083	mianserin 10mg tablets
47363	mianserin 20mg tablet (berk pharmaceuticals ltd)
4329	mianserin 20mg tablets
6255	mianserin 30mg tablets
31168	mirtazapine
6421	mirtazapine 15mg orodispersible tablets
43253	mirtazapine 15mg orodispersible tablets (a a h pharmaceuticals ltd)
43241	mirtazapine 15mg orodispersible tablets (aurobindo pharma ltd)
43248	mirtazapine 15mg orodispersible tablets (focus pharmaceuticals ltd)
55482	mirtazapine 15mg orodispersible tablets (generics (uk) ltd)
43246	mirtazapine 15mg orodispersible tablets (genus pharmaceuticals ltd)
58291	mirtazapine 15mg orodispersible tablets (pfizer ltd)
43237	mirtazapine 15mg orodispersible tablets (teva uk ltd)
48698	mirtazapine 15mg orodispersible tablets sugar free
54012	mirtazapine 15mg orodispersible tablets sugar free (sandoz ltd)
6795	mirtazapine 15mg tablets
43239	mirtazapine 15mg tablets (a a h pharmaceuticals ltd)
53699	mirtazapine 15mg tablets (actavis uk ltd)
59953	mirtazapine 15mg tablets (almus pharmaceuticals ltd)
46668	mirtazapine 15mg tablets (arrow generics ltd)
43242	mirtazapine 15mg tablets (genus pharmaceuticals ltd)
54342	mirtazapine 15mg tablets (medreich plc)
54644	mirtazapine 15mg tablets (pfizer ltd)
43257	mirtazapine 15mg tablets (teva uk ltd)
16154	mirtazapine 15mg/ml oral solution sugar free
53321	mirtazapine 15mg/ml oral solution sugar free (a a h pharmaceuticals ltd)

47966	mirtazapine 15mg/ml oral solution sugar free (rosemont pharmaceuticals ltd)
6488	mirtazapine 30mg orodispersible tablets
43250	mirtazapine 30mg orodispersible tablets (a a h pharmaceuticals ltd)
53648	mirtazapine 30mg orodispersible tablets (actavis uk ltd)
48185	mirtazapine 30mg orodispersible tablets (almus pharmaceuticals ltd)
59694	mirtazapine 30mg orodispersible tablets (phoenix healthcare distribution ltd)
742	mirtazapine 30mg tablets
47945	mirtazapine 30mg tablets (a a h pharmaceuticals ltd)
40160	mirtazapine 30mg tablets (actavis uk ltd)
54792	mirtazapine 30mg tablets (alliance healthcare (distribution) ltd)
60538	mirtazapine 30mg tablets (de pharmaceuticals)
56209	mirtazapine 30mg tablets (phoenix healthcare distribution ltd)
6481	mirtazapine 45mg orodispersible tablets
43235	mirtazapine 45mg orodispersible tablets (a a h pharmaceuticals ltd)
43236	mirtazapine 45mg orodispersible tablets (actavis uk ltd)
43256	mirtazapine 45mg orodispersible tablets (focus pharmaceuticals ltd)
43247	mirtazapine 45mg orodispersible tablets (genus pharmaceuticals ltd)
43234	mirtazapine 45mg orodispersible tablets (teva uk ltd)
49820	mirtazapine 45mg orodispersible tablets sugar free
6854	mirtazapine 45mg tablets
33337	mirtazapine 45mg tablets (a a h pharmaceuticals ltd)
58625	mirtazapine 45mg tablets (actavis uk ltd)
59954	mirtazapine 45mg tablets (almus pharmaceuticals ltd)
2883	moclobemide 150mg tablets
41747	moclobemide 150mg tablets (teva uk ltd)
5187	moclobemide 300mg tablets
4194	molipaxin 100mg capsules (zentiva)
4003	molipaxin 150mg tablets (zentiva)
4874	molipaxin 50mg capsules (zentiva)
8174	molipaxin 50mg/5ml oral liquid (sanofi)
13621	molipaxin cr 150mg tablets (aventis pharma)
3349	nardil 15mg tablets (archimedes pharma uk ltd)
4554	nefazodone 100mg tablets
4011	nefazodone 200mg tablets
9534	nefazodone starter pack
4118	nortriptyline 10mg capsule
3183	nortriptyline 10mg tablets

55970	nortriptyline 10mg tablets (king pharmaceuticals ltd)
39145	nortriptyline 10mg/5ml liquid
7678	nortriptyline 25mg capsule
3903	nortriptyline 25mg tablets
48216	nortriptyline 25mg tablets (a a h pharmaceuticals ltd)
12368	norval 10mg tablet (bencard)
11956	norval 20mg tablet (bencard)
12192	norval 30mg tablet (bencard)
54747	optimax 500mg capsules (merck serono ltd)
5611	optimax 500mg tablets (merck serono ltd)
20504	optimax wv tablet (e. merck)
14740	oxactin 20mg capsules (discovery pharmaceuticals ltd)
12221	pacitron 500mg tablet (rorer pharmaceuticals ltd)
10787	parnate 10mg tablet (goldshield pharmaceuticals ltd)
35021	paroxetine 10mg tablets
59288	paroxetine 10mg tablets (actavis uk ltd)
527	paroxetine 10mg/5ml oral suspension sugar free
50	paroxetine 20mg tablets
34419	paroxetine 20mg tablets (a a h pharmaceuticals ltd)
32899	paroxetine 20mg tablets (actavis uk ltd)
33978	paroxetine 20mg tablets (generics (uk) ltd)
40892	paroxetine 20mg tablets (genus pharmaceuticals ltd)
34351	paroxetine 20mg tablets (ivax pharmaceuticals uk ltd)
55023	paroxetine 20mg tablets (medreich plc)
1397	paroxetine 30mg tablets
34587	paroxetine 30mg tablets (a a h pharmaceuticals ltd)
40165	paroxetine 30mg tablets (actavis uk ltd)
3356	parstelin tablet (glaxosmithkline consumer healthcare)
32546	paxoran 10mg tablet (ranbaxy (uk) ltd)
29756	paxoran 20mg tablet (ranbaxy (uk) ltd)
7979	pertofran 25mg tablet (novartis pharmaceuticals uk ltd)
4321	phenelzine 15mg tablets
43673	politid xl 150mg capsules (actavis uk ltd)
41299	politid xl 75mg capsules (actavis uk ltd)
33074	praminil 10mg tablet (ddsa pharmaceuticals ltd)
21820	prepadine 25mg capsules (teva uk ltd)
21819	prepadine 75mg tablets (teva uk ltd)
24700	prondol 15mg tablet (wyeth pharmaceuticals)
31672	prondol 30mg tablet (wyeth pharmaceuticals)

26822	prothiaden
27616	prothiaden
51758	prothiaden 25mg capsules (stephar (u.k.) ltd)
1169	prothiaden 25mg capsules (teofarma)
2320	prothiaden 75mg tablets (teofarma)
11187	protriptyline 10mg tablet
7756	protriptyline 5mg tablet
418	prozac 20mg capsules (eli lilly and company ltd)
48220	prozac 20mg capsules (lexon (uk) ltd)
57532	prozac 20mg capsules (waymade healthcare plc)
252	prozac 20mg/5ml liquid (eli lilly and company ltd)
4907	prozac 60mg capsules (eli lilly and company ltd)
37256	prozep 20mg/5ml oral solution (chemidex pharma ltd)
33779	prozit 20mg/5ml oral solution (pinewood healthcare)
48199	ranfaxine xl 75mg capsules (ranbaxy (uk) ltd)
29786	ranflutin 20mg capsules (ranbaxy (uk) ltd)
2356	reboxetine 4mg tablets
41314	rodomel xl 150mg capsules (teva uk ltd)
41033	rodomel xl 75mg capsules (teva uk ltd)
35112	seroxat 10mg tablets (glaxosmithkline uk ltd)
841	seroxat 20mg tablets (glaxosmithkline uk ltd)
3601	seroxat 20mg/10ml liquid (glaxosmithkline uk ltd)
1575	seroxat 30mg tablets (glaxosmithkline uk ltd)
55537	seroxat 30mg tablets (lexon (uk) ltd)
54081	sertraline 25mg/5ml oral suspension
35258	sinepin 25mg capsules (marlborough pharmaceuticals ltd)
35493	sinepin 50mg capsules (marlborough pharmaceuticals ltd)
10413	sinequan 10mg capsules (pfizer ltd)
12129	sinequan 25mg capsules (pfizer ltd)
12125	sinequan 50mg capsules (pfizer ltd)
14519	sinequan 75mg capsules (pfizer ltd)
59753	sunveniz xl 150mg tablets (sun pharmaceuticals uk ltd)
27568	surmontil
8928	surmontil 10mg tablets (sanofi)
2532	surmontil 25mg tablets (sanofi)
2531	surmontil 50mg capsules (sanofi)
40817	tardcaps xl 150mg capsules (ixl pharma ltd)
40815	tardcaps xl 75mg capsules (ixl pharma ltd)
30376	thaden 25mg capsules (opus pharmaceuticals ltd)

21157	thaden 75mg tablets (opus pharmaceuticals ltd)
39809	tifaxin xl 150mg capsules (genus pharmaceuticals ltd)
39770	tifaxin xl 75mg capsules (genus pharmaceuticals ltd)
2579	tofranil 10mg tablet (novartis pharmaceuticals uk ltd)
56501	tofranil 25mg tablets (lexon (uk) ltd)
7910	tofranil 25mg tablets (novartis pharmaceuticals uk ltd)
4404	tofranil 25mg/5ml syrup (novartis pharmaceuticals uk ltd)
57751	tonpular xl 150mg capsules (wockhardt uk ltd)
52716	tonpular xl 75mg capsules (wockhardt uk ltd)
3783	tranylcypromine 10mg tablets
41654	tranylcypromine 10mg tablets (amco)
3955	tranylcypromine with trifluoperazine tablet
1730	trazodone 100mg capsules
34580	trazodone 100mg capsules (a a h pharmaceuticals ltd)
19181	trazodone 100mg capsules (generics (uk) ltd)
41709	trazodone 100mg capsules (teva uk ltd)
41710	trazodone 100mg capsules (zentiva)
12710	trazodone 150mg modified-release tablets
4020	trazodone 150mg tablets
30983	trazodone 150mg tablets (generics (uk) ltd)
29857	trazodone 150mg tablets (teva uk ltd)
34470	trazodone 150mg tablets (zentiva)
55137	trazodone 150mg/5ml oral suspension
55138	trazodone 250mg/5ml oral solution
57226	trazodone 25mg/5ml oral suspension
3355	trazodone 50mg capsules
34003	trazodone 50mg capsules (a a h pharmaceuticals ltd)
29339	trazodone 50mg capsules (generics (uk) ltd)
41609	trazodone 50mg capsules (teva uk ltd)
34421	trazodone 50mg capsules (zentiva)
6442	trazodone 50mg/5ml oral solution sugar free
59931	trazodone 50mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)
24890	trifluoperazine with tranylcypromine 1mg + 10mg tablet
25085	trimipramine
25045	trimipramine
4310	trimipramine 10mg tablets
42228	trimipramine 10mg tablets (a a h pharmaceuticals ltd)
53808	trimipramine 10mg tablets (phoenix healthcare distribution ltd)
2039	trimipramine 25mg tablets

45226	trimipramine 25mg tablets (a a h pharmaceuticals ltd)
57978	trimipramine 25mg tablets (waymade healthcare plc)
2533	trimipramine 50 mg tab
3196	trimipramine 50mg capsules
1453	triptafen m 2mg+10mg tablet (goldshield pharmaceuticals ltd)
1208	triptafen tablets (amco)
38827	triptafen-m tablets (mercury pharma group ltd)
8726	tryptizol 10mg tablet (merck sharp & dohme ltd)
8878	tryptizol 10mg/5ml sugar free oral solution (merck sharp and dohme ltd)
182	tryptizol 10mg/ml injection (merck sharp & dohme ltd)
54686	tryptophan 500mg capsules
4422	tryptophan 500mg tablets
8844	tryptophan with ascorbic acid and pyridoxine powder
40295	valdoxan 25mg tablets (servier laboratories ltd)
40514	venaxx xl 150mg capsules (amco)
40515	venaxx xl 75mg capsules (amco)
50081	venlablue xl 150mg capsules (bluefish pharmaceuticals ab)
59035	venlablue xl 37.5mg capsules (bluefish pharmaceuticals ab)
49511	venlablue xl 75mg capsules (bluefish pharmaceuticals ab)
58726	venladex xl 150mg tablets (dexcel-pharma ltd)
58681	venladex xl 75mg tablets (dexcel-pharma ltd)
55424	venlafaxine
55501	venlafaxine 150mg modified-release capsule (hillcross pharmaceuticals ltd)
2654	venlafaxine 150mg modified-release capsules
60549	venlafaxine 150mg modified-release capsules (kent pharmaceuticals ltd)
43334	venlafaxine 150mg modified-release capsules (sandoz ltd)
39360	venlafaxine 150mg modified-release tablets
50934	venlafaxine 150mg/5ml oral solution
40054	venlafaxine 225mg modified-release tablets
58837	venlafaxine 37.5mg modified-release capsules
45806	venlafaxine 37.5mg modified-release tablets
301	venlafaxine 37.5mg tablets
56662	venlafaxine 37.5mg tablets (a a h pharmaceuticals ltd)
59923	venlafaxine 37.5mg tablets (bristol laboratories ltd)
51361	venlafaxine 37.5mg tablets (ranbaxy (uk) ltd)
51699	venlafaxine 37.5mg/5ml oral solution
13237	venlafaxine 37.5mg/5ml oral suspension
2617	venlafaxine 50mg tablets

470	venlafaxine 75mg modified-release capsules
59563	venlafaxine 75mg modified-release capsules (kent pharmaceuticals ltd)
43203	venlafaxine 75mg modified-release capsules (sandoz ltd)
39359	venlafaxine 75mg modified-release tablets
1222	venlafaxine 75mg tablets
60449	venlafaxine 75mg tablets (a a h pharmaceuticals ltd)
56457	venlafaxine 75mg tablets (teva uk ltd)
53326	venlafaxine 75mg/5ml oral solution
40062	venlalic xl 150mg tablets (db ashbourne ltd)
40407	venlalic xl 225mg tablets (db ashbourne ltd)
45818	venlalic xl 37.5mg tablets (db ashbourne ltd)
40059	venlalic xl 75mg tablets (db ashbourne ltd)
44936	venlaneo xl 150mg capsules (kent pharmaceuticals ltd)
44937	venlaneo xl 75mg capsules (kent pharmaceuticals ltd)
40092	vensir xl 150mg capsules (morningside healthcare ltd)
40277	vensir xl 75mg capsules (morningside healthcare ltd)
40517	vexarin xl 150mg capsules (generics (uk) ltd)
42600	vexarin xl 75mg capsules (generics (uk) ltd)
40764	viepax 37.5mg tablets (dexcel-pharma ltd)
40917	viepax 75mg tablets (dexcel-pharma ltd)
40049	viepax xl 150mg tablets (dexcel-pharma ltd)
40048	viepax xl 75mg tablets (dexcel-pharma ltd)
12309	viloxazine hcl 50mg tablets
12111	vivalan 50mg tablet (astrazeneca uk ltd)
4726	zispin 30mg tablets (organon laboratories ltd)
60370	zispin soltab 15mg orodispersible tablets (mawdsley-brooks & company ltd)
6846	zispin soltab 15mg orodispersible tablets (merck sharp & dohme ltd)
50892	zispin soltab 15mg orodispersible tablets (necessity supplies ltd)
10083	zispin soltab 30mg orodispersible tablets (merck sharp & dohme ltd)
53543	zispin soltab 30mg orodispersible tablets (necessity supplies ltd)
15268	zispin soltab 45mg orodispersible tablets (merck sharp & dohme ltd)

Appendix A8- List of anxiolytics/ hypnotics

Prodcode	Product name
7444	Ativan 4mg/1ml solution for injection ampoules (Pfizer Ltd)
61443	Buspirone 10mg tablets (A A H Pharmaceuticals Ltd)
16169	Librium 100mg Injection (Roche Products Ltd)
61450	Lorazepam 1mg tablets (A A H Pharmaceuticals Ltd)
64729	Lorazepam 1mg tablets (Genesis Pharmaceuticals Ltd)
64876	Lorazepam 2mg/5ml oral suspension
664	Lorazepam 4mg/1ml solution for injection ampoules
61886	Lorazepam 5mg/5ml oral suspension
64775	Nitrazepam 10mg/5ml oral suspension
63665	Noctamid 0.5mg Tablet (Schering Health Care Ltd)
62645	Temazepam 20mg Tablet (Lagap)
60825	Temazepam 20mg tablets (Sandoz Ltd)
63674	Temazepam 30mg gel-fill capsules
65190	Zolpidem 10mg tablets (Zentiva)
65637	Zopiclone 7.5mg tablets (Phoenix Healthcare Distribution Ltd)
63592	Zopiclone 7.5mg tablets (Sigma Pharmaceuticals Plc)
9696	alprazolam 250microgram tablets
11486	alprazolam 500microgram tablets
15615	amobarbital 100mg tablets
17102	amobarbital 15mg tablets
15614	amobarbital 200mg tablets
4134	amobarbital 30mg tablets
21460	amobarbital 50mg / secobarbital sodium 50mg capsules
8548	amobarbital sodium 200mg capsules
28146	amobarbital sodium 60mg capsules
14414	amobarbital sodium 60mg tablets
13411	amytal 100mg tablet (flynn pharma ltd)
12010	amytal 15mg tablet (flynn pharma ltd)
27481	amytal 200mg tablet (flynn pharma ltd)
8713	amytal 30mg tablet (flynn pharma ltd)
12452	anxon 15mg capsule (beecham research laboratories)
12130	anxon 30mg capsule (beecham research laboratories)
36581	atensine 10mg tablet (rorer pharmaceuticals ltd)
10954	ativan 1mg tablet (wyeth pharmaceuticals)
17830	ativan 2.5mg tablet (wyeth pharmaceuticals)
45367	bio-melatonin 3mg tablets (imported (denmark))

22424	bromazepam 1.5mg tablets
55774	bromazepam 3mg tablets
19941	bromazepam 3mg tablets
9008	buspar 10mg tablets (ixl pharma ltd)
49504	buspar 10mg tablets (lexon (uk) ltd)
2394	buspar 5mg tablets (ixl pharma ltd)
40153	buspirone 10mg tablet (galen ltd)
5385	buspirone 10mg tablets
46847	buspirone 10mg tablets (actavis uk ltd)
28880	buspirone 5mg tablet (galen ltd)
3574	buspirone 5mg tablets
59095	buspirone 5mg tablets (a a h pharmaceuticals ltd)
45275	buspirone 5mg tablets (actavis uk ltd)
43240	buspirone 5mg tablets (generics (uk) ltd)
8624	butobarbital 100mg tablets
25893	centrax 10mg tablet (parke-davis research laboratories)
4632	chloral 200mg/5ml paediatric oral solution
30249	chloral 500mg capsules
3580	chloral hydrate 143.3mg/5ml oral solution
55892	chloral hydrate 1g/5ml oral solution
4018	chloral hydrate 1g/5ml oral suspension
51578	chloral hydrate 200mg/5ml oral solution
60006	chloral hydrate 250mg/5ml oral solution
1784	chloral hydrate 500 mg cap
19073	chloral hydrate 500mg/5ml mixture (rosemont pharmaceuticals ltd)
12898	chloral hydrate 500mg/5ml mixture bp 2000
60204	chloral hydrate 500mg/5ml oral solution sugar free
4017	chloral hydrate 500mg/5ml oral suspension
58185	chloral hydrate 600mg/5ml oral solution
45225	chloral hydrate oral solution
9063	chloral mix
13473	chloral syr
41574	chlordiazepoxide 10mg capsule (approved prescription services ltd)
41629	chlordiazepoxide 10mg capsule (ddsa pharmaceuticals ltd)
41581	chlordiazepoxide 10mg capsule (ivax pharmaceuticals uk ltd)
1463	chlordiazepoxide 10mg capsules
45241	chlordiazepoxide 10mg capsules (a a h pharmaceuticals ltd)
41583	chlordiazepoxide 10mg capsules (actavis uk ltd)
41988	chlordiazepoxide 10mg tablet (ddsa pharmaceuticals ltd)

5294	chlordiazepoxide 10mg tablets
3147	chlordiazepoxide 10mg tablets
40386	chlordiazepoxide 25mg tablet (ddsa pharmaceuticals ltd)
6516	chlordiazepoxide 25mg tablets
8550	chlordiazepoxide 25mg tablets
41606	chlordiazepoxide 5mg capsule (approved prescription services ltd)
34928	chlordiazepoxide 5mg capsule (ddsa pharmaceuticals ltd)
2122	chlordiazepoxide 5mg capsules
35936	chlordiazepoxide 5mg capsules (a a h pharmaceuticals ltd)
41582	chlordiazepoxide 5mg capsules (actavis uk ltd)
28879	chlordiazepoxide 5mg tablet (ddsa pharmaceuticals ltd)
6025	chlordiazepoxide 5mg tablets
4543	chlordiazepoxide 5mg tablets
43438	chlordiazepoxide 5mg tablets (a a h pharmaceuticals ltd)
12038	chlormezanone 200mg tablets
38265	circadin 2mg modified-release tablets (flynn pharma ltd)
3110	clobazam 10mg capsules
3111	clobazam 10mg tablets
55481	clobazam 10mg/5ml oral suspension sugar free
54759	clobazam 5mg/5ml oral suspension sugar free
2535	clomethiazole 157.5mg/5ml oral solution sugar free
563	clomethiazole 192mg capsules
59170	clomethiazole 192mg capsules (a a h pharmaceuticals ltd)
58361	clomethiazole 31.5mg/ml oral solution sugar free (a a h pharmaceuticals ltd)
4483	clonazepam 2.5mg/ml drops sugar free
32500	clonazepam 250micrograms/5ml oral solution
57664	clonazepam 250micrograms/5ml oral suspension
2073	clonazepam 2mg tablets
53739	clonazepam 2mg tablets (sigma pharmaceuticals plc)
13200	clonazepam 2mg/5ml oral solution sugar free
50108	clonazepam 2mg/5ml oral solution sugar free
34491	clonazepam 2mg/5ml oral solution sugar free (rosemont pharmaceuticals ltd)
58460	clonazepam 312.5micrograms/5ml oral suspension
1559	clonazepam 500microgram tablets
58482	clonazepam 500microgram tablets (a a h pharmaceuticals ltd)
59396	clonazepam 500microgram tablets (almus pharmaceuticals ltd)
53311	clonazepam 500microgram tablets (phoenix healthcare distribution ltd)

45077	clonazepam 500microgram/5ml oral solution (rosemont pharmaceuticals ltd)
47066	clonazepam 500micrograms/5ml oral solution
48544	clonazepam 500micrograms/5ml oral solution sugar free
14743	clonazepam 500micrograms/5ml oral suspension
17637	clonazepam 500micrograms/5ml solution sugar free
1134	cloral betaine 707mg tablets
3956	dalmane 15mg capsules (meda pharmaceuticals ltd)
3105	dalmane 30mg capsules (meda pharmaceuticals ltd)
9111	diazepam 10mg capsules
2083	diazepam 10mg rectubes (wockhardt uk ltd)
8334	diazepam 10mg suppositories
41689	diazepam 10mg suppository (sinclair is pharma plc)
54695	diazepam 10mg tablet (m & a pharmachem ltd)
1400	diazepam 10mg tablets
41632	diazepam 10mg tablets (a a h pharmaceuticals ltd)
34807	diazepam 10mg tablets (actavis uk ltd)
34293	diazepam 10mg tablets (generics (uk) ltd)
46913	diazepam 10mg tablets (ivax pharmaceuticals uk ltd)
34340	diazepam 10mg tablets (ranbaxy (uk) ltd)
41607	diazepam 10mg tablets (teva uk ltd)
4176	diazepam 10mg/2.5ml rectal solution tube
34614	diazepam 10mg/2.5ml rectal solution tube (sandoz ltd)
51335	diazepam 10mg/5ml oral solution
58959	diazepam 10mg/5ml oral solution (am distributions (yorkshire) ltd)
12849	diazepam 10mg/5ml oral suspension
9045	diazepam 1mg/5ml suspension
18488	diazepam 2.5mg rectubes (wockhardt uk ltd)
5842	diazepam 2.5mg/1.25ml rectal solution tube
53566	diazepam 2.5mg/5ml oral solution
9430	diazepam 2.5mg/5ml oral suspension
23820	diazepam 20mg rectal tubes
3870	diazepam 2mg capsules
34876	diazepam 2mg tablet (berk pharmaceuticals ltd)
28347	diazepam 2mg tablet (crosspharma ltd)
45135	diazepam 2mg tablet (m & a pharmachem ltd)
34561	diazepam 2mg tablet (regent laboratories ltd)
46	diazepam 2mg tablets
33672	diazepam 2mg tablets (a a h pharmaceuticals ltd)

34524	diazepam 2mg tablets (actavis uk ltd)
45313	diazepam 2mg tablets (almus pharmaceuticals ltd)
34338	diazepam 2mg tablets (generics (uk) ltd)
34677	diazepam 2mg tablets (ivax pharmaceuticals uk ltd)
29945	diazepam 2mg tablets (ranbaxy (uk) ltd)
34335	diazepam 2mg tablets (teva uk ltd)
56236	diazepam 2mg tablets (wockhardt uk ltd)
2352	diazepam 2mg/5ml oral solution
32853	diazepam 2mg/5ml oral solution (sandoz ltd)
10274	diazepam 2mg/5ml oral solution sugar free
53461	diazepam 2mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)
20968	diazepam 2mg/5ml oral solution sugar free (actavis uk ltd)
51985	diazepam 2mg/5ml oral suspension
3205	diazepam 5mg
38410	diazepam 5mg rectal tubes (hillcross pharmaceuticals ltd)
2078	diazepam 5mg rectubes (wockhardt uk ltd)
8344	diazepam 5mg suppository
34892	diazepam 5mg tablet (berk pharmaceuticals ltd)
34681	diazepam 5mg tablet (crosspharma ltd)
47	diazepam 5mg tablets
34635	diazepam 5mg tablets (a a h pharmaceuticals ltd)
32296	diazepam 5mg tablets (actavis uk ltd)
59407	diazepam 5mg tablets (de pharmaceuticals)
34615	diazepam 5mg tablets (generics (uk) ltd)
46966	diazepam 5mg tablets (ivax pharmaceuticals uk ltd)
45218	diazepam 5mg tablets (ranbaxy (uk) ltd)
45244	diazepam 5mg tablets (sandoz ltd)
57838	diazepam 5mg tablets (sovereign medical ltd)
34482	diazepam 5mg tablets (teva uk ltd)
57749	diazepam 5mg tablets (waymade healthcare plc)
6747	diazepam 5mg/2.5ml rectal solution tube
34033	diazepam 5mg/2.5ml rectal solution tube (sandoz ltd)
9065	diazepam 5mg/5ml oral solution
42503	diazepam 5mg/5ml oral solution (a a h pharmaceuticals ltd)
59122	diazepam 5mg/5ml oral solution (am distributions (yorkshire) ltd)
34045	diazepam 5mg/5ml oral solution (sandoz ltd)
8842	diazepam rectal 2 mg/ml sol
4587	diazepam rectal 4 mg sol
16734	diazepam rectubes 20mg rectal tubes (c p pharmaceuticals ltd)

10909	diazepam s/r 10 mg cap
8758	dichloralphenazone 225mg/5ml oral solution
7748	dichloralphenazone 650mg tablets
23205	dormonoct 1mg tablet (hoechst marion roussel)
10278	epistatus 10mg/ml oromucosal solution (special products ltd)
12484	equanil 200mg tablet (wyeth pharmaceuticals)
12512	equanil 400mg tablet (wyeth pharmaceuticals)
36611	euhypnos 10mg/5ml oral solution (pharmacia ltd)
29441	euhypnos forte 20mg capsule (pharmacia ltd)
28703	evacalm 5mg tablet (unimed pharmaceuticals ltd)
14480	flunitrazepam 1mg tablets
24422	flurazepam 10 mg tab
12278	flurazepam 15 mg tab
3950	flurazepam 15mg capsules
18928	flurazepam 30 mg tab
7566	flurazepam 30mg capsules
8487	frisium 10mg capsule (aventis pharma)
27895	gentian alkaline and phenobarbital mixture
3491	heminevrin 192mg capsules (astrazeneca uk ltd)
23796	ketazolam 15mg capsule
28360	ketazolam 30mg capsule
11958	lexotan 1.5mg tablet (roche products ltd)
9721	lexotan 3mg tablet (roche products ltd)
8913	librium 10mg capsule (icn pharmaceuticals france s.a.)
24599	librium 10mg capsules (meda pharmaceuticals ltd)
17294	librium 10mg tablet (icn pharmaceuticals france s.a.)
32231	librium 25mg tablet (icn pharmaceuticals france s.a.)
12477	librium 5mg capsule (icn pharmaceuticals france s.a.)
18125	librium 5mg capsules (meda pharmaceuticals ltd)
9048	librium 5mg tablet (icn pharmaceuticals france s.a.)
5150	loprazolam 1mg tablets
41596	loprazolam 1mg tablets (zentiva)
21437	loramet 1mg capsule (wyeth pharmaceuticals)
10409	lorazepam .5 mg tab
14417	lorazepam 1 mg sus
1088	lorazepam 1mg tablets
41391	lorazepam 1mg tablets (arrow generics ltd)
36200	lorazepam 1mg tablets (generics (uk) ltd)
45829	lorazepam 1mg tablets (sandoz ltd)

33086	lorazepam 1mg tablets (teva uk ltd)
39284	lorazepam 1mg tablets (thornton & ross ltd)
37745	lorazepam 1mg/5ml oral solution
37566	lorazepam 1mg/5ml oral suspension
2091	lorazepam 2.5mg tablets
57268	lorazepam 2.5mg tablets (sandoz ltd)
35932	lorazepam 2.5mg tablets (teva uk ltd)
42814	lorazepam 2.5mg tablets (thornton & ross ltd)
23002	lorazepam 5 mg tab
46896	lorazepam 500micrograms/5ml oral solution
13279	lorazepam 500micrograms/5ml oral suspension
56551	lorazepam 5mg/5ml oral solution
3357	lormetazepam 1mg capsule
34534	lormetazepam 1mg tablet (wyeth pharmaceuticals)
3354	lormetazepam 1mg tablets
34516	lormetazepam 1mg tablets (generics (uk) ltd)
34692	lormetazepam 1mg tablets (genus pharmaceuticals ltd)
48517	lormetazepam 1mg/5ml oral suspension
3687	lormetazepam 500microgram tablets
34292	lormetazepam 500microgram tablets (a a h pharmaceuticals ltd)
34642	lormetazepam 500microgram tablets (generics (uk) ltd)
34361	lormetazepam 500microgram tablets (genus pharmaceuticals ltd)
10790	medazepam 10mg capsule
21464	medazepam 5mg capsule
26391	melatonin 10mg capsules
54717	melatonin 10mg/5ml oral suspension
10068	melatonin 1mg capsules
17663	melatonin 1mg tablets
50258	melatonin 1mg/1ml oral liquid sugar free
57406	melatonin 1mg/5ml oral solution
52683	melatonin 1mg/5ml oral suspension
14221	melatonin 1mg/ml sugar free oral solution
13023	melatonin 2.5mg capsules
14210	melatonin 2.5mg/5ml oral suspension
52303	melatonin 20mg capsules
7099	melatonin 2mg capsules
38208	melatonin 2mg modified-release tablets
52079	melatonin 2mg tablets
52487	melatonin 2mg/5ml oral solution

49196	melatonin 2mg/5ml oral suspension
14145	melatonin 3mg capsules
16993	melatonin 3mg modified-release capsules
55860	melatonin 3mg modified-release capsules (imported (united states))
14250	melatonin 3mg tablets
58692	melatonin 3mg/5ml oral solution
52289	melatonin 3mg/5ml oral suspension
50115	melatonin 4mg capsules
58566	melatonin 4mg/5ml oral solution
49576	melatonin 500microgram tablets
35224	melatonin 5mg capsules
56393	melatonin 5mg tablets
45975	melatonin 5mg/5ml oral solution
55100	melatonin 5mg/5ml oral solution (drug tariff special order)
45783	melatonin 5mg/5ml oral suspension
48436	melatonin 6mg capsules
55191	melatonin 6mg/5ml oral solution
53064	melatonin 6mg/5ml oral suspension
45230	melatonin capsule
41961	melatonin tablet
3639	meprobamate 200mg tablet
10676	meprobamate 400 mg cap
2828	meprobamate 400mg tablets
8464	meprobamate with bendroflumethiazide tablet
11326	meprobamate with ethoheptazine citrate and aspirin tablet
15022	methylphenobarbital 200mg tablet
23768	methylphenobarbital 30mg tablet
23767	methylphenobarbital 60mg tablet
18976	methyprylone 200mg tablet
55931	midazolam 10mg/1ml oromucosal solution pre-filled oral syringes
48715	midazolam 10mg/2ml oromucosal solution pre-filled syringes (special order)
58685	midazolam 10mg/5ml oral solution
7301	midazolam 10mg/ml buccal solution
49595	midazolam 10mg/ml oral solution
49095	midazolam 10mg/ml oromucosal solution
52845	midazolam 12.5mg/5ml oral suspension
48817	midazolam 2.5mg/0.5ml oromucosal solution pre-filled syringes (special order)
45695	midazolam 2.5mg/ml oral solution

48807	midazolam 5mg/1ml oromucosal solution pre-filled syringes (special order)
52954	midazolam 7.5mg tablets
50618	midazolam 7.5mg/1.5ml oromucosal solution pre-filled syringes (special order)
44764	midazolam maleate buccal solution
43450	midazolam oral solution
24642	milonorm 400mg tablet (wallace manufacturing chemists ltd)
3524	mogadon 5mg capsule (roche products ltd)
7786	mogadon 5mg tablet (icn pharmaceuticals france s.a.)
19450	mogadon 5mg tablets (meda pharmaceuticals ltd)
15492	nitrados 5mg tablet (rorer pharmaceuticals ltd)
3686	nitrazepam 10mg tablet
7924	nitrazepam 2.5mg/5ml oral suspension
2407	nitrazepam 5mg capsule
34964	nitrazepam 5mg tablet (berk pharmaceuticals ltd)
34770	nitrazepam 5mg tablet (ddsa pharmaceuticals ltd)
35	nitrazepam 5mg tablets
34408	nitrazepam 5mg tablets (a a h pharmaceuticals ltd)
41385	nitrazepam 5mg tablets (actavis uk ltd)
34806	nitrazepam 5mg tablets (generics (uk) ltd)
46953	nitrazepam 5mg tablets (ranbaxy (uk) ltd)
34686	nitrazepam 5mg tablets (teva uk ltd)
34555	nitrazepam 5mg tablets (wockhardt uk ltd)
9814	nitrazepam 5mg/5ml oral suspension
10789	nobrium 10mg capsule (roche products ltd)
10791	nobrium 5mg capsule (roche products ltd)
18291	noctamid 1mg tablet (schering health care ltd)
2950	noctec 500mg capsule (e r squibb and sons ltd)
18925	noludar 200mg tablet (roche products ltd)
12293	normison 10mg capsule (wyeth pharmaceuticals)
21454	normison 20mg capsule (wyeth pharmaceuticals)
25273	oxanid 10mg tablet (m a steinhard ltd)
41542	oxazepam 10mg tablet (ivax pharmaceuticals uk ltd)
4566	oxazepam 10mg tablets
36604	oxazepam 10mg tablets (a a h pharmaceuticals ltd)
41531	oxazepam 10mg tablets (actavis uk ltd)
41553	oxazepam 10mg tablets (thornton & ross ltd)
7652	oxazepam 15 mg cap
41601	oxazepam 15mg tablet (ivax pharmaceuticals uk ltd)

4141	oxazepam 15mg tablets
41411	oxazepam 15mg tablets (a a h pharmaceuticals ltd)
41602	oxazepam 15mg tablets (actavis uk ltd)
46946	oxazepam 15mg tablets (thornton & ross ltd)
4140	oxazepam 30mg capsule
8721	oxazepam 30mg tablet
24321	paxane 30mg capsule (m a steinhard ltd)
4496	phenobarbital 100mg tablet
57247	phenobarbital 100mg/5ml oral suspension
41973	phenobarbital 15mg tablet (celltech pharma europe ltd)
5439	phenobarbital 15mg tablets
59868	phenobarbital 15mg tablets (a a h pharmaceuticals ltd)
59795	phenobarbital 15mg tablets (bristol laboratories ltd)
59574	phenobarbital 15mg tablets (kent pharmaceuticals ltd)
29306	phenobarbital 15mg tablets (teva uk ltd)
202	phenobarbital 15mg/5ml elixir
59232	phenobarbital 15mg/5ml elixir (a a h pharmaceuticals ltd)
58905	phenobarbital 15mg/5ml elixir (alliance healthcare (distribution) ltd)
59065	phenobarbital 15mg/5ml elixir (thornton & ross ltd)
60212	phenobarbital 15mg/5ml oral solution
34275	phenobarbital 15mg/5ml oral solution (william ransom)
60648	phenobarbital 15mg/5ml oral suspension
39618	phenobarbital 20mg/5ml oral solution
55019	phenobarbital 250mg/5ml oral suspension
57722	phenobarbital 25mg/5ml oral solution
1576	phenobarbital 30mg tablets
25543	phenobarbital 30mg tablets (a a h pharmaceuticals ltd)
33323	phenobarbital 30mg tablets (actavis uk ltd)
59715	phenobarbital 30mg tablets (alliance healthcare (distribution) ltd)
58846	phenobarbital 30mg tablets (almus pharmaceuticals ltd)
59136	phenobarbital 30mg tablets (bristol laboratories ltd)
56880	phenobarbital 30mg tablets (kent pharmaceuticals ltd)
28945	phenobarbital 30mg tablets (teva uk ltd)
58532	phenobarbital 34mg/5ml oral suspension
51326	phenobarbital 50mg/5ml oral solution
10273	phenobarbital 50mg/5ml oral solution
59917	phenobarbital 50mg/5ml oral solution (drug tariff special order)
35164	phenobarbital 50mg/5ml oral suspension
47812	phenobarbital 60mg tablet (celltech pharma europe ltd)

1399	phenobarbital 60mg tablets
58891	phenobarbital 60mg tablets (a a h pharmaceuticals ltd)
24138	phenobarbital 60mg tablets (actavis uk ltd)
60059	phenobarbital 60mg tablets (kent pharmaceuticals ltd)
33372	phenobarbital 60mg tablets (teva uk ltd)
59013	phenobarbital 60mg/5ml oral solution
45370	phenobarbital 75mg/5ml oral solution
55502	phenobarbital 75mg/5ml oral suspension
55796	phenobarbital sodium 15mg/5ml oral solution
60598	phenobarbital sodium 15mg/5ml oral suspension
3225	phenobarbital sodium 30mg tablet
50442	phenobarbital sodium 50mg/5ml oral solution
19907	phenobarbital sodium 60mg tablet
12443	potassium bromide & chloral mix
32796	potassium bromide & chloral mixture
32538	potassium bromide & valerian mxtire
37325	remnos 10mg tablet (ddsa pharmaceuticals ltd)
14613	secobarbital sodium 100mg capsules
26775	secobarbital sodium 50mg capsules
12264	seconal sodium 100mg capsules (flynn pharma ltd)
12539	seconal sodium 50mg capsules (flynn pharma ltd)
13471	sodium amytal 200mg capsules (flynn pharma ltd)
13470	sodium amytal 200mg tablet (flynn pharma ltd)
14415	sodium amytal 60mg capsules (flynn pharma ltd)
14416	sodium amytal 60mg tablet (flynn pharma ltd)
58922	sodium dl-3-hydroxybutyrate powder (special products ltd)
36312	sodium oxybate 500mg/ml oral solution sugar free
33070	solis 5mg capsule (galen ltd)
23874	somnite 2.5mg/5ml oral suspension (norgine pharmaceuticals ltd)
18859	somnwell 707mg film coated tablet (huntley pharmaceuticals ltd)
5306	sonata 10mg capsules (meda pharmaceuticals ltd)
9598	sonata 5mg capsules (meda pharmaceuticals ltd)
13447	soneryl 100mg tablets (flynn pharma ltd)
8345	stesolid 10mg rectal tube (actavis uk ltd)
5793	stesolid 10mg rectal tubes (dumex ltd)
4395	stesolid 5mg rectal tube (actavis uk ltd)
3741	stilnoct 10mg tablets (sanofi)
3126	stilnoct 5mg tablets (sanofi)
27847	surem 5mg capsule (galen ltd)

56781	tapclob 10mg/5ml oral suspension (martindale pharmaceuticals ltd)
54934	tapclob 5mg/5ml oral suspension (martindale pharmaceuticals ltd)
38418	temazepam 10mg capsule (berk pharmaceuticals ltd)
41718	temazepam 10mg capsule (hillcross pharmaceuticals ltd)
921	temazepam 10mg capsules
20245	temazepam 10mg gel-fill capsules
41516	temazepam 10mg tablet (ivax pharmaceuticals uk ltd)
41562	temazepam 10mg tablet (pharmacia ltd)
33648	temazepam 10mg tablet (wyeth pharmaceuticals)
20	temazepam 10mg tablets
34331	temazepam 10mg tablets (a a h pharmaceuticals ltd)
45254	temazepam 10mg tablets (actavis uk ltd)
56927	temazepam 10mg tablets (ethigen ltd)
56811	temazepam 10mg tablets (f.maltby & sons ltd)
34508	temazepam 10mg tablets (generics (uk) ltd)
45283	temazepam 10mg tablets (genus pharmaceuticals ltd)
34002	temazepam 10mg tablets (ivax pharmaceuticals uk ltd)
49589	temazepam 10mg tablets (sandoz ltd)
34406	temazepam 10mg tablets (teva uk ltd)
15110	temazepam 10mg/5ml oral solution (generics (uk) ltd)
780	temazepam 10mg/5ml oral solution sugar free
32847	temazepam 10mg/5ml oral solution sugar free (a a h pharmaceuticals ltd)
55836	temazepam 10mg/5ml oral solution sugar free (focus pharmaceuticals ltd)
27367	temazepam 10mg/5ml oral solution sugar free (rosemont pharmaceuticals ltd)
7569	temazepam 15mg capsules
38424	temazepam 20mg capsule (berk pharmaceuticals ltd)
41653	temazepam 20mg capsule (hillcross pharmaceuticals ltd)
2403	temazepam 20mg capsules
32320	temazepam 20mg gel-fill capsules
36602	temazepam 20mg tablet (pharmacia ltd)
30779	temazepam 20mg tablet (wyeth pharmaceuticals)
1729	temazepam 20mg tablets
41717	temazepam 20mg tablets (a a h pharmaceuticals ltd)
46964	temazepam 20mg tablets (actavis uk ltd)
34572	temazepam 20mg tablets (generics (uk) ltd)
46078	temazepam 20mg tablets (genus pharmaceuticals ltd)
30985	temazepam 20mg tablets (ivax pharmaceuticals uk ltd)
46939	temazepam 20mg tablets (teva uk ltd)

10430	temazepam 30mg capsules
8798	temazepam gelthix 10mg capsule (pharmacia ltd)
23120	temazepam gelthix 15mg capsule (pharmacia ltd)
12462	temazepam gelthix 20mg capsule (pharmacia ltd)
20801	temazepam gelthix 30mg capsule (pharmacia ltd)
23493	temazepam planpak
7567	temazepam planpak capsule (manufacturer unknown)
31163	temazepam s/f
13612	temazepam ud 10ml 10 mg/5ml eli
28058	temazepam ud 5ml 10 mg/5ml eli
8303	tenavoid tablet (edwin burgess ltd)
3973	tensium 10mg tablets (ddsa pharmaceuticals ltd)
1909	trancopal 200mg tablet (sanofi-synthelabo ltd)
46909	triazolam (roi) 125microgram tablet
55303	triazolam 0.125mg tablet (berk pharmaceuticals ltd)
41822	triazolam 0.25mg tablet (berk pharmaceuticals ltd)
7571	triazolam 125microgram tablet
2404	triazolam 250microgram tablet
10513	triclofos 500mg/5ml oral solution
31951	triclofos 500mg/5ml oral solution (ucb pharma ltd)
44302	tropium 10mg tablets (dr reddy's laboratories (uk) ltd)
27880	tropium 5mg capsules (dr reddy's laboratories (uk) ltd)
30273	tropium 5mg tablets (dr reddy's laboratories (uk) ltd)
221	tuinal 100mg pulvules (flynn pharma ltd)
20514	valium 10mg suppository (roche products ltd)
10402	valium 10mg tablet (roche products ltd)
20164	valium 2mg capsule (roche products ltd)
2401	valium 2mg tablet (roche products ltd)
30321	valium 2mg/5ml oral solution (roche products ltd)
19299	valium 5mg capsule (roche products ltd)
28698	valium 5mg suppository (roche products ltd)
4338	valium 5mg tablet (roche products ltd)
35142	vytalonin 3mg tablet (idis world medicines)
20800	welldorm
20679	welldorm
3928	welldorm 143.3mg/5ml elixir (marlborough pharmaceuticals ltd)
2300	welldorm 707mg tablets (marlborough pharmaceuticals ltd)
10802	xanax 250microgram tablets (pfizer ltd)
12598	xanax 500microgram tablets (pfizer ltd)

35810	xyrem 500mg/ml oral solution (ucb pharma ltd)
5352	zaleplon 10mg capsules
5916	zaleplon 5mg capsules
5058	zileze 3.75 tablets (opus pharmaceuticals ltd)
15852	zileze 7.5 tablets (opus pharmaceuticals ltd)
52022	zimovane 7.5mg tablets (lexon (uk) ltd)
3320	zimovane 7.5mg tablets (sanofi)
4187	zimovane ls 3.75mg tablets (sanofi)
42089	zolpidem 10mg tablet (winthrop pharmaceuticals ltd)
5459	zolpidem 10mg tablets
30981	zolpidem 10mg tablets (a a h pharmaceuticals ltd)
33841	zolpidem 10mg tablets (generics (uk) ltd)
41539	zolpidem 10mg tablets (ivax pharmaceuticals uk ltd)
43560	zolpidem 10mg tablets (teva uk ltd)
29869	zolpidem 5mg tablet (winthrop pharmaceuticals ltd)
2017	zolpidem 5mg tablets
31710	zolpidem 5mg tablets (a a h pharmaceuticals ltd)
41697	zolpidem 5mg tablets (ivax pharmaceuticals uk ltd)
41696	zolpidem 5mg tablets (teva uk ltd)
721	zopiclone 3.75mg tablets
34612	zopiclone 3.75mg tablets (a a h pharmaceuticals ltd)
29219	zopiclone 3.75mg tablets (actavis uk ltd)
57937	zopiclone 3.75mg tablets (almus pharmaceuticals ltd)
30377	zopiclone 3.75mg tablets (generics (uk) ltd)
30056	zopiclone 3.75mg tablets (ivax pharmaceuticals uk ltd)
34897	zopiclone 3.75mg tablets (kent pharmaceuticals ltd)
34777	zopiclone 3.75mg tablets (teva uk ltd)
46799	zopiclone 3.75mg/5ml oral solution
14365	zopiclone 3.75mg/5ml oral suspension
66	zopiclone 7.5mg tablets
43445	zopiclone 7.5mg tablets (a a h pharmaceuticals ltd)
24135	zopiclone 7.5mg tablets (actavis uk ltd)
33663	zopiclone 7.5mg tablets (generics (uk) ltd)
33045	zopiclone 7.5mg tablets (ivax pharmaceuticals uk ltd)
34874	zopiclone 7.5mg tablets (kent pharmaceuticals ltd)
34372	zopiclone 7.5mg tablets (pliva pharma ltd)
45353	zopiclone 7.5mg tablets (sandoz ltd)
34823	zopiclone 7.5mg tablets (teva uk ltd)
59640	zopiclone 7.5mg/5ml oral suspension

Appendix B- Vaccination Schedule changes in the UK between 1992-2017

Year	Vaccine routine change
1992	Added Hib conjugate
1999	Added Men-C conjugate
2001	Added pre-school acellular pertussis
2004	Changed live polio vaccine to inactivated polio Added Pneumococcal polysaccharide (PPV)
2006	Added Pneumococcal conjugate (PCV7) Combined Hib/Men-C
2010	Added Pneumococcal conjugate (PCV13)
2013	Added rotavirus and flu vaccine Men-C stopped for 4-month-olds
2015	Men-B introduced
2016	Men-C stopped for 3-month-olds
2017	Hep-B added to 5-in-1

* This table illustrates the changes to vaccine routine from 1991's schedule which included diphtheria, tetanus, BCG, MMR, pertussis and live polio

Appendix C1- Asthma readcodes

Readcode	Medcode	Description
173A.00	5867	Exercise induced asthma
173c.00	2575	Occupational asthma
173d.00	18116	Work aggravated asthma
178..00	11022	Asthma trigger
1780	41017	Aspirin induced asthma
1O2..00	11370	Asthma confirmed
2126200	10996	Asthma resolved
212G.00	11839	Asthma resolved
663..11	81	Asthma monitoring
663d.00	20876	Emergency asthma admission since last appointment
663e.00	25181	Asthma restricts exercise
6.63E+02	26861	Asthma sometimes restricts exercise
6.63E+102	26506	Asthma severely restricts exercise
663f.00	26504	Asthma never restricts exercise
663h.00	8484	Asthma - currently dormant
663j.00	9177	Asthma - currently active
663m.00	3378	Asthma accident and emergency attendance since last visit
663n.00	7416	Asthma treatment compliance satisfactory
663N000	30815	Asthma causing night waking
663N100	38146	Asthma disturbs sleep weekly
663N200	13175	Asthma disturbs sleep frequently
663O.00	13173	Asthma not disturbing sleep
663O000	38143	Asthma never disturbs sleep
663p.00	7191	Asthma treatment compliance unsatisfactory
663q.00	13174	Asthma daytime symptoms
663r.00	39570	Asthma causes night symptoms 1 to 2 times per month
663s.00	12697	Asthma never causes daytime symptoms
663t.00	28982	Asthma causes daytime symptoms 1 to 2 times per month
663u.00	7378	Asthma causes daytime symptoms 1 to 2 times per week
663v.00	13064	Asthma causes daytime symptoms most days
663V000	3458	Occasional asthma
663V100	3018	Mild asthma
663V200	13065	Moderate asthma
663V300	3366	Severe asthma
663w.00	7229	Asthma limits walking up hills or stairs
663x.00	10887	Asthma limits walking on the flat
663y.00	9018	Number of asthma exacerbations in past year
66Y5.00	9552	Change in asthma management plan
66Y9.00	9663	Step up change in asthma management plan
66YA.00	18223	Step down change in asthma management plan
66YC.00	41020	Absent from work or school due to asthma
66YJ.00	10043	Asthma annual review

66YK.00	13176	Asthma follow-up
66YP.00	31167	Asthma night-time symptoms
66YQ.00	19167	Asthma monitoring by nurse
66YR.00	30458	Asthma monitoring by doctor
8791	24506	Further asthma - drug prevent.
8793	29645	Asthma control step 0
8794	16785	Asthma control step 1
8795	16667	Asthma control step 2
8796	18224	Asthma control step 3
8797	20886	Asthma control step 4
8798	20860	Asthma control step 5
8B3j.00	10274	Asthma medication review
8CR0.00	25791	Asthma clinical management plan
8H2P.00	7058	Emergency admission; asthma
8HTT.00	18763	Referral to asthma clinic
9N1d.00	5515	Seen in asthma clinic
9NI8.00	92109	Asthma outreach clinic
9OJ1.00	46529	Attends asthma monitoring
9OJA.00	19539	Asthma monitoring check done
9OJA.11	8355	Asthma monitored
c11z.00	63597	Other disorder of pancreatic internal secretion NOS
c135.00	1045	Diabetes insipidus
c332.00	3451	Other paraproteinaemias
H312000	5798	Chronic asthmatic bronchitis
H33..00	78	Asthma
H330.00	7146	Extrinsic (atopic) asthma
H330000	14777	Extrinsic asthma without status asthmaticus
H330011	5627	Hay fever with asthma
H330100	27926	Extrinsic asthma with status asthmaticus
H330.11	2290	Allergic asthma
H330111	6707	Extrinsic asthma with asthma attack
H330.12	1208	Childhood asthma
H330.13	15248	Hay fever with asthma
H330.14	7731	Pollen asthma
H330z00	45782	Extrinsic asthma NOS
H331.00	5267	Intrinsic asthma
H331000	29325	Intrinsic asthma without status asthmaticus
H33..11	1555	Bronchial asthma
H331100	58196	Intrinsic asthma with status asthmaticus
H331.11	3665	Late onset asthma
H331111	18323	Intrinsic asthma with asthma attack
H331z00	45073	Intrinsic asthma NOS
H332.00	25796	Mixed asthma
H333.00	185	Acute exacerbation of asthma

H334.00	40823	Brittle asthma
H33z.00	4442	Asthma unspecified
H33z000	4892	Status asthmaticus NOS
H33z011	233	Severe asthma attack
h33z100	232	Asthma attack
H33z.11	32727	Hyperreactive airways disease
H33z111	8335	Asthma attack NOS
H33z200	12987	Late-onset asthma
H33zz00	16070	Asthma NOS
H33zz11	4606	Exercise induced asthma
H33zz12	21232	Allergic asthma NEC
H35y600	93353	Sequoiosis (red-cedar asthma)
H35y700	39478	Wood asthma
H47y000	47684	Detergent asthma
493	46189	Asthma
L4930LO	74458	Late onset asthma
Y0601JB	58231	Asthma clinic attendance
Y060 JB	58203	Clinic asthma
Y060 LE	83551	Asthma group
Y100 AR	74702	Asthma routine assessment

Appendix C2- Eczema readcodes

Readcode	Medcode	Description
M12z100	230	Eczema NOS
M112.00	610	Infantile eczema
M101.12	653	Seborrhoeic eczema
M12z111	1095	Discoid eczema
M113.00	1240	Flexural eczema
M12z200	1424	Infected eczema
M111.00	1741	Atopic dermatitis/eczema
14F1.00	2859	H/O: eczema
M12z300	3699	Hand eczema
M119.00	4684	Discoid eczema
M102.11	5000	Pustular eczema
A540.00	5395	Eczema herpeticum - Kaposi's varicelliform eruption
M114.00	5869	Allergic (intrinsic) eczema

Appendix C3- Allergic rhinitis readcodes

Readcode	Medcode	Description
H170.11	121	Hay fever - pollens
H172.11	3798	Hay fever - unspecified allergen
H330011	5627	Hay fever with asthma
12D4.00	7020	FH: Hay fever
14B1.00	9302	H/O: hay fever
H330.13	15248	Hay fever with asthma
H171.14	16134	Hay fever - other allergen
H17..00	175	Allergic rhinitis
H172.00	775	Allergic rhinitis due to unspecified allergen
H17z.00	964	Allergic rhinitis NOS
H170.00	1838	Allergic rhinitis due to pollens
H171.00	2372	Allergic rhinitis due to other allergens
Hyu2100	47599	[X]Other allergic rhinitis
Hyu2000	72490	[X]Other seasonal allergic rhinitis

Appendix C4- Food Allergy readcodes

Readcode	Medcode	Description
SN58.00	489	Food allergy
14M1.00	7418	H/O: food allergy
SN58600	98106	Seafood allergy
SN58000	4425	Egg allergy
SN58200	4882	Peanut allergy
J432.12	7179	Cow's milk allergy
SN58300	10182	Nut allergy
13A6.00	19613	Milk free diet - allergy
13A7.00	19615	Egg free diet - allergy
SN58100	26729	Egg protein allergy
ZC2CF00	63205	Dietary advice for food allergy
SN5A.00	94213	Oral allergy syndrome
SN58400	95867	Wheat allergy
SN58500	98127	Fish allergy
SN58700	98281	Shellfish allergy
SN58800	102590	Mushroom allergy
SN58911	104300	Strawberry allergy
9NIX.00	104313	Seen by clinical allergy - service
SN58900	104326	Allergy to strawberries
SN58A00	106668	Allergy to soya
SN58B00	109017	Allergy to banana
2126D00	109068	Cow's milk protein allergy symptoms resolved
8CA4S11	110242	Dietary advice for food allergy
SN58C00	110403	Allergy to tomato

Appendix D- Smoking read codes

Readcode	Medcode	Description
1371	33	Never smoked tobacco
1371.11	11788	Non-smoker
1372	12958	Trivial smoker - < 1 cig/day
1372.11	12941	Occasional smoker
1373	12944	Light smoker - 1-9 cigs/day
1374	1878	Moderate smoker - 10-19 cigs/d
1375	3568	Heavy smoker - 20-39 cigs/day
1376	1822	Very heavy smoker - 40+cigs/d
1377	12961	Ex-trivial smoker (<1/day)
1378	12957	Ex-light smoker (1-9/day)
1379	12955	Ex-moderate smoker (10-19/day)
6791	2111	Health ed. - smoking
137..11	12942	Smoker - amount smoked
137A.00	12956	Ex-heavy smoker (20-39/day)
137B.00	12959	Ex-very heavy smoker (40+/day)
137b.00	31114	Ready to stop smoking
137c.00	30423	Thinking about stopping smoking
137C.00	12964	Keeps trying to stop smoking
137d.00	30762	Not interested in stopping smoking
137e.00	41979	Smoking restarted
137F.00	12946	Ex-smoker - amount unknown
137f.00	46321	Reason for restarting smoking
137G.00	12240	Trying to give up smoking
137H.00	12947	Pipe smoker
137h.00	62686	Minutes from waking to first tobacco consumption
137j.00	97210	Ex-cigarette smoker
137J.00	12943	Cigar smoker
137K.00	776	Stopped smoking
137K000	99838	Recently stopped smoking
137L.00	60	Current non-smoker
137l.00	100495	Ex roll-up cigarette smoker
137M.00	12945	Rolls own cigarettes
137m.00	101338	Failed attempt to stop smoking
137N.00	26470	Ex pipe smoker
137O.00	19488	Ex cigar smoker
137P.00	93	Cigarette smoker
137P.11	1823	Smoker
137Q.00	12952	Smoking started
137Q.11	12951	Smoking restarted
137R.00	10558	Current smoker

137S.00	90	Ex smoker
137T.00	12878	Date ceased smoking
137V.00	12966	Smoking reduced
13p..00	10211	Smoking cessation milestones
13p0.00	34126	Negotiated date for cessation of smoking
13p1.00	34127	Smoking status at 4 weeks
13p2.00	34374	Smoking status between 4 and 52 weeks
13p3.00	41405	Smoking status at 52 weeks
13p4.00	10898	Smoking free weeks
13p5.00	38112	Smoking cessation programme start date
13p5000	101764	Practice based smoking cessation programme start date
13p6.00	28886	Carbon monoxide reading at 4 weeks
13p7.00	103208	Smoking status at 12 weeks
13p8.00	102951	Lost to smoking cessation follow-up
38DH.00	97643	Fagerstrom test for nicotine dependence
67H6.00	98137	Brief intervention for smoking cessation
745H.00	74907	Smoking cessation therapy
745H000	81440	Nicotine replacement therapy using nicotine patches
745H100	85975	Nicotine replacement therapy using nicotine gum
745H200	85247	Nicotine replacement therapy using nicotine inhalator
745H300	89464	Nicotine replacement therapy using nicotine lozenges
745H400	94958	Smoking cessation drug therapy
745Hy00	91708	Other specified smoking cessation therapy
745Hz00	90522	Smoking cessation therapy NOS
8B2B.00	9833	Nicotine replacement therapy
8B3f.00	25106	Nicotine replacement therapy provided free
8B3Y.00	32572	Over the counter nicotine replacement therapy
8BP3.00	67178	Nicotine replacement therapy provided by community pharmacis
8CAg.00	41042	Smoking cessation advice provided by community pharmacist
8CAL.00	7622	Smoking cessation advice
8CdB.00	103507	Stop smoking service opportunity signposted
8H7i.00	18573	Referral to smoking cessation advisor
8HBM.00	98245	Stop smoking face to face follow-up
8HBP.00	105710	Smoking cessation 12 week follow-up
8HkQ.00	98154	Referral to NHS stop smoking service
8HTK.00	10742	Referral to stop-smoking clinic
8I2I.00	66409	Nicotine replacement therapy contraindicated
8I2J.00	63717	Bupropion contraindicated
8IAj.00	100099	Smoking cessation advice declined
9km..00	98447	Ex-smoker annual review - enhanced services administration
9km..11	100963	Ex-smoker annual review
9kn..00	98177	Non-smoker annual review - enhanced services administration

9kn..11	101878	Non-smoker annual review
9ko..00	98347	Current smoker annual review - enhanced services admin
9ko..11	104310	Current smoker annual review
9N2k.00	11356	Seen by smoking cessation advisor
9NS0200	102361	Referral for smoking cessation service offered
E023.00	6359	Nicotine withdrawal
E251.00	32687	Tobacco dependence
E251000	95610	Tobacco dependence, unspecified
E251100	70746	Tobacco dependence, continuous
E251300	72706	Tobacco dependence in remission
E251z00	68658	Tobacco dependence NOS
ZG23300	9045	Advice on smoking
ZRaM.00	47273	Motives for smoking scale
ZRao.00	91513	Occasions for smoking scale
ZRBm200	63666	Fagerstrom test for nicotine dependence
ZRBm211	63299	FTND - Fagerstrom test for nicotine dependence
ZRh4.00	59866	Reasons for smoking scale
ZRh4.11	49418	RFS - Reasons for smoking scale
ZV11600	72700	[V]Personal history of tobacco abuse
ZV4K000	12954	[V]Tobacco use
ZV6D800	35055	[V]Tobacco abuse counselling

Appendix E- ICD-10 and ICD-9 codes for cancer

Cancer Definition	**UK [ICD-10]**	**Sweden [ICD-9]**
Lymphoid and haematopoietic	C81-C96	200-208
Eye, brain, central nervous system	C69-C72	190-192
Mesothelial and soft tissue	C45-C49	171
Urinary tract	C64-C68	188-189
Lip, oral cavity, pharynx	C00-C14	140-149
Digestive organs	C15-C26	150-159
Respiratory & intrathoracic organs	C30-C39	160-165
Bone and articular cartilage	C40-C41	170
Skin	C43-C44	172-173
Breast	C50-C50	174-175
Female genital organs	C51-C58	179-184
Male genital organs	C60-C63	185-187
Thyroid and other endocrine glands	C73-C75	193-194
Ill-defined, secondary, unspecified	C76-C80	195-198, 199.1
Multiple sites	C97-C97	199
*In situ neoplasms	D00-D09	230-234
*Bening neoplasms	D10-D36	210.0 - 229.9
*Neoplasms of uncertain or unknown behaviour	D37-D48	235.0 - 239.9

*Excluded from the analyses

Appendix F1- Sensitivity Analysis examining data prior and after introduction of QoF

Up to Date Vaccinations at	Primary Analysis Adjusted Model- 1 [a] (n= 479, 949)	Excluding children who were born before 2005 (n=283, 921)
2 Year		
Unexposed to maternal mental illness	**REF**	**REF**
Exposed to any maternal mental illness	0·86 (0·84-0·88)	0·84 (0·81-0·87)
Psychotic disorder	0·86 (0·71-1·03)	0·79 (0·61-1·01)
Depressive disorder	0·86 (0·84-0·88)	0·82 (0·80-0·85)
Anxiety disorder	0·86 (0·83-0·89)	0·87 (0·82-0·92)
Eating disorder	0·94 (0·77-1·16)	1·11 (0·78-1·58)
Personality disorder	0·75 (0·58-0·98)	0·82 (0·56-1·20)
Substance and alcohol abuse	0·50 (0·44-0·58)	0·51 (0·42-0·62)
5 Year		
Unexposed to maternal mental illness	**REF**	**REF**
Exposed to any maternal mental illness	0·86 (0·84-0·88)	0·84 (0·81-0·87)
Psychotic disorder	0·71 (0·62-0·82)	0·67 (0·55-0·83)
Depressive disorder	0·86 (0·84-0·88)	0·83 (0·80-0·86)
Anxiety disorder	0·84 (0·82-0·87)	0·82 (0·78-0·86)
Eating disorder	0·83 (0·71-0·98)	0·84 (0·64-1·11)
Personality disorder	0·64 (0·52-0·78)	0·55 (0·41-0·73)
Substance and alcohol abuse	0·50 (0·45-0·56)	0·49 (0·41-0·58)

[a:] Adjusted for sex of the child, child ethnicity delivery year, maternal age, practice level deprivation quintile and region.

Appendix F2- Sensitivity analysis examining the effect of late registered children

Up to Date Vaccinations at	Primary Analysis Adjusted Model- 1[a] (n= 479, 949)	Excluding late registered children (n=474, 010)
2 Year		
Unexposed to maternal mental illness	**REF**	**REF**
Exposed to any maternal mental illness	0·86 (0·84-0·88)	0·86 (0·84-0·88)
Psychotic disorder	0·86 (0·71-1·03)	0·83 (0·69-1·00)
Depressive disorder	0·86 (0·84-0·88)	0·86 (0·84-0·88)
Anxiety disorder	0·86 (0·83-0·89)	0·86 (0·83-0·89)
Eating disorder	0·94 (0·77-1·16)	0·96 (0·78-1·17)
Personality disorder	0·75 (0·58-0·98)	0·76 (0·58-0·99)
Substance and alcohol abuse	0·50 (0·44-0·58)	0·49 (0·43-0·57)
5 Year		
Unexposed to maternal mental illness	**REF**	**REF**
Exposed to any maternal mental illness	0·86 (0·84-0·88)	0·86 (0·84-0·88)
Psychotic disorder	0·71 (0·62-0·82)	0·70 (0·61-0·81)
Depressive disorder	0·86 (0·84-0·88)	0·85 (0·33-0·87)
Anxiety disorder	0·84 (0·82-0·87)	0·84 (0·81-0·87)
Eating disorder	0·83 (0·71-0·98)	0·84 (0·72-0·99)
Personality disorder	0·64 (0·52-0·78)	0·62 (0·50-0·77)
Substance and alcohol abuse	0·50 (0·45-0·56)	0·50 (0·45-0·56)

[a:] Adjusted for sex of the child, child ethnicity delivery year, maternal age, practice level deprivation quintile and region

Appendix F3- Odds Ratio of girls receiving MMR vaccine uptake compared to boys in years

	Adjusted Model 1[a]	
Years	**aOR (95%CI)**	**P value**
1993-94	0·96 (0·84-1·09)	0·535
1995-96	1·02 (0·92-1·14)	0·695
1997-98	1·05 (0·96-1·15)	0·303
1999-00	1·17 (1·09-1·23)	<0·001
2001-02	1·16 (1·10-1·22)	<0·001
2003-04	1·08 (1·02-1·14)	0·005
2005-06	1·11 (1·05-1·17)	<0·001
2007-08	1·09 (1·03-1·15)	<0·001
2009-10	1·02 (0·96-1·09)	0·486
2011-12	1·06 (0·98-1·15)	0·168
2013-14	1·13 (1·03-1·23)	0·012
2015	1·20 (1·03-1·39)	0·018

[a:] Adjusted for child ethnicity delivery year, maternal age, practice level deprivation quintile and region

Appendix F4- Odds Ratio of receiving vaccinations at age two among children with and without mentally ill mothers: adjusted variables

	Adjusted Model 1[a]		Adjusted Model 2[b]	
Up to Date Vaccinations at	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
2 Year				
Unexposed to maternal mental illness	**REF**		**REF**	
Exposed to any maternal mental illness	0·86 (0·84-0·88)	<0·001	0·86 (0·84-0·88)	<0.001
Child Sex (Female)	1·07 (1·06-1·09)	<0·001	1·07 (1·06-1·09)	<0.001
Delivery Year	1·09 (1·08-1·09)	<0·001	1·08 (1·08-1·09)	<0.001
Delivery Year^2	1·01 (1·00-1·01)	<0·001	1·01 (1·00-1·01)	<0.001
Maternal Age	1·00 (1·00-1·00)	<0·001	1·00 (1·00-1·00)	<0.001
Maternal Age^2	1·00 (1·00-1·00)	<0·001	1·00 (1·00-1·00)	<0.001
Prenatal GP Consultation	-	-	1·02 (1·01-1·02)	<0·001
Ethnicity				
White	**REF**		**REF**	
Asian/ British Asian	1·26 (1·18-1·34)	<0·001	1·25 (1·17-1·34)	<0·001
Black/Black British	0·84 (0·78-0·91)	<0·001	0·84 (0·78-0·91)	<0·001
Mixed	0·84 (0·78-0·90)	<0·001	0·84 (0·78-0·90)	<0·001
Other	1·02 (0·92-1·13)	0·727	1·02 (0·92-1·12)	0·769
Unknown	0·77 (0·75-0·79)	<0·001	0·77 (0·75-0·79)	<0·001
UK IMD Quintile				
(Based on GP Location)				
1 (least deprived)	REF			
2	0·93 (0·89-0·96)	<0·001	0·93 (0·90-0·96)	<0·001
3	0·92 (0·89-0·95)	<0·001	0·92 (0·89-0·96)	<0·001
4	0·87 (0·85-0·90)	<0·001	0·87 (0·85-0·91)	<0·001
5 (most deprived)	0·80 (0·78-0·83)	<0·001	0·81 (0·87-0·83)	<0·001
Region				
South Central	**REF**		**REF**	
North East	1·01 (0.93-1.09)	0·830	1·02 (0·94-1·11)	0·578
North West	0·93 (0.89-0.97)	0·002	0·94 (0·90-0·98)	0·008
Yorkshire & The Humber	1·08 (1.01-1.14)	0·017	1·09 (1·02-1·16)	0·007
East Midlands	1·33 (1.25-1.41)	<0·001	1·34 (1·26-1·43)	<0·001
West Midlands	0·99 (0.94-1.04)	0·633	1·00 (0·95-1·05)	0·927
East of England	0·90 (0.86-0.94)	<0·001	0·91 (0·87-0·95)	<0·001
South West	0·88 (0.84-0.93)	<0·001	0·89 (0·85-0·93)	<0·001
London	0·57 (0.54-0.59)	<0·001	0·58 (0·55-0·60)	<0·001
South East Coast	0·83 (0.79-0.87)	<0·001	0·84 (0·80-0·88)	<0·001
Northern Ireland	0·90 (0.85-0.95)	<0·001	0·90 (0·85-0·96)	<0·001
Scotland	0·95 (0.90-0.99)	0·029	0·95 (0·91-1·00)	0·052
Wales	0·81 (0.78-0.85)	<0·001	0·82 (0·78-0·86)	<0·001

Appendix F5- Odds Ratio of receiving vaccinations at age five among children with and without mentally ill mothers: adjusted variables

	Adjusted Model 1		Adjusted Model 2	
Up to Date Vaccinations at	**OR (95% CI)**	***P* value**	**OR (95% CI)**	**P value**
5 Year				
Unexposed to maternal mental illness	**REF**		**REF**	
Exposed to any maternal mental illness	0·80 (0·84-0·88)	<0·001	0·85 (0·84-0·87)	<0·001
Child Sex (Female)	1·07 (1·05-1·09)	<0·001	1·07 (1·05-1·09)	<0·001
Delivery Year	1·11 (1·11-1·12)	<0·001	1·11 (1·11-1·12)	<0·001
Delivery Year^2	1·01 (1·01-1·01)	<0·001	1·01 (1·01-1·01)	<0·001
Maternal Age	1·00 (1·00-1·00)	<0·001	1·00 (1·00-1·00)	<0·001
Maternal Age^2	1·00 (1·00-1·00)	<0·001	1·00 (1·00-1·00)	<0·001
Prenatal GP Consultation	-	-	1·02 (1·02-1·03)	<0·001
Ethnicity				
White	**REF**		**REF**	
Asian/ British Asian	1·14 (1·07-1·22)	<0·001	1·13 (1·06-1·21)	<0·001
Black/Black British	0·84 (0·77-0·92)	<0·001	0·83 (0·76-0·91)	<0·001
Mixed	0·80 (0·74-0·87)	<0·001	0·80 (0·73-0·86)	<0·001
Other	0·99 (0·88-1·10)	0.840	0·99 (0·88-1·10)	0.799
Unknown	0·80 (0·78-0·82)	<0·001	0·81 (0·79-0·83)	<0·001
UK IMD Quintile *(Based on GP Location)*				
1 (least deprived)	**REF**	**-**	**REF**	
2	0·96 (0·93-1·00)	0·034	0·96 (0·93-1·00)	0.053
3	0·94 (0·91-0·97)	<0·001	0·94 (0·91-0·98)	0.001
4	0·88 (0·86-0·91)	<0·001	0·89 (0·86-0·92)	<0·001
5 (most deprived)	0·76 (0·74-0·79)	<0·001	0·76 (0·74-0·79)	<0·001
Region				
South Central	**REF**		**REF**	
North East	1·15 (1·06-1·25)	0·001	1·17 (1·08-1·27)	<0·001
North West	0·98 (0·94-1·03)	0·425	0·99 (0·95-1·04)	0·807
Yorkshire & The Humber	1·00 (0·94-1·06)	0·970	1·01 (0·95-1·08)	0·711
East Midlands	1·38 (1·30-1·47)	<0·001	1·40 (1·32-1·49)	<0·001
West Midlands	1·08 (1·03-1·13)	0·002	1·09 (1·04-1·15)	<0·001
East of England	0·92 (0·88-0·96)	<0·001	0·93 (0·89-0·98)	0·003
South West	1·01 (0·97-1·07)	0·572	1·02 (0·97-1·07)	0·476
London	0·56 (0·53-0·58)	<0·001	0·57 (0·54-0·59)	<0·001
South East Coast	0·91 (0·86-0·95)	<0·001	0·92 (0·87-0·96)	<0·001
Northern Ireland	1·09 (1·02-1·16)	0·007	1·09 (1·03-1·16)	0·006
Scotland	1·11 (1·06-1·17)	<0·001	1·12 (1·07-1·18)	<0·001
Wales	0·88 (0·84-0·92)	<0·001	0·88 (0·84-0·93)	<0·001

Appendix G1- Atopy- Cox Regression; Adjusted Variables in Model 1- Without smoking maternal smoking

ADJUSTED VARIABLES	ASTHMA			ALLERGIC RHINITIS			ECZEMA			FOOD ALLERGY		
	HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*	HR	95%CI	*p*
Maternal Mental Illness												
Common Mental Illness	1.19	1.16-1.22	<0.0001	1.16	1.13- 1.20	<0.001	1.00	0.99- 1.01	0.985	0.96	0.91- 1.01	0.133
Serious Mental Illness	1.04	0.90-1.21	0.566	0.96	0.80- 1.14	0.608	0.91	0.83- 1.00	0.04	1.04	0.75- 1.46	0.796
Addict	1.01	0.91-1.12	0.883	0.91	0.80- 1.05	0.188	0.87	0.81- 0.93	<0.001	0.59	0.41- 0.84	0.004
Other MMI	1.08	0.97-1.20	0.163	1.04	0.91- 1.19	0.57	1.06	0.99- 1.13	0.101	1.08	0.82- 1.43	0.569
Maternal Atopy History												
Maternal asthma	1.82	1.78-1.87	<0.001	1.20	1.16- 1.24	<0.001	1.07	1.05- 1.08	<0.001	1.36	1.28- 1.43	<0.001
Maternal allergic rhinitis	1.21	1.18- 1.24	<0.001	2.05	1.99- 2.11	<0.001	1.19	1.18- 1.21	<0.001	1.34	1.27- 1.41	<0.001
Maternal eczema	1.13	1.10- 1.16	<0.001	1.25	1.22- 1.29	<0.001	1.34	1.32- 1.36	<0.001	1.26	1.20- 1.32	<0.001
Maternal food allergy	1.21	1.10-1.33	<0.001	1.12	0.99- 1.26	0.071	1.23	1.17- 1.29	<0.001	2.31	2.01- 2.65	<0.001
Antibiotic use during pregnancy	1.19	1.16-1.22	<0.001	1.12	1.09- 1.15	<0.001	1.05	1.04- 1.06	<0.001	1.03	0.98- 1.08	0.309
Maternal age	0.99	0.99-0.99	<0.001	1.00	0.99- 1.00	0.054	1.00	1.00- 1.00	0.872	1.04	1.03- 1.04	<0.001
Maternal age centered & sq	1.00	1.00-1.00	0.183	1.00	1.00- 1.00	<0.001	1.00	1.00- 1.00	<0.001	1.00	1.00- 1.00	<0.001
Child Sex												
Female						**REF**						
Male	1.39	1.36-1.42	<0.001	1.39	1.35- 1.43	<0.001	1.14	1.13- 1.15	<0.001	1.26	1.2- 1.32	<0.001
Child Ethnicity												
White						**REF**						
Asian/British Asian	1.27	1.20-1.35	<0.001	1.64	1.54- 1.74	<0.001	1.52	1.48- 1.56	<0.001	1.62	1.47- 1.78	<0.001
Black/ black British	1.11	1.01-1.22	0.032	2.20	2.02- 2.40	<0.001	1.51	1.45- 1.57	<0.001	1.47	1.28- 1.70	<0.001
Mixed	1.24	1.15-1.34	<0.001	1.62	1.49- 1.76	<0.001	1.18	1.14- 1.22	<0.001	1.46	1.29- 1.66	<0.001
Other	1.05	0.93-1.17	0.428	1.35	1.19- 1.52	<0.001	1.30	1.24- 1.37	<0.001	1.51	1.27- 1.79	<0.001
Unknown	0.62	0.59-0.66	<0.001	0.80	0.75- 0.85	<0.001	0.92	0.90- 0.95	<0.001	0.67	0.57- 0.77	<0.001

Table K1 Cont'd	ASTHMA			ALLERGIC RHINITIS			ECZEMA			FOOD ALLERGY		
	HR	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***
Birth Season												
Winter						**REF**						
Spring	0.96	0.93-0.99	0.021	1.04	1.00- 1.08	0.037	0.92	0.91- 0.94	<0.001	0.78	0.73- 0.83	<0.001
Summer	0.99	0.96-1.02	0.338	0.90	0.87- 0.94	<0.001	0.98	0.97- 1.00	0.045	0.87	0.81- 0.92	<0.001
Fall	1.01	0.98-1.04	0.693	0.96	0.92- 1.00	0.031	1.06	1.04- 1.07	<0.001	1.09	1.02- 1.16	0.007
Birth year	0.91	0.91-0.92	<0.001	0.96	0.95- 0.96	<0.001	0.98	0.98- 0.98	<0.001	1.06	1.05- 1.06	<0.001
Birth year centered&sq	1.00	1.00-1.00	<0.001	1.00	1.00- 1.00	<0.001	1.00	1.00- 1.00	0.089	1.00	1.00- 1.00	<0.001
GP IMD**												
1 (least deprived)						**REF**						
2	1.10	1.05-1.14	<0.001	0.95	0.91- 1.00	0.053	0.94	0.92- 0.96	<0.001	0.76	0.70- 0.81	<0.001
3	1.07	1.03-1.11	0.001	0.96	0.91- 1.00	0.066	0.90	0.89- 0.92	<0.001	0.73	0.68- 0.79	<0.001
4	1.18	1.13-1.23	<0.001	0.93	0.89- 0.98	0.002	0.86	0.84- 0.87	<0.001	0.74	0.69- 0.80	<0.001
5 (most deprived)	1.17	1.13-1.22	<0.001	0.93	0.89- 0.97	0.001	0.89	0.87- 0.90	<0.001	0.65	0.60- 0.70	<0.001
Region												
South Central						**REF**						
North East	0.72	0.66-0.79	<0.001	0.97	0.87- 1.08	0.579	1.10	1.06- 1.15	<0.001	0.90	0.74- 1.09	0.265
North West	1.00	0.96-1.04	0.993	1.17	1.10- 1.23	<0.001	1.02	1.00- 1.04	0.07	0.67	0.61- 0.73	<0.001
Yorkshire & The Humber	0.72	0.67-0.77	<0.001	1.12	1.03- 1.21	0.009	0.98	0.95- 1.02	0.374	0.74	0.62- 0.88	<0.001
East Midlands	0.82	0.76-0.89	<0.001	1.23	1.13- 1.35	<0.001	1.02	0.98- 1.06	0.272	0.75	0.62- 0.90	0.002
West Midlands	0.93	0.89-0.98	0.003	1.29	1.22- 1.36	<0.001	1.01	0.99- 1.04	0.243	0.79	0.72- 0.88	<0.001
East of England	1.02	0.97-1.07	0.392	1.14	1.07- 1.20	<0.001	1.03	1.01- 1.06	0.015	0.94	0.86- 1.03	0.210
South West	0.99	0.94-1.03	0.552	0.91	0.86- 0.97	0.004	0.94	0.92- 0.96	<0.001	0.63	0.57- 0.71	<0.001
London	0.84	0.80-0.89	<0.001	1.08	1.02- 1.15	0.01	0.97	0.94- 0.99	0.008	1.04	0.95- 1.13	0.396
South East Coast	0.86	0.82-0.90	<0.001	0.89	0.84- 0.95	<0.001	0.97	0.95- 0.99	0.012	0.77	0.70- 0.85	<0.001
Northern Ireland	1.21	1.10-1.33	<0.001	0.96	0.84- 1.10	0.559	0.82	0.78- 0.86	<0.001	0.95	0.80- 1.14	0.595
Scotland	1.03	0.97-1.09	0.337	0.91	0.85- 0.98	0.01	0.85	0.83- 0.88	<0.001	0.92	0.82- 1.02	0.104
Wales	0.96	0.89-1.03	0.239	1.17	1.07- 1.27	<0.001	1.01	0.97- 1.04	0.604	0.62	0.54- 0.73	<0.001

**Based on GP postcode

Appendix G2- Atopy-Cox Regression; Model 2- Fully Adjusted

ADJUSTED VARIABLES	ASTHMA			ALLERGIC RHINITIS			ECZEMA			FOOD ALLERGY		
	HR	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***
Maternal Mental Illness												
Common Mental Illness	1.17	1.15-1.20	<0.0001	1.17	1.14-1.21	<0.0001	1.02	1.00-1.03	0.023	0.99	0.94-1.05	0.854
Serious Mental Illness	1.04	0.90-1.20	0.629	0.97	0.81-1.15	0.714	0.93	0.85-1.01	0.093	1.08	0.78-1.51	0.641
Addict	0.98	0.88-1.09	0.713	0.92	0.80-1.05	0.222	0.91	0.85-0.97	0.007	0.65	0.45-0.93	0.018
Other MMI	1.08	0.97-1.20	0.176	1.05	0.92-1.20	0.49	1.06	0.99-1.14	0.083	1.11	0.84-1.47	0.465
Maternal Atopy History												
Maternal asthma	1.81	1.77-1.86	<0.0001	1.20	1.16-1.24	<0.0001	1.07	1.06-1.09	<0.0001	1.37	1.3-1.45	<0.0001
Maternal allergic rhinitis	1.21	1.18-1.24	<0.0001	2.04	1.98-2.10	<0.0001	1.18	1.17-1.20	<0.0001	1.32	1.25-1.4	<0.0001
Maternal eczema	1.13	1.10-1.15	<0.0001	1.25	1.21-1.29	<0.0001	1.34	1.32-1.35	<0.0001	1.26	1.2-1.33	<0.0001
Maternal food allergy	1.21	1.10-1.34	<0.0001	1.12	0.99-1.27	0.065	1.22	1.16-1.28	<0.0001	2.26	1.97-2.6	<0.0001
Antibiotic use during pregnancy	1.19	1.16-1.21	<0.0001	1.12	1.09-1.15	<0.0001	1.05	1.04-1.06	<0.0001	1.04	0.99-1.09	0.171
Maternal Smoking Status*												
Never							**REF**					
Former	1.04	1.00-1.08	0.073	0.97	0.93-1.02	0.201	1.00	0.98-1.01	0.655	1.02	0.95-1.10	0.599
Current	1.09	1.06-1.12	<0.0001	0.95	0.92-0.98	0.001	0.89	0.88-0.90	<0.0001	0.78	0.74-0.83	<0.0001
Maternal age	0.99	0.99-0.99	<0.0001	1.00	0.99-1.00	0.020	1.00	1.00-1.00	<0.0001	1.03	1.03-1.04	<0.0001
Maternal age centered & sq	1.00	1.00-1.00	0.158	1.00	1.00-1.00	<0.0001	1.00	1.00-1.00	<0.0001	1.00	1.00-1.000	<0.0001
Child Sex												
Female							**REF**					
Male	1.39	1.36-1.42	<0.0001	1.39	1.35-1.43	<0.0001	1.14	1.13-1.15	<0.0001	1.26	1.2-1.32	<0.0001
Child Ethnicity												
White							**REF**					
Asian/British Asian	1.32	1.24-1.39	<0.0001	1.61	1.52-1.71	<0.0001	1.47	1.43-1.51	<0.0001	1.53	1.39-1.69	<0.0001
Black/ black British	1.12	1.02-1.23	0.019	2.19	2.01-2.38	<0.0001	1.48	1.42-1.54	<0.0001	1.43	1.24-1.66	<0.0001
Mixed	1.24	1.15-1.33	<0.0001	1.63	1.50-1.77	<0.0001	1.18	1.14-1.22	<0.0001	1.45	1.28-1.65	<0.0001
Other	1.06	0.95-1.19	0.316	1.34	1.18-1.51	<0.0001	1.28	1.22-1.34	<0.0001	1.45	1.22-1.73	<0.0001
Unknown	0.63	0.59-0.67	<0.0001	0.81	0.75-0.86	<0.0001	0.92	0.89-0.95	<0.0001	0.66	0.57-0.77	<0.0001

Table K2 Cont'd	ASTHMA			ALLERGIC RHINITIS			ECZEMA			FOOD ALLERGY		
	HR	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***	**HR**	**95%CI**	***p***
Birth Season												
Winter						**REF**						
Spring	0.96	0.93-0.99	0.017	1.04	1.00-1.08	0.037	0.92	0.91-0.94	<0.0001	0.78	0.73-0.83	<0.0001
Summer	0.98	0.95-1.02	0.332	0.91	0.87-0.94	<0.0001	0.99	0.97-1.00	0.06	0.87	0.81-0.93	<0.0001
Fall	1.01	0.97-1.04	0.738	0.96	0.92-1.00	0.029	1.06	1.04-1.07	<0.0001	1.09	1.02-1.16	0.007
Birth year	0.91	0.91-0.92	<0.0001	0.96	0.95-0.96	<0.0001	0.98	0.98-0.98	<0.0001	1.06	1.05-1.06	<0.0001
Birth year centered&sq	1.00	1.00-1.00	<0.0001	1.00	1.00-1.00	<0.0001	1.00	1.00-1.00	0.07	1.00	1.00-1.00	<0.0001
GP IMD**												
1 (least deprived)						**REF**						
2	1.09	1.05-1.14	<0.0001	0.95	0.91-1.00	0.053	0.94	0.92-0.96	<0.0001	0.77	0.71-0.82	<0.0001
3	1.06	1.02-1.11	0.003	0.96	0.91-1.00	0.061	0.91	0.89-0.93	<0.0001	0.75	0.70-0.81	<0.0001
4	1.17	1.12-1.21	<0.0001	0.93	0.89-0.98	0.003	0.86	0.85-0.88	<0.0001	0.76	0.71-0.82	<0.0001
5 (most deprived)	1.16	1.11-1.20	<0.0001	0.93	0.89-0.97	0.001	0.89	0.88-0.91	<0.0001	0.67	0.62-0.73	<0.0001
Region												
South Central						**REF**						
North East	0.72	0.65-0.79	<0.0001	0.96	0.86-1.07	0.479	1.11	1.06-1.15	<0.0001	0.87	0.72-1.06	0.172
North West	1.00	0.96-1.05	0.889	1.17	1.10-1.23	<0.0001	1.03	1.00-1.05	0.023	0.67	0.61-0.74	<0.0001
Yorkshire & The Humber	0.73	0.68-0.78	<0.0001	1.11	1.03-1.21	0.011	0.98	0.95-1.02	0.395	0.72	0.61-0.86	<0.0001
East Midlands	0.83	0.77-0.89	<0.0001	1.23	1.12-1.34	<0.0001	1.02	0.98-1.06	0.333	0.74	0.61-0.89	0.001
West Midlands	0.94	0.89-0.98	0.006	1.29	1.22-1.36	<0.0001	1.02	0.99-1.04	0.199	0.79	0.71-0.87	<0.0001
East of England	1.02	0.98-1.07	0.335	1.14	1.07-1.21	<0.0001	1.04	1.01-1.06	0.003	0.94	0.86-1.03	0.204
South West	0.99	0.94-1.04	0.656	0.91	0.86-0.97	0.003	0.95	0.92-0.97	<0.0001	0.63	0.57-0.70	<0.0001
London	0.84	0.80-0.89	<0.0001	1.09	1.02-1.16	0.008	0.97	0.95-1.00	0.021	1.02	0.94-1.12	0.584
South East Coast	0.86	0.82-0.91	<0.0001	0.89	0.84-0.95	<0.0001	0.97	0.95-1.00	0.027	0.77	0.70-0.85	<0.0001
Northern Ireland	1.21	1.10-1.33	<0.0001	0.96	0.84-1.10	0.573	0.82	0.78-0.86	<0.0001	0.95	0.79-1.13	0.546
Scotland	1.03	0.97-1.09	0.300	0.91	0.84-0.98	0.01	0.85	0.83-0.88	<0.0001	0.91	0.82-1.01	0.091
Wales	0.96	0.89-1.03	0.245	1.17	1.08-1.28	<0.0001	1.01	0.98-1.05	0.448	0.62	0.54-0.73	<0.0001

*During child's life including pregnancy
**Based on GP postcode

Appendix G3- Atopy- Sensitivity Analysis

Main Analysis					
	Person-Years, 1,000	**Eczema Cases *N***	**Eczema Rate, per 1,000 person-years (95%CI)**	**Adjusted HR Model 2 †† (95%CI)**	***p***
Eczema					
Unexposed	1803.80	130512	72.4 (71.9-72.6)	**REF**	-
CMI	922.01	49096	53.3 (52.8-53.7)	1.02 (1.00-1.03)	0.023
SMI	14.64	642	43.9 (40.6-47.4)	0.93 (0.85-1.01)	0.093
Addiction	28.04	1125	40.1 (37.8-42.5)	0.91 (0.85-0.97)	0.007
Other MMI	22.32	1240	55.6 (52.6-58.7)	1.06 (0.99-1.14)	0.083
Sensitivity Analysis (W/o infantile eczema and 3yr+)					
Eczema					
Unexposed	1702.05	16261	9.6 (9.4-9.7)	**REF**	-
CMI	884.46	10387	11.7 (11.5-12.0)	1.06 (1.02-1.10)	<0.0001
SMI	14.18	177	12.5 (10.8-14.6)	1.06 (0.88-1.26)	0.55
Addiction	27.17	308	11.3 (10.1-12.7)	1.02 (0.88-1.17)	0.823
Other MMI	21.39	261	12.0 (10.8-13.8)	1.08 (0.93-1.25)	0.319

CMI Common Mental Illness; SMI Serious Mental Illness
I†† Adjusted for all variables in model one, plus maternal smoking

Appendix G4- Atopy- Post-Hoc Analysis Adjusted Hazard Ratios showing the association between child hospital inpatient admission for any skin disorders and maternal addiction (N= 112,813 children)

	Person-Years, 1,000	**Cases *N***	**Atopy Rate per 1,000 person-years (95%CI)**	**Adjusted HR Model 2 †† (95%CI)**	***p***
Eczema (Main Analysis)					
Unexposed	1803.8	130512	72.4 (71.96-72.75)	**REF**	-
Maternal Addiction	28.04	1125	40.2 (37.84-42.53)	0.91 (0.85-0.97)	0.007
Any Skin Disorders* ***(Post-Hoc Analysis)***					
Unexposed	582.87	1635	2.8 (2.7-2.9)	**REF**	-
Maternal Addiction	7.57	27	3.6 (2.5-5.2)	1.47 (0.98-2.22)	0.063

†† Adjusted for all variables in model one, plus maternal smoking
*Children were required to have an eczema diagnosis in primary care.