Investigating the health and care needs of pregnant women with multiple long-term conditions

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Thesis submitted in fulfilment of the Degree of Doctor of Philosophy in Population Health
Hilary term 2024

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Abstract

Background:

UK National surveillance data of maternal deaths and severe maternal morbidities suggests that multiple long-term conditions (MLTC, also called multimorbidity) may be an important factor in inequitable maternal and perinatal outcomes. Despite this, MLTC in pregnancy is under-researched and detailed information about the epidemiology and magnitude of associated risk of adverse outcomes is lacking. This thesis aims to use routine data to provide a better understanding of the burden and consequences of MLTC in pregnancy, including the implications for future clinical practice, policy-making and research.

Methods:

A cohort of pregnant women was identified for inclusion in the component studies of this thesis using two principal data sources: Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES APC). A bespoke list of health conditions was selected for investigation based on structured literature review and expert consensus. The exposure of MLTC was defined as any combination of two or more physical health, mental health or infectious conditions, and was measured at the start of each pregnancy. The epidemiology of MLTC in pregnancy was described including temporal and geographic trends over a ten-year period. Logistic regression was used to investigate the association between MLTC and severe adverse outcomes (severe maternal morbidity, stillbirth, neonatal death) in pregnancy and the immediate postpartum period. Cox regression was used to investigate the association between MLTC and severe (acute psychosis and self-harm) and common (postnatal anxiety and/or depression) maternal mental health conditions up to one year after birth.

Findings:

Among 422,091 pregnancies to 331,517 women across a 10-year period, the prevalence of MLTC was 16.9% with a significant trend towards increasing prevalence across the study. MLTC was observed to be more common among women who were older, women who were obese, women who were living in deprivation and women who were current/ex-smokers. The predominant MLTC type was co-morbid physical and mental health conditions (54%), with mental-health only MLTC being the second commonest (31%), and physical-health only MLTC being the least common type (15%). Complex MLTC (3 or more pre-existing health conditions) was found in 31% of pregnancies among women with MLTC.

Of the original cohort of pregnant women, 146,307 pregnancies among 121,211 women were found to have a corresponding validated record of delivery within HES APC. MLTC in pregnancy was observed to be associated with an increased odds of severe maternal morbidity (aOR 1.59, 95% CI 1.43-1.76) and neonatal death (aOR1.94, 95% CI 1.29-2.91). The rate of severe maternal morbidity was higher among women with complex MLTC and women with physical and mixed MLTC. There was no difference in the rate of stillbirth among pregnancies to women with MLTC and women without MLTC. Women with MLTC in pregnancy were at increased risk of experiencing both severe (acute psychosis aHR 4.87, 95%CI 2.98-7.95; self-harm aHR 3.52, 95% CI 2.81-4.2) and common perinatal mental health disorders (aHR 3.86, 95%CI 3.75-3.98), up to one year after birth. Again, a differential risk was observed based on both type and complexity of MLTC.

Conclusion:

The work presented in this thesis demonstrates the potential for routinely collected data to be used to conduct robust and comprehensive epidemiological pregnancy research. MLTC was observed to be a common health concern among pregnant women, and is likely to become increasingly prevalent in the future. MLTC has been shown to be an important component of inequitable maternal and perinatal outcomes, even up to one year after birth. Future work should concentrate on understanding individual, structural and healthcare factors that underlie these findings.

Impact of Covid-19

The first year of my DPhil coincided with the start of the Covid-19 pandemic. My initial plan for Hilary and Trinity term 2020 had been to attend the Big Data Epidemiology training course (March 2020) and to hold the multi-professional advisory panel (June 2020). Both of these were delayed, which impacted my ability to advance my work around planning the CPRD analysis. At the end of March 2020, I was required by Health Education England to return to clinical practice. Due to the immediacy of this request it was not possible to finish any outstanding work prior to redeployment, or to rearrange my workplan in advance to account for the disruption. I spent April and May 2020 working on an Emergency Covid-19 rota. Due to the number of hours I needed to work clinically including participating on a back-up-rota to cover short-term sickness, I was unable to work on my DPhil during this time. At the end of this period of redeployment access to the NPEU building was still restricted which meant I was unable to request access to my data. At this point I decided jointly with my supervisors to undertake a systematic review (which had not been a planned part of my thesis previously) as we felt this offered the best chance of completing a substantial piece of work given the circumstances. Additionally, my mother who had been providing some care to my daughter prior to the pandemic was unable to continue to do this between March 2020 and April 2020, which increased my caring responsibilities.

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Word count 48,743

Acknowledgements

First and foremost, I must give my sincerest thanks to my supervisors Professor Marian Knight, Professor Fiona Alderdice and Associate Professor Claire Carson. It has been a great honour to learn from three such brilliant academics, and I am indebted to them for their sound advice and guidance. On a personal note, for me this thesis has spanned a pregnancy in the middle of a global pandemic, a new diagnosis of an autoimmune illness and an unanticipated career change. It would not have been possible to navigate these challenges and complete this work without the generosity and commitment of my supervisory team – thank you.

My experience has been greatly enriched by the supportive and exceptional academic community found within the National Perinatal Epidemiology Unit. One cannot fail to be inspired by so many people undertaking such vitally important research. I also give my thanks to my colleagues working in Maternity, Public Health and General Practice who have provided collaboration and encouragement in equal measure. I am additionally grateful for the funding provided by the Department of Population Health at the University of Oxford and the Medical Research Council Doctoral Training Partnership which allowed this research to happen.

Finally, this work would not exist without the unfailing support of my family and friends. My wonderful parents Claire and Andrew who have always supported my ambitions and helped me to find my talents. My lovely husband Martin who is one of the kindest humans I know, and who has been instrumental in keeping everything afloat while I have finished this thesis. And last but not least, my precious daughters Freya and Ivy, who brim over with wit and enthusiasm for life. It is never anything less than a joy and a privilege to be your mother.

Statement of Authorship

I confirm that the work presented in this thesis is my own. I conceptualised the research, gained the required approvals for data access, cleaned and curated the data for use, and conducted the analyses. I wrote the component chapters of this thesis and prepared all the included tables and figures. Professor Marian Knight, Professor Fiona Alderdice, and Associate Professor Claire Carson supervised this research. They provided advice on study design, statistical analysis, interpretation of the findings and feedback about the thesis.

I was assisted by Nia Roberts (Senior Outreach Librarian) at the University of Oxford Bodleian Healthcare Libraries in the design of the literature search used for the systematic review. Dr Gbemisola David-West, Dr Mariana Tome and Dr Saba Fatima assisted me with the literature screening and data extraction for the systematic review, and have given their permission for this work to be presented in this thesis.

In addition to my supervisory team, the following people were part of an advisory panel who assisted in the identification of the individual health conditions used measure the exposure of MLTC:

Dr Anita Banerjee (Consultant Obstetric Physician)

Ms Zoe Vowles (Research Midwife)

Ms Kirsty Kitchen (Head of Policy and Communications at Birth Companions)

Dr Judy Shakespeare (General Practitioner)

Dr Sarah Hudson (Specialty trainee in Anaesthetics)

Miss Kit Robertson (Specialty trainee in Obstetrics and Gynaecology, now Consultant Obstetrician)

Dr Sarah Hillman (General Practitioner and NIHR Clinical Lecturer in Primary Care Warwick University)

Dr Lucy Mackillop (Consultant Obstetric Physician)

Professor Lucy Chappel (Consultant Obstetrician and now Chief Scientific Advisor Department of Health and Social Care)

Dr Elizabeth Ford (Reader in Health Data Science, Brighton and Sussex Medical School)

Dr William Birts (Consultant Anaesthetist), Dr Phil Duggleby (Consultant Anaesthetist), Dr Charlotte Frise (Consultant Obstetric Physician) and Dr Michael Yousef (Consultant Perinatal Psychiatrist) were unable to participate in the advisory panel, but kindly provided individual feedback on the included health conditions.

Dr Becky MacGregor (General Practitioner) and Dr Sarah Hillman (General Practitioner and NIHR Clinical Lecturer in Primary Care Warwick University) assisted in the construction of the code lists used to identify pre-existing health conditions and other covariates from the datasets.

Abbreviations

AXIS	Appraisal Tool for Cross-Sectional Studies
BMI	Body Mass Index
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMHD	Common Mental Health Disorder
CPRD	Clinical Practice Research Datalink
DAG	Directed Acyclic Graph
EHR	Electronic Health Record
EMBASE	Excerpta Medica Database
EMIS	Egton Medical Information Systems
EMMOI	English Maternal Morbidity Outcome Indicator
ESRC	Economic and Social Research Council
GAD-2	Generalised Anxiety Disorder 2-item Questionnaire
aHR	Adjusted Hazard Ratio
HR	Hazard Ratio
HES-APC	Hospital Episode Statistics Admitted Patient Care
HRA	Health Research Authority
ICD-10	International Classification of Diseases 10th Revision
IMD	Index of Multiple Deprivation
INOSS	International Obstetric Surveillance Systems
ISAC	Independent Scientific Advisory Council
LSOA	Lower layer Super Output Areas
MBRRACE-UK	Mothers and Babies Reducing Risk through Audit and Confidential Enquiry – UK
MEDLINE	Medical Literature Analysis and Retrieval System Online
MetaQAT	Meta Quality Appraisal Tool
MLTC	Multiple Long-Term Conditions
NHS	National Health Service
NHS-e	National Health Service England
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
ONS	Office for National Statistics
OPCS-4	Classification of Interventions and Procedures
OR	Odds Ratio
aOR	Adjusted Odds Ratio
PROSPERO	International Prospective Register of Systematic Reviews
SAIL	Secure Anonymised Information Linkage
eSGA	Extremely Small for Gestational Age
SGA	Small for Gestational Age
SMM	Severe Maternal Morbidity
UK	United Kingdom of Great Britain and Northern Ireland
UKOSS	UK Obstetric Surveillance System
WHO	World Health Organisation

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Chapter 1: Introduction

1.1 Multiple long-term conditions as an evolving health concern

Multiple long-term conditions (MLTC) or multimorbidity, is most typically defined as the presence of two or more chronic health conditions within the same individual. This can be combinations of physical health conditions, mental health conditions and infectious conditions, but may also include symptom complexes such as chronic pain or frailty. Epidemiological studies both within the UK and globally show that MLTC is a common health phenomenon and that the prevalence of individuals living with MLTC is rising steadily. A recent systematic review and meta-analysis (1) inclusive of 52 countries has estimated the global prevalence of MLTC to be 37.2%. Women are consistently found to have a higher prevalence of MLTC compared to men (2), and a large retrospective cohort study conducted by Cassell et al. estimated the prevalence of MLTC in the UK population to be 27.2% across all age groups (3).

The importance of MLTC as an evolving health concern is illustrated by the inequitable health outcomes experienced by individuals with MLTC. These include lower health-related quality of life, spending more years living with disability and facing a higher risk of premature mortality (4-7). While the development of MLTC can be influenced by individual and behavioural factors such as advancing age, obesity or smoking, the influence of wider social determinants of health such as living in socioeconomic deprivation (8-10) or not having secure high-quality employment on the development and progression of MLTC are increasingly well recognised (11). It has previously been estimated that the onset of MLTC occurs between 10-15 years earlier in individuals who are living in

socioeconomic deprivation (10) and that the onset of complex MLTC (3 or more conditions) was 7 years earlier among those living in the most deprived regions compared to those living in the most affluent regions (9).

In addition to the associated health and social inequalities, MLTC presents significant challenges for the organisation and delivery of healthcare. Individuals with MLTC often use more healthcare compared to individuals without MLTC, are frequently exposed to polypharmacy and are more likely to require their healthcare to be delivered across multiple different parts of the health system (12-15). The complexities of this are compounded by current systems and guidance being traditionally structured to provide care and services to individuals with single-disease diagnoses (16). This contributes to individuals with MLTC reporting high levels of unmet healthcare need and high levels of treatment burden and fatigue (17-19). A limited number of studies on the experiences of healthcare workers highlight a lack of continuity of care, deficits in specific guidance and training, short appointment times and siloed working practices as barriers to the provision of high-quality care for individuals with MLTC (20, 21).

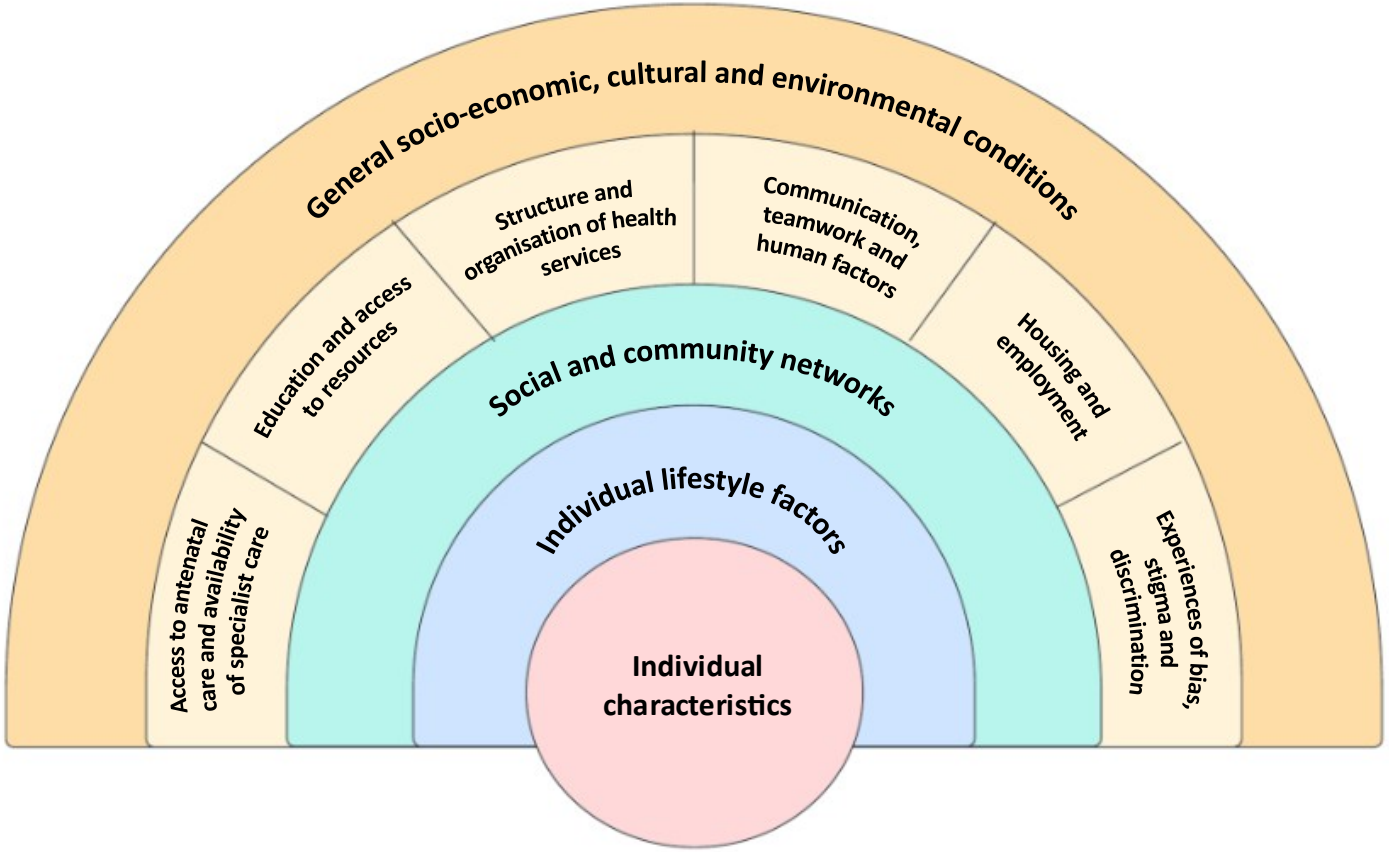
While MLTC is commonly considered to be a feature of ageing populations, a seminal study conducted by Barnett et al. showed that proportionally, a greater number of individuals in the UK living with MLTC are under the age of 65 years old (10). Despite this observation, MLTC has been less comprehensively researched among younger adults compared to older adults to date. This is particularly pertinent when considering that health conditions of interest, drivers of MLTC and relevant health outcomes are not necessarily the same in different populations or across age groups. There is a paucity of research within certain population groups with respect to MLTC, including women of reproductive age and pregnant women. This is recognised within the current

NIHR strategic framework on MLTC research which outlines the need for research on MLTC to occur across the entire life-course, including at critical life transitions such as pregnancy (22).

1.2 MLTC and pregnancy

'Maternal health' is commonly understood to describe the health of women during pregnancy, birth and in the postnatal period. Maternal health is considered to be reflective of the health of the population overall, as well as the quality of available healthcare (23). The rates of adverse outcomes related to pregnancy such as maternal death, severe maternal morbidity (SMM), stillbirth and neonatal death can be used to monitor the overall state of maternal health and to compare health inequalities between different population groups. Good maternal health implies the absence of high rates of preventable maternal and perinatal morbidity and mortality. The conceptual model presented in Figure 1.1 outlines the determinants of maternal health.

Figure 1.1. Conceptual model of the determinants of maternal health

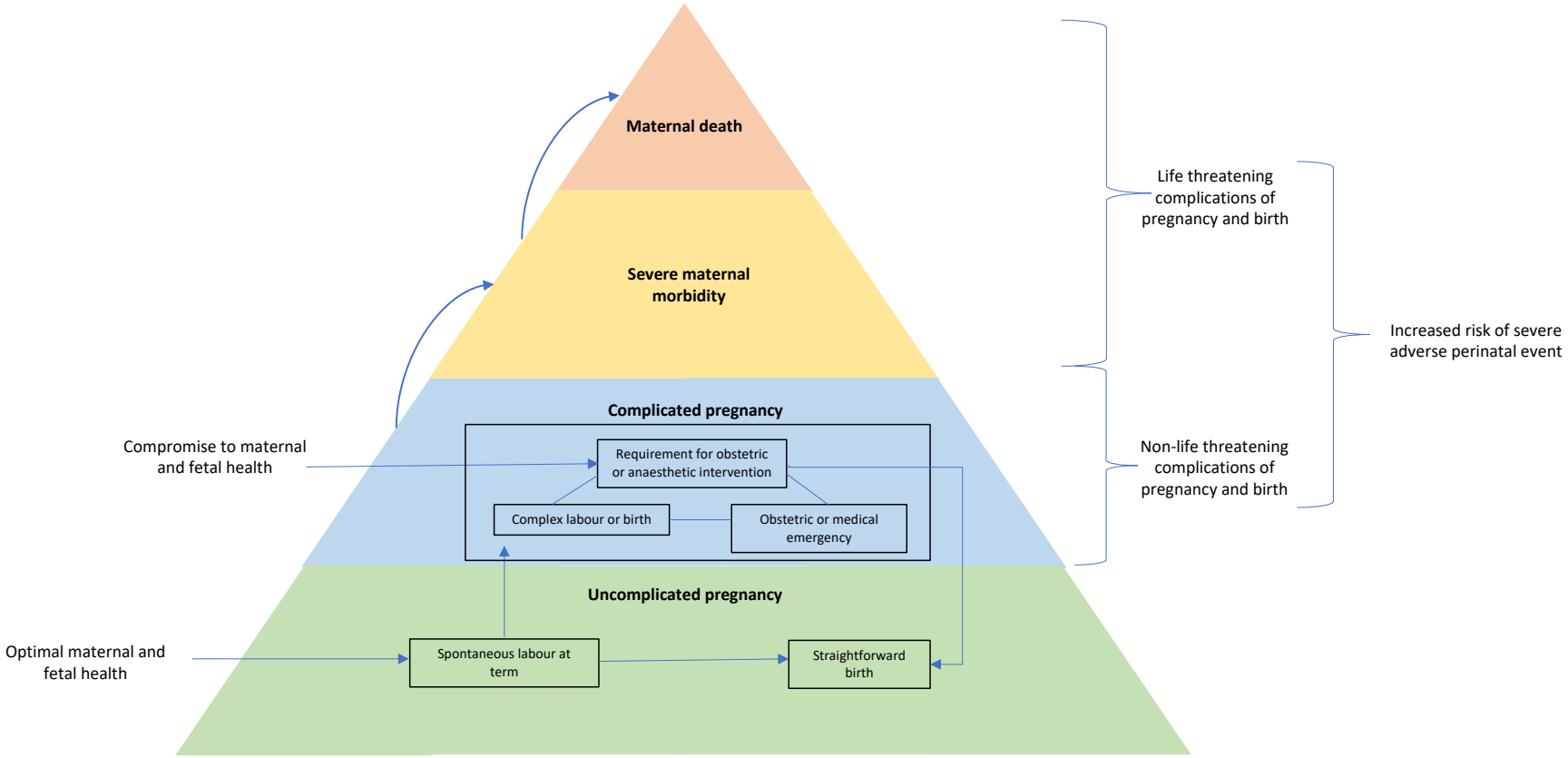


This diagram has been adapted from Dahlgren and Whitehead's seminal model of health determinants and is based on findings from MBRRACE-UK and other literature exploring the social determinants of maternal health (24-37) .

The determinants of maternal health operate at the level of individuals and individual behaviours, social and community networks and wider socioeconomic, cultural and environmental factors. The wider determinants of health have been shown to have a substantive contribution to health outcomes, however, they are among the factors that individuals are least likely to have significant influence or control over. The intersection between the different determinants of maternal health can act to create increased risk of poor health outcomes for certain women. This has previously been described as some individuals facing a constellation of biases with regard to risk of severe adverse events in pregnancy and the postnatal period (38).

The conceptual model presented in Figure 1.2 illustrates that maternal health exists as a continuum between uncomplicated pregnancy through to maternal death. Compromise to maternal or fetal health has the potential to establish a pathway leading to severe maternal morbidity or maternal death. The inextricable relationship between maternal and perinatal health invariably means that poor maternal health outcomes can lead to poor perinatal health outcomes. The interconnected nature of the maternal health continuum means that it is plausible to assume that if a population group experiences a disproportionate burden of maternal death, they are also likely to experience a disproportionate burden of severe maternal morbidity and non-life-threatening complications related to pregnancy. It also means that although events such as maternal death and severe maternal morbidity are rare in high-income countries, developing a more comprehensive understanding of the associations and drivers of these outcomes will generate new insight into how further improvements to maternal and perinatal health could be achieved.

Figure 1.2. Conceptual model of the continuum of maternal health



This model has been adapted from Vandenberghe et al. (39), and is based on the original 'The Pyramid of Disease' presented by Say et al. (40) and the findings from MBRRACE-UK and other literature exploring factors associated with maternal death and severe maternal morbidity (27-30, 33, 41-45).

In the UK, rates of maternal and perinatal mortality are collated through a process of confidential enquiry (MBRRACE-UK: Mothers and Babies Reducing Risk Through Audit and Confidential Enquiry-UK). Evidence from the maternal death enquiry consistently shows that certain groups within the populations are more likely to die during or after pregnancy, or experience severe morbidity related to pregnancy. Among these groups are women with pre-existing or multiple health conditions, suggesting that MLTC may be an important driver of inequalities in maternal and perinatal health (27-30). A study by Nair et al. investigating factors associated with maternal death from direct pregnancy complications in the UK further demonstrates the importance of pre-existing medical conditions to adverse maternal health outcomes. In this study pre-existing medical conditions accounted for 66% of the increased risk of maternal death (41). Despite the signal of importance generated by the findings of the confidential enquiry, MLTC in pregnancy is under-researched at present and the magnitude of the association between MLTC and severe adverse maternal and perinatal outcomes related to pregnancy has not previously been delineated.

In the UK, maternity care pathways are structured to facilitate regular contact with healthcare professionals from the start of pregnancy until after birth (46). This allows for the provision of screening, delivery of antenatal education and health promotion, and the identification and management of risk factors that might adversely affect maternal and fetal wellbeing. Many women will follow a standard schedule of maternity care, delivered predominately in community settings by midwives. Women who are assessed to have either pre-existing or evolving risk factors will have care that is jointly provided between community midwifery services and specialist secondary care providers such as obstetricians,

medical physicians or psychiatrists (46). The exact composition of this joint care is often dependent on the workforce and resources available within local settings.

The Maternity Transformation Programme in England was established to accomplish the strategic vision set by the 2016 'Better Births' report published by the National Maternity Review (47). A key workstream in this programme is the establishment of maternal medicine networks which aim to facilitate the provision of specialist care by obstetric physicians (a doctor with specialist medical training in the care of medical complications of pregnancy) to women with pre-existing medical conditions (48). Alongside the establishment of maternal medicine networks, the expansion of pre-existing perinatal mental health services and networks is being undertaken to allow a greater number of women to have access to specialist perinatal mental healthcare during pregnancy and in the postpartum period (49, 50). While the establishment of maternal medicine networks and expansion of perinatal mental healthcare are clearly important for maternal health, these services are being developed in parallel to one another rather than in an integrated way. This arguably may perpetuate the ongoing existence of siloed healthcare, rather than advancing the delivery of holistic patient-centred care.

1.3 Routinely collected data in pregnancy research

Routinely collected data refers to data that in the first instance is collected and used for purposes other than research (51). Examples of routinely collected data are electronic health and prescription records, data collected for administrative purposes such as insurance

renumeration and legally recorded data such as death certification (51). Routinely collected datasets can contain information about millions of individuals within the population across substantial periods of time, and are often relatively cost-effective to use. These factors have been instrumental in driving the popularisation of using routinely collected data in health research over the last two decades. The structure of healthcare in the UK requires patients to be registered with a primary care provider to access all types of care except emergency care. Furthermore, it is common for general practitioners to be involved in the coordination of care and ongoing management of many different health conditions. Most recent estimates provided by NHS Digital show that over 62 million patients in England are registered with a general practitioner (52), making primary care data a potentially rich source of information about the health status of individuals. It is also the case that most women who give birth in the UK will do so with an NHS hospital or midwifery-led facility. Again, routinely collected data from secondary care is a potentially rich source of information about births and pregnancy-related health events. The linkage of electronic health records between primary and secondary care has allowed for increasingly comprehensive epidemiological studies to be undertaken. Additional linkages between electronic health records and other data sources such as deprivation indices and death registration data further increases the scope and utility of routinely collected data in health research.

The increasing use of routinely collected data has however been accompanied by a necessary and growing appreciation of its limitations and complexities. Due to not being collected for research purposes, routinely collected data can often have large amounts of missing data, and the variables contained within the dataset may not map comprehensively

to the research questions asked. Despite being derived from real-world settings, it should not be assumed that routinely collected data sources offer a perfect facsimile of the general population or processes occurring within healthcare. In particular, the extent to which these data sources are representative or inclusive of vulnerable, marginalised or minority groups of the population is an important consideration (53-59). This issue raises ethical questions as to how to ensure that increasing reliance on routinely collected data for answering research and policy questions is adequately scrutinised so as not to perpetuate or widen health inequalities among vulnerable communities (60-62).

A large amount of research involving pregnant populations has traditionally been conducted using observational cohort methods. It would therefore be easy to suppose that there is a natural alignment between pregnancy research and the opportunities afforded by using routinely collected data. The recent development of virtual registries derived from primary care data containing pregnancy episodes and outcomes has hugely increased the scope for routinely collected data to be used to answer research questions involving pregnancy (63-65). This includes one of the main data sources used in this thesis, the CPRD pregnancy register (63). These virtual pregnancy registers are however both relatively new to pregnancy research and iterative in their use, with the majority of the methodological decisions around how to clean, curate, identify populations of interest and ensure quality of the data left to discretion of individual researchers (66). While research using routinely collected data has the potential to make a substantive contribution to the knowledge base, there is a need for ongoing robust appraisal of the role and utility of this type of data in pregnancy research.

1.4 Rationale for research

The rationale for this research is as follows:

1. MLTC is an important evolving health concern due to its association with several inequitable health outcomes. It is recommended that MLTC research should occur across the entirety of the life course, and account for critical life-transitions such as pregnancy. Studies of MLTC specifically in women of reproductive age, or among pregnant populations are minimal at present. This impedes the identification of future practice, policy and research directions.
2. Rates of severe adverse outcomes related to pregnancy are not equally distributed across the population. The findings of MBRRACE-UK provide a strong signal that MLTC might be an important driver of inequitable maternal and perinatal health outcomes. The current body of literature provides an incomplete picture of the burden, risk factors and consequences of MLTC in pregnancy.
3. Routinely collected data is increasingly commonly used in health research and is likely to become a progressively more prominent feature of the evidence-base in pregnancy research. Undoubtedly routinely collected data offers substantial research potential, however, careful appraisal of the role and utility of this type of data in pregnancy research is required.

1.5 Thesis aims and objectives

This thesis aims to use routinely collected data to provide a better understanding of the burden and consequences of MLTC in pregnancy including the implications for future clinical practice, policy-making and research.

The specific objectives are:

1. To appraise the definition and operationalisation of MLTC in existing population-based prevalence studies of MLTC inclusive of women of reproductive age to assess the extent to which these are suitable for use in MLTC research in pregnant populations.
2. To describe and evaluate the methodological approach and decisions taken to construct a pregnancy cohort from the CPRD pregnancy register and HES APC dataset with data of suitable quality for undertaking research.
3. To describe the epidemiology of MLTC in pregnancy in the UK across a ten-year period.
4. To investigate the association between MLTC in pregnancy and severe adverse maternal and perinatal outcomes in pregnancy and the immediate postpartum period.
5. To investigate the association between MLTC in pregnancy and severe and common maternal mental health outcomes in the extended postnatal period.

1.6 Thesis outline and structure

This thesis is organised into seven component chapters as follows:

In **chapter 1**, the background and context to this thesis are discussed, and the rationale for the research is given. The aim, objectives, outline, and structure of the thesis are described.

In **chapter 2**, the findings of a systematic review and narrative synthesis exploring definitions and operationalisations of MLTC in previous population-based prevalence studies that are inclusive of women of reproductive age are presented. Four principles are identified to guide how MLTC should be defined and operationalised in research involving pregnant populations (research objective 1).

In **chapter 3**, an overview of the data sources and study variables used in the following three studies is given. The methodological approach and decisions taken in the management and curation of the dataset are described and evaluated (research objective 2).

In **chapter 4**, the epidemiology of MLTC in pregnancy in the UK is described, including temporal and geographic trends over a ten-year period (research objective 3).

In **chapter 5**, the results of an investigation into the association between MLTC in pregnancy and severe adverse maternal and perinatal outcomes during pregnancy and the immediate postpartum period is presented (research objective 4).

In **chapter 6**, the results of an investigation into the association between MLTC in pregnancy and common and severe maternal mental health outcomes in the extended postnatal period is presented (research objective 5).

In **chapter 7**, an overview of the key findings of the research are summarised and the optimal use of routinely collected data in future pregnancy research is discussed. The wider implications of this thesis with regard to clinical practice, policy making, and research are presented.

1.7 Use of language in this thesis

Within this thesis I have used terms such as pregnant woman, women of reproductive age, maternal health and women's health to describe the themes, concepts and populations of interest to the research. This is in alignment with the views and policies of the National Perinatal Epidemiology Unit from where this research was conducted. I do acknowledge, however, that not all people who have a requirement for maternity or reproductive health care identify as women, and that it is important that any changes to the structure or delivery of health services does not widen inequalities for these individuals.

Chapter 2: Definitions and operationalisations of multimorbidity in women of reproductive age: a systematic review and narrative synthesis

2.1 Introduction and research objectives

The published literature on MLTC is extensive and ever expanding. This reflects both the increasing prevalence of MLTC globally (1), and its significant contribution to inequalities in health outcomes (4, 7, 67). As a clinical entity MLTC is a heterogenous concept, and whether an individual is considered to have MLTC is subject to many potential caveats (68-71). This makes conducting research in MLTC that is both meaningful and relevant challenging. Recent clinical and methodological research guidance has sought to standardise approaches to the conceptualisation, definition and operationalisation (i.e. the individual health conditions included in the definition) of MLTC in the general adult population. The guidance most relevant to research and clinical practice in UK settings is summarised in Figure 2.1 (22, 72, 73).

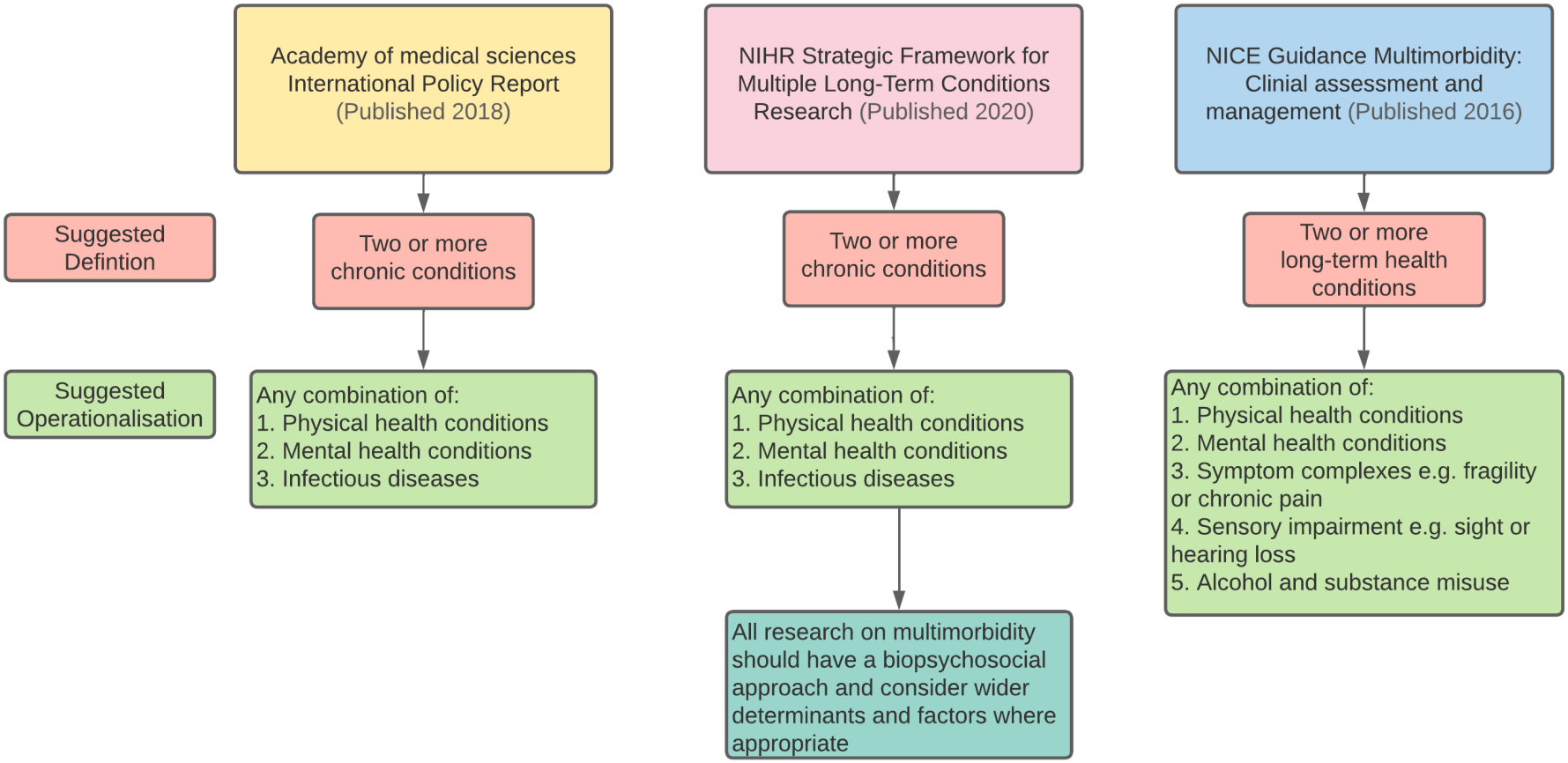
Currently there is no clinical guidance on MLTC in pregnancy, and no specific methodological guidance regarding how MLTC should be defined and operationalised in pregnancy research. A number of systematic reviews have previously highlighted wide variations in how MLTC has been defined and operationalised in the existing literature (74). This has clear implications for the extent to which previous studies are applicable to different population groups or comparable to one another. This is important for two reasons when considering MLTC and pregnancy. First, if health conditions more likely to affect women of reproductive

age have not been included in the operationalisation of MLTC, then the disease burden faced by this group of the population is likely to have been underestimated previously. Second, if health conditions known to be important to maternal and perinatal outcomes have not been included in the operationalisation of MLTC, then the extent to which the current literature around MLTC is applicable to pregnant populations is limited. Whether previous research studies investigating the epidemiology of MLTC have included conditions that are most relevant to women of reproductive age and maternal and perinatal health is unclear at present. This is a critical research gap to examine, as well as being a first and necessary step towards informing the design of the research studies presented in the latter part of this thesis.

This chapter addresses research objective 1 of this thesis:

To appraise the definition and operationalisation of MLTC in existing population-based prevalence studies inclusive of women of reproductive age in order to assess the extent to which these are suitable for use in MLTC research in pregnant populations.

Figure 2.1. Schematic representation of the main guidance most relevant to UK clinical practice on the definition and operationalisation of MLTC



2.2 Methods

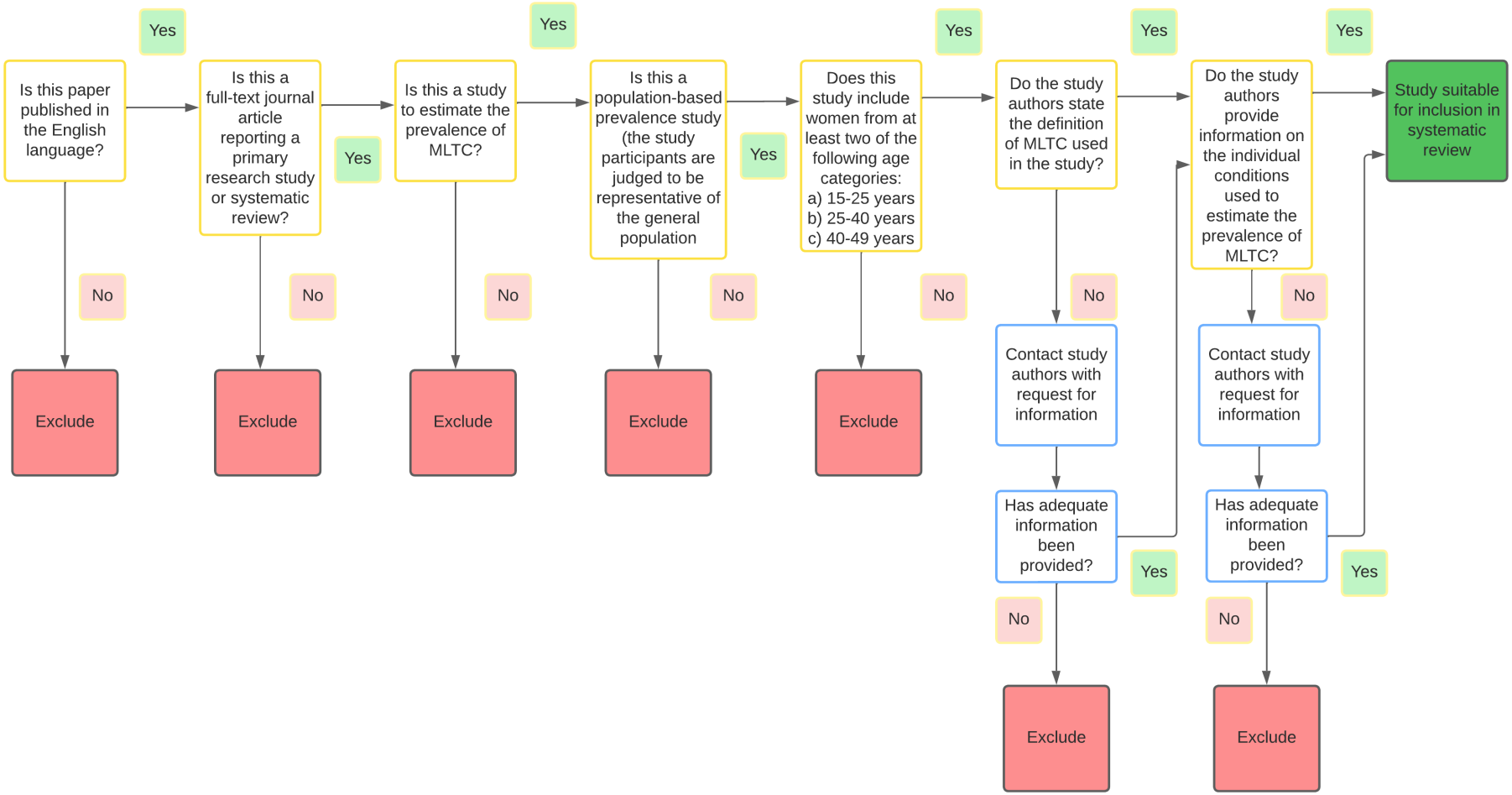
2.2.1 Protocol for systematic review

A protocol for this systematic review was written and registered with PROSPERO prior to the preliminary literature searches being undertaken (75).

2.2.2 Eligibility criteria

The inclusion and exclusion criteria for this systematic review are detailed in Figure 2.2.

Figure 2.2. Flow diagram detailing the study inclusion and exclusion criteria



2.2.3 Database searches

An electronic literature search was undertaken of four bibliographic databases from the inception date of the respective database until the 8th of July 2020. The databases searched were Ovid (MEDLINE), Embase, Web of Science and CINAHL. The search strategy was developed with the assistance of the Bodleian Healthcare Libraries Outreach Librarian (NR) and was designed to identify population-based studies investigating the prevalence of MLTC. The search strategy used for each database is included in appendix A (Tables A1 to A4). Reference lists of eligible studies were hand searched, and forward and backward citation searching through Web of Science and Google Scholar was used to ensure all relevant studies were identified. Systematic reviews on relevant topics were retained for reference searching, but not included in the final narrative synthesis. The searches were repeated on 1st February 2022, and all new papers identified as suitable for inclusion were integrated into the analysis.

2.2.4 Study selection and data extraction

All papers identified by the searches were imported into a reference management platform (EndNote) and duplicates were removed. The titles and abstracts were then screened by the first reviewer (RD) for eligibility for inclusion in the review. Following this, a full-text screen was undertaken by the first reviewer (RD) against the pre-specified eligibility criteria outlined in the study protocol. A sample of 35% of papers identified as potentially eligible for inclusion were independently screened by a team of second reviewers (SF, GDW, MT). Disagreements over study selection were resolved through discussion with input from a third reviewer (MK) when necessary. Data were extracted for each study into a bespoke

data collection form. The data for all studies were independently extracted by two reviewers and compared to ensure accuracy prior to synthesis.

The following data were extracted for each study:
Study title; Primary Author; Study years; Included countries; Study objectives; Study design; Data sources used in study; Number of participants in study population; Age range of participants; Number of women of reproductive age in study population; Inclusion/Exclusion criteria applied to population; Definition of MLTC used in study; Description of methodology used to choose definition of MLTC; Number of conditions in operationalisation as stated by study; Individual health conditions in operationalisation; Description of methodology used to choose conditions included in operationalisation of MLTC; Description of how individuals with relevant conditions were identified; Inclusion/Exclusion criteria applied to individual conditions by study; Social and demographic information reported about study population; Description of how prevalence is reported; Disaggregation of data; Additional outcomes reported by the study.

2.2.5 Critical appraisal

A critical appraisal was undertaken by the first reviewer (RD) using the MetaQat critical appraisal tool (76) in conjunction with CASP appraisal tool for cohort studies (77) and the AXIS appraisal too for cross-sectional studies (78) to further aid the identification of important sources of bias. The MetaQAT critical appraisal tool provides a framework for assessing study quality across four domains of relevancy, reliability, validity and applicability through the construction of narrative responses to component questions and prompts

followed by an overall summative assessment of each component question. This tool was selected as it allows for the domain questions to be flexibly adapted to best suit the specific research questions of the review and for different study designs and types of evidence to be appraised within the same framework. The concepts and questions explored within each domain item for the MetaQAT critical appraisal framework are outlined in Table 2.1.

Table 2.1. MetaQAT framework domains, component questions and assessment outcomes used for critical appraisal

Domain	Questions and prompts considered as part of appraisal	Assessment outcome	
Assessment of relevancy *Assessment of whether the study addresses a topic relevant to the issue under investigation*	**1. Does the study meet the pre-defined eligibility criteria for the systematic review?**		Yes
			No
			Unclear or partially met
Assessment of reliability *Assessment of the completeness of reporting and reproducibility of the research*	**1. Is the study clearly presented?** • Rationale for study clearly stated • Conduct of the study clearly described • All relevant results presented • Context of findings discussed with regard to wider literature **2. Are the methodology and results clearly described?** • Methods reported in sufficient detail to replicate the study • Study population and inclusion/exclusion criteria described		Yes
			No
			Unclear or partially met
Assessment of validity *Assessment of the internal and external validity of the study*	**1. Is the study methodology appropriate for the scope of research?** • Study design congruent with research questions • Study design suitable to estimate prevalence of MLTC **2. Is the methodology free from bias?** • Significant sources of methodological bias or error in study **3. Are the conclusion of the study explicit and transparent?** • Study conclusions logically follow from results presented		Yes
			No
			Unclear or partially met
Assessment of applicability *Assessment of the extent to which the study can be applied to research in pregnant populations*	**1. Is this study applicable to research in pregnant populations?** • Extent to which results can meaningfully be used to understand MLTC in pregnancy		Yes
			No
			Unclear or partially met

The findings of the critical appraisal were used to inform the discourse of the narrative synthesis, and no studies were excluded from the synthesis based on the critical appraisal.

2.2.6 Data synthesis

The data collected from each study were integrated and appraised through narrative synthesis using the relevant principles described in the Economic and Social Research Council (ESRC) guidance on the conduct of narrative synthesis in systematic reviews (79) and the Cochrane guidance on synthesis without meta-analysis (80, 81).

In the first instance, textual and tabulated descriptions of the data were created using information from the data collection form and critical appraisal. These descriptions were used to explore the methodological processes through which study groups selected a definition of MLTC and how they chose individual health conditions to operationalise their definition. Following on from this, individual conditions were organised into morbidity categories and the number of times different conditions were included across all papers was mapped against information about the natural history and progression of individual conditions. This allowed us to evaluate the extent to which conditions relevant to women's health or pregnancy outcomes had been included within previous studies. Lastly, textual and tabulated descriptions of the data were used to explore the inclusion and use of information relating to the social and demographic characteristics of the study population. In particular, the extent to which social determinants of health relevant to maternal and perinatal outcomes in pregnancy had been included was critically evaluated.

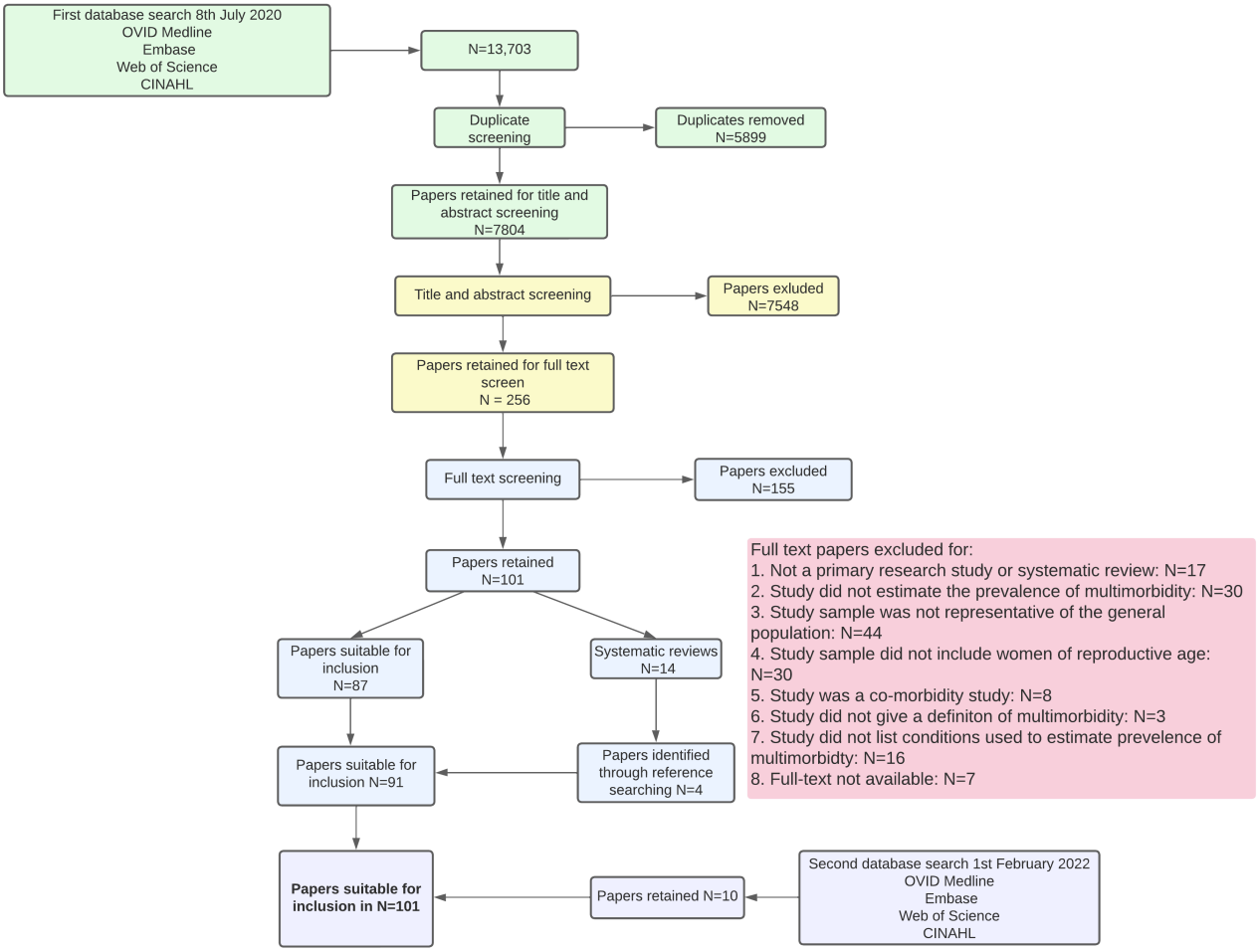
Materials relating to data synthesis were prepared by the first reviewer (RD) and emerging themes of the analysis were identified and refined between three reviewers (RD, MK, FA). The process of narrative synthesis was conducted in an iterative fashion to ensure consistency between existing and emerging themes and to allow consensus to be reached between reviewers on the overall findings of the analysis.

2.3 Results

2.3.1 Study selection

The results of the study selection process are detailed in Figure 2.3.

Figure 2.3. Flow diagram of the study selection process



2.3.2 Study characteristics

A total of 101 papers were identified as suitable for inclusion in this systematic review. The characteristics of the included studies are show in Table 2.2. While all of the papers included in this review were population-based prevalence studies inclusive of women of reproductive age, none were specifically studies of MLTC in women of reproductive age, or women who were pregnant.

Table 2.2. Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Adams (82)	2017	United States of America	Cross-sectional with telephone survey	483,865	Behavioural Risk Factor Surveillance System	Two or more conditions	12	No description given
Afshar (83)	2015	Burkina Faso, Ghana, Kenya, Morocco, Namibia, South Africa, Brazil, Dominican Republic, Paraguay, Uruguay, Bosnia, Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Latvia, Ukraine, Bangladesh, Mauritius, Pakistan, Sri Lanka, Laos, Malaysia, Myanmar, Nepal, Philippines, Spain	Cross-sectional with Survey	122,404	WHO World Health Survey	Two or more conditions	6	Conditions chosen based on those thought by the study team to be amenable to self-report and reflective of health system coverage
Agborsangaya (84)	2012	Canada	Cross-sectional with survey	5,010	Health Quality Council of Alberta Patient Experience Survey	Two or more conditions	16	No description given
Agborsangaya (85)	2013	Canada	Cross-sectional with survey	4803	Health Quality Council of Alberta Patient Experience Survey	Two or more conditions	16	Conditions chosen based on those included in the Health Quality Council of Alberta Patient Experience Survey
Agrawal (86)	2016	China, India, Ghana, Mexico, Russian Federation, South Africa	Cross-sectional with questionnaire and face-to-face interviews	44,715	WHO study on global ageing and adult health	Two or more conditions	9	No description given

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Agur (2)	2016	Scotland	Cross-sectional with EPR	1,751,814	Electronic Patient Records from 314 Scottish General Practices	Two or more conditions	40 (32 physical health conditions and 8 mental health conditions)	Conditions chosen based on health conditions used in another MLTC study (10)
Ahmadi (87)	2021	Iran	Baseline data from prospective cohort study	10075	Study questionnaire from Shahr-e-Kord PERSIAN cohort study	Two or more conditions	27	No description given
Alaba (88)	2013	South Africa	Cross-sectional with questionnaire	11,638	South African National Income Dynamics Study	Two or more conditions	6	No description given
Aoki (89)	2018	Japan	Cross-sectional with survey	3,256	NORM study	Two or more conditions	17	No description given
Araujo (90)	2018	Brazil	Cross-sectional with face-to-face interviews	4001	Brazilian National Health Survey	Two or more conditions	12	Conditions same as those used in the Brazilian National Health Survey
Ba (91)	2019	Vietnam	Cross-sectional with face-to-face interviews	1680	N/A	Two or more conditions	9	No description given
Barnett (10)	2012	Scotland	Cross-sectional using routinely collected health care data	1,751,841	Electronic Patient Records from 314 Scottish General Practices	Two or more conditions	40	Conditions chosen based on recommendations systematic review (92), those identified in Quality Outcomes Framework for UK General Practice and those identified as important by NHS Scotland

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Basham (93)	2019	Canada	Cross-sectional with telephone survey	110,924	Canadian Community Health Survey	3 or more chronic conditions	14	Conditions chosen based on recommendations from systematic review (70)
Boersma (94)	2020	United States	Cross-sectional with survey	24,417	National Health Interview Survey	Two or more conditions	10	Conditions chosen based on those included in the US Department of Health and Human Services strategic framework for optimising health and quality of life for individuals with MLTC
Booth (95)	2014	UK	Longitudinal cohort	223,089	Clinical Practice Research Datalink	Two or more conditions	11	Conditions chosen based on those thought by the study team to reflect the most common disorders associated with obesity
Cabassa (96)	2013	United States of America	Cross-sectional with survey	33,107	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)	Two or more conditions	10	No description given
Carvalho (97)	2017	Brazil	Cross-sectional	64, 308	National Health Survey	Two or more conditions	14	Conditions chosen based on recommendations from systematic review (98)

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Cassell (3)	2018	England	Retrospective cohort using electronic health record data	403,985	Clinical Practice Research Datalink	Two or more conditions	36 conditions in paper (note 37 conditions listed on Cambridge CPRD website)	Conditions chosen based on health conditions used in another MLTC study (10)
Chen (99)	2020	Netherlands	Cross-sectional using survey data and data from pharmacy and claims databases	Unclear how many participants covered by the dataset. For the health survey (used for health outcomes) 7,741 respondents	Pharmacy and insurance claims database and health survey.	Two or more conditions	21	Conditions chosen based on those used in another MLTC study (100)
Chung (101)	2015	Hong Kong	Cross-sectional with survey	25,780	Thematic Household Survey	Two or more conditions	46	Conditions chosen based on health conditions used in another MLTC study (102)
Cimarras-Otal (103)	2014	Spain	Cross-sectional with survey	22,190	European Health Interview Survey	Two or more conditions	20	No description given
Craig (104)	2021	Jamaica	Cross-sectional with survey	Not reported	Jamaican Health and Lifestyle Survey	Two or more conditions	11	Conditions chosen based on recommendations from systematic review (92)
Diaz (105)	2015	Norway	Retrospective cohort using electronic health record data	3,349,721 Norwegian citizens and 389,807 Immigrants	National population register linked to the Norwegian health economics administration database	Two or more conditions	114	Conditions chosen based on health conditions used in another MLTC study (106)
Forslund (107)	2021	Sweden	Cross-section with routinely collected healthcare data	2,323,667	Swedish VAL database	Two or more conditions	40	Conditions chosen based on those used in another MLTC study (10)

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Fortin (68)	2017	Canada	Cross-sectional with survey and routinely collected administrative health data	1,178	Program of research on the evolution of a cohort investigating health system effects (PRECISE) and RAMQ database	The presence of 2 or more, 3 or more and 4 or more of 12 chronic conditions	12	No description given
Frolich (108)	2019	Denmark	Cross-sectional using routinely collected data from linked registries	1,397,173	Danish national patient registry, Danish national prescription registry, Danish national health service registry, National diabetes registry	Two or more conditions	16	No description given
Fu (109)	2014	Taiwan	Cross-sectional using routinely collected administrative data	2000 (999,635), 2005 (999,974), 2010 (999,998)	National Health Insurance Research Database	Two or more conditions	15	Conditions chosen based on those which were most prevalent within the National Health Insurance Research Database
Fuchs (110)	2012	Germany	Cross-sectional with survey	21,262	German Health Update Interview Survey	Two or more conditions	22 (categorised into 9 disease categories for analysis)	Conditions chosen based on those included in the German Health Update Interview Survey

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Garcia-Olmos (111)	2012	Spain	Cross-sectional using routinely collected healthcare data	198,670	Primary care electronic health records	Two or more conditions	26	Conditions chosen based on health conditions used in another MLTC study (112) and those thought by the study team to have a high prevalence and/or impact on health services
Ge (113)	2018	Singapore	Cross-sectional with survey	1,942	Population Health Index Survey and National Healthcare Group Chronic Disease Management System (CDMS) database	Two or more conditions	17	No description given
Geda (114)	2021	Canada	Cross-sectional with survey	109,659	Canadian Community Health Survey (CCHS)	Two or more conditions	14	Conditions chosen based on those included in the Canadian Community Health Survey
Gimeno-Feliu (115)	2017	Spain	Cross-sectional with routinely collected data from electronic health records	1,092,279	Baseline data from EpiChron cohort study	Two or more conditions	114	Conditions chosen based on those used in another MLTC study (106)

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Gupta (116)	2016	United States of America	Cross-sectional with survey	18,052	Behavioural Risk Factor Surveillance System	Having two chronic conditions or having three or more chronic conditions	12	Conditions chosen based on those included in the US Department of Health and Human Services strategic framework for optimising health and quality of life for individuals with MLTC and those included in the Behaviour Risk Factor Surveillance System Survey
Han (117)	2018	United States of America	Cross-sectional with survey	115,335	National Survey on Drug Use and Health	Two or more conditions	12	Conditions chosen based on those thought by the study team to be most relevant to substance abuse
Hayek (118)	2017	Israel	Cross-sectional with telephone survey	4,325	Israeli National Health Interview Survey	Two or more conditions	10	No description given
Hone (119)	2021	Brazil	Cross-sectional using primary health care registration records	3,173,289	Primary health care records linked to welfare claims, hospitalisation and mortality records	Two or more conditions	53	Conditions chosen based on those used in other MLTC studies (10, 120, 121)

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Hosseinpoor (122)	2012	Bangladesh, Bosnia and Herzegovina, Burkina Faso, Chad, Cote d'Ivoire, Croatia, Czech Republic, Dominican Republic, Ecuador, Estonia, Ethiopia, Georgia, Ghana, India, Kazakhstan, Kenya, Democratic Republic, Latvia, Malawi, Malaysia, Mauritania, Mauritius, Morocco, Myanmar, Namibia, Pakistan, Paraguay, Russia, Senegal, South Africa, Sri Lanka, Tunisia, Ukraine, Uruguay, Viet Nam, Zambia, Zimbabwe	Cross-sectional with survey	170, 298	World Health Survey	Two or more conditions	5	Conditions same as those used in the World Health Survey

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Hu (123)	2019	Taiwan	Cross-sectional using routinely collected administrative data	2003 - (1,215,723), 2013 - (1,429,527)	National Health Insurance Research Database	Two or more conditions	20	Condition chosen based on those thought by the study team to represent the greatest burden of disease based on healthcare costs, requirement for long-term care, reduced health-related quality of life, hospitalisations, and death
Ioakeim-Skofa (124)	2020	Spain	Cross-sectional using routinely collected electronic health care data	1,253,292	Baseline data from EpiChron cohort study	Two or more conditions	114	Conditions chosen based on those used in another MLTC study (106)
Jankovic (125)	2018	Serbia	Cross-sectional with survey	13,765	National Health Survey (Serbia)	Two or more conditions	13	No description given
Jawed (126)	2020	Pakistan	Cross-sectional with face-to-face interviews	1500	IMPACT study	Two or more conditions	16	No description given
Jovic (127)	2016	Serbia	Cross-sectional with survey	13,103	National Health Survey (Serbia)	Two or more conditions	12	No description given
Jovic (128)	2016	Serbia	Cross-sectional with survey	13,103	National Health Survey (Serbia)	Two or more conditions	13	No description given
Katkireddi (129)	2017	Scotland	Prospective cohort study	3466	West of Scotland Twenty-07 cohort study	Two or more conditions	40	Conditions chosen based on those used in another MLTC study (10)

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Keats (130)	2017	Canada	Cross-sectional analysis of baseline data from survey as part of PATH study	18,709	Atlantic Partnership for Tomorrow's Health (PATH) study	Two or more conditions	18	No description given
Khan (131)	2019	Bangladesh	Cross-sectional with face-to-face interviews	12,338	Bespoke survey	Two or more conditions	6	Conditions chosen based on those reported for Bangladesh within the WHO non-communicable disease report
Kiliari (132)	2014	Cyprus	Cross-sectional with face-to-face interviews	465	Bespoke questionnaire	Two or more conditions	27	No description given
Kim (133)	2020	South Korea	Cross-sectional with survey	68,590	Korean national Health and Nutrition Examination Survey	Two or more conditions	28	Conditions chosen based on those included in the Korean national Health and Nutrition Examination Survey
King (134)	2018	United States of America	Cross-sectional	573,030	National health and nutritional examination survey	Two or more conditions	11	Conditions chosen based on those included in the National Health and Nutrition Examination Survey

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Kone (135)	2021	Canada	Cross-sectional using routinely collected healthcare data	12,143,428 in 2003, 12,907,659 in 2009 and 13,738,113 in 2016	Routinely collected data from administrative health databases linked to secondary care database, pharmacy database and insurance claims database	Two or more conditions	18	Conditions chosen based on those thought by the study team to have a high prevalence or to contribute to high economic costs or health system burden in Canada
Kumar (136)	2015	India	Cross-sectional with survey	89755	Bespoke survey	Two or more conditions	5	No description given
Kuwornu (137)	2014	Canada	Cross-sectional with survey	3,284	Canadian Community Health Survey	Two or more conditions	15	Conditions chosen based on those that were most prevalent in the Canadian Community Health Survey
Lai (138)	2019	Hong Kong	Cross-sectional with survey	69,636	Thematic Household Survey	Two or more conditions	14	No description given
Laires (139)	2019	Portugal	Cross-sectional with survey	15,196	Portuguese National Health Interview Survey	Two or more conditions	13	Conditions chosen based on those included in the Portuguese National Health Interview Survey
Larsen (140)	2017	Denmark	Cross-sectional with survey	162,283	Danish national health survey	Two or more conditions	15	No description given

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Lebenbaum (141)	2018	Canada	Cross-sectional with Survey	288,300	National Population Health Survey and the Canadian Community Health Survey	Two or more conditions	10	Conditions chosen based on those included in the National Population Health Survey and the Canadian Community Health Survey
Lee (142)	2015	China, India, Ghana, Mexico, Russian Federation, South Africa	Cross-sectional with survey	44,464	WHO Study on global ageing and adult health	Two or more conditions	9	No description given
Lenzi (143)	2016	Italy	Cross-sectional with routinely collected administrative and healthcare data	3,759,836	Five linked databases: Hospital discharge record database mental health information system, residential mental healthcare discharge records, outpatient pharmaceutical database, regional mortality register database	Two or more conditions	26	Conditions chosen based in those included in Charslson (144) and Elixhauser (145) multimorbidity indices, and those recommended in systematic review (92)
Li (146)	2016	England	Cross-sectional analysis of baseline data from YHS	27,806	Yorkshire Health Study	Two or more conditions	12	No description given

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Lowe (147)	2017	Australia	Cross-sectional with survey	12,604	National Health Survey Australian Bureau of Statistics	The presence of 2+ and 3+ conditions	107	Conditions chosen based on recommendations from systematic review (92) and those thought by study team to have a high prevalence and high impact on individuals and the health care system
Loza (148)	2009	Spain	Cross-sectional with survey	2192	EPISER health survey	Two or more conditions	9 categories of diseases	No description given
Lund Jensen (149)	2017	Denmark	Prospective cohort with information about multimorbidity collected at baseline	239,537	Participants identified from Danish National Health Survey and linked to Danish national patient register, Danish cancer register, Danish diabetes register, Danish psychiatric central register, Danish national prescription register	Moderate multimorbidity (two to three conditions) and Severe multimorbidity (four or more conditions)	39	Conditions chosen based on those used in another MLTC study (150)
Macinko (151)	2019	Brazil, Columbia, El Salvador, Panama, Jamaica, Mexico	Cross-sectional	Approximately 1500 interviewed per country where study was conducted	Inter-American Development Bank International Primary Care Survey	Two or more conditions	8	Conditions chosen based on those thought by the study team to have the highest prevalence in Latin American Countries

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Marques (152)	2018	Austria, Belgium, Switzerland, Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Hungary, Ireland, Lithuania, Netherlands, Norway, Poland, Portugal, Sweden, Slovenia, UK, Israel	Cross-sectional with survey and face-to-face interviews	25,713	European Social Survey	Two or more conditions	9	No description given
Meems (153)	2015	Netherlands	Cross-sectional with questionnaire	8,726	Lifelines Cohort Study (baseline data)	Two or more conditions	12 systems based 'morbidity domains'	No description given
Mokraoui (71)	2016	Canada	Cross-sectional analysis of PRECISE	1718 participants recruited from the general population and 789 participants recruited from primary care clinics	Program of research on the evolution of a cohort investigating health system effects (PRECISE)	Three different definitions of MLTC were used: 1. The presence of two or more chronic conditions. 2. The presence of three or more chronic conditions. 3. Disease Burden Morbidity Assessment tool score of 10 or higher	21	Conditions chosen based on those included in the Disease Burden Morbidity Assessment Tool (154)

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Mondor (155)	2018	Canada	Cross-sectional using routinely collected administrative data and health survey data	113,627	Canadian Community Health Survey linked to administrative health data	Two or more conditions	17	Conditions chosen based on those used in other MLTC studies (156-160) and those thought by the study team to have a high prevalence and economic burden
Navickas (161)	2015	Lithuania	Retrospective cohort study using routinely collected administrative data linked to demographic data from the Lithuanian Department of Statistics	2,632,377	National Health Insurance Fund Database	Two or more conditions	32	Conditions chosen based on those used in another MLTC study (10)
Newman (162)	2019	United States of America	Cross-sectional with survey	76,186	Behavioural Risk Factor Surveillance System	Two or more conditions	12	Conditions chosen based on those included in the Behavioural Risk Factor Surveillance System

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Newman (163)	2020	United States of America	Cross-sectional with telephone survey	450,462	Behavioural Risk Factor Surveillance System Survey	Two or more conditions	12	Conditions chosen based on those included in the US Department of Health and Human Services strategic framework for optimising health and quality of life for individuals with MLTC and those included in the Behaviour Risk Factor Surveillance System Survey
Nicholson (164)	2019	Canada	Retrospective cohort with routinely collected data from electronic medical records	367,743	Canadian Primary Care Sentinel Surveillance Network	At least two and at least three chronic conditions	20	Conditions chosen based on those used in other MLTC studies (10) and based on recommendation from systematic review (92)
Nunes (165)	2017	Brazil	Cross-sectional with survey	60,202	Brazilian National Health Survey	2 or more and 3 or more morbidities	22	No description given
Ornstein (166)	2013	United States of America	Cross-sectional with routinely collected electronic health data	667,379	PPRNet	The presence of two or more or three or more chronic conditions	24	No description given

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Orueta (167)	2014	Basque country	Cross-sectional with routinely collected health and administrative data	22,627,070	PREST database	Two or more conditions	52	Conditions chosen based on those used in another MLTC study (10) and those recommended by systematic review (92)
Pache (168)	2015	Switzerland	Cross-sectional and through clinical evaluation for psychiatric disorders	6,733	The Cohorte Lausannoise Study	Two or more conditions	35	No description given
Pati (169)	2014	India	Cross-sectional using survey	10,973	WHO study on global ageing and adult health	Two or more conditions	9	Conditions chosen based on those included in the WHO Study on Global Ageing and Adult Health
Pefoyo (156)	2015	Canada	Cross-sectional with routinely collected administrative data	2003 (12,242,273), 2009 (13,068,845)	Linked provincial health administrative databases	Two or more conditions	16	Conditions chosen based on those thought by the study team to be clinically relevant and have a high burden on cost to the healthcare system
Puth (170)	2017	Germany	Cross-sectional with survey	19,294	German Health Update Interview Survey	Two or more conditions	17	Conditions chosen based on those used in another MLTC study (102)

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Ramond-Roquin (171)	2016	Canada	Cross-sectional	1,710	Program of research on the evolution of a cohort investigating health system effects (PRECISE)	Two or more conditions and three or more conditions	21 (a separate analysis of 6 conditions also conducted to assess the effect of this on prevalence)	Conditions chosen based on those included in the Disease Burden Morbidity Assessment Tool (154)
Roberts (172)	2015	Canada	Cross-sectional using survey	105,416	Canadian Community Health Survey	Having two or more and three or more chronic diseases	9	Conditions chosen based on those included in the Canadian Community Health Survey
Rocca (173)	2014	United States of America	Cross-sectional using routinely collected health and administrative data	138,858	Rochester epidemiology project liked to routinely collected health and administrative health care records	The presence of two or more conditions (multimorbidity) and the presence of five or more conditions (complex multimorbidity)	20	Conditions chosen based on those included in the US Department of Health and Human Services strategic framework for optimising health and quality of life for individuals with MLTC
Ruel (174)	2014	Australia	Prospective cohort	1,854	Northwest Adelaide Longitudinal Study	Two or more conditions	8	Conditions chosen based on those thought by the study team to be associated with objective test measurements (e.g. blood pressure reading or blood test result) to confirm diagnosis

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Ryan (175)	2018	Canada	Cross-sectional using routinely collected health and administrative data	13,581,191	Ontario registered persons database linked to the Ontario Health Insurance Plan and the Health Services Delivery databases	The presence of three or more of 17 chronic conditions examined	17	Conditions chosen based on those identified for inclusion within the Canadian Institute for Health Research community-based primary health care signature initiative
Rzewuska (176)	2017	Brazil	Cross-sectional using survey	60,202	National Health Survey	Two or more conditions	16	Conditions same as those used in the Brazilian National Health Survey
Salisbury (106)	2011	England	Retrospective cohort using electronic health record data	99,997	General Practice Research Database	MLTC was defined in two ways based on two different operationalisations: 1. More than one of 17 chronic conditions incentivised under the QOF. 2. One or more of a much wider list of chronic conditions identified from the Johns Hopkins Adjusted Clinical Groups case mix system	17 conditions included for the Quality Outcomes Framework definition and 114 conditions chosen for the ACG definition	Conditions chosen based on those included in the Quality Outcomes Framework for UK Primary Care and those thought by the study team to represent chronic conditions within the Johns Hopkins Adjusted Clinical Groups case mix system

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Schoitz (177)	2017	Denmark	Cross-sectional	1,397,173	Danish national patient registry, Danish national prescription registry, Danish national health service registry, National diabetes registry	Two or more conditions	16	No description given
Shi (178)	2015	Australia	Cross-sectional with telephone interview and survey	36,663	South Australian Monitoring and Surveillance System	Two or more conditions	9	No description given
Singh (179)	2019	Pakistan	Prospective cohort	16,287	Cardiometabolic Risk Reduction in South Asia Surveillance Study	Two or more conditions	5	Conditions chosen based on those thought by the study team to have a high prevalence in the population
Steffler (180)	2021	Canada	Retrospective cohort	12,770,341 in 2008 and 13,821,055 in 2017	Routinely collected data from administrative health databases linked to secondary care database and insurance claims database	Two or more conditions	85	Conditions chosen based on those included in the Canadian Institute for Health Information Case-mix methodology (a coding system designed to aggregate similar types of acute inpatient care)

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Subramaniam (181)	2014	Singapore	Cross-sectional with survey	6616	Singapore mental health study survey	Two or more conditions	15 (categorised into 8 types of physical disorder). This study also collected information on mental health conditions, but these were not included in the definition of multimorbidity	Conditions chosen based on those included in the WHO World Mental Health Survey Initiative
Taleshan (182)	2018	Denmark	Prospective cohort study	101,894 migrants and 611,934 Danish-born participants	Danish National Patient Registry linked to the Danish Cancer Registry	Two or more conditions	21	Conditions chosen based on those included in Charlson comorbidity index (144) and psychiatric conditions identified as being associated with increased risk of suicide (183)
van den Akker (184)	2019	Belgium	Retrospective cohort using electronic health record data	159,964	Intego (Flemish-Belgian general practice morbidity registration network)	Two or more conditions	91	No description given
van Oostrom (185)	2016	Netherlands	Retrospective cohort using electronic health record data and Health survey data	Not reported	NIVEL Primary Care database and continuous Health Survey conducted by Statistics Netherlands	Two or more conditions	28 for the electronic health record analysis and 11 for the health survey analysis	Conditions chosen based on those thought by the study team to have a high prevalence in the population

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Verest (186)	2019	Netherlands	Cross-sectional analysis of baseline data from survey as part of HELIUS study	23,942	Healthy Life in an Urban Setting (HELIUS) study	Two or more conditions	20	No description given
Vinjerui (187)	2020	Norway	Cross-sectional with survey	30,027	HUNT Study	Three or more chronic conditions affecting three or more different body (organ) systems within on condition without defining an index condition (complex multimorbidity)	51	No description given
Violan (188)	2013	Spain	Cross-sectional using survey and routinely collected health data	15,926 (health survey) and 1,597,258 (SIDIAP)	Health Survey for Catalonia and Information System for the Development of research in Primary Care (SIDIAP) database	Two or more conditions	27	Conditions chosen based on those included in the Health Survey for Catalonia
Wang (189)	2015	China	Cross-sectional with survey and face-to-face interviews	21,475	Jilin Provincial Chronic Disease Survey	Two or more conditions	18	No description given

Table 2.2. (continued) Characteristics of studies included in review

Primary author	Year of study publication	Countries included in study	Study design	Number of participants in study population	Data sources used in study	Definition of MLTC	Number of health conditions included in operationalisation of MLTC	Description of how health conditions were chosen to operationalise MLTC
Wang (190)	2014	China	Cross-sectional with survey	162,464	Guangdong province community household survey derived from the National Health Services Survey conducted in 2008	Two or more conditions	40	Conditions chosen based on those used in another MLTC study (10) and based on recommendation from systematic review (92)
Wang (191)	2017	Australia	Cross-sectional with survey	8820	National Survey of Mental Health and Wellbeing	Two or more chronic conditions (multimorbidity) or three or more chronic conditions (complex multimorbidity)	9	Conditions chosen based on those thought by the study team to significantly contribute to the global burden of morbidity and those identified as National health priority areas by the Australian Bureau of Statistics
Ward (192)	2013	United States of America	Cross-sectional with survey	27,157	National Health Interview Survey	Two or more conditions	10	Conditions chosen based on those included in the National Health Interview Survey
Willadsen (193)	2018	Denmark	Prospective cohort	3,092,063	Danish civil registration system linked to Danish national patient register, Danish cancer registry and the Danish psychiatric central research register	Having diagnoses from two or more different groups (diagnoses organised into 10 different groups)	10 organ systems	Conditions chosen based on those used in previous MLTC studies (10, 120) and those recommended in systematic review (70, 92)

2.3.3 Critical appraisal

The findings of the critical appraisal are show in appendix A (Table A5). The majority of the studies reviewed scored highly across the domains of relevancy, reliability and validity. For the domain of applicability, no studies were considered to present results that were completely transferable to understanding MLTC in pregnant populations.

2.3.4 Definitions of MLTC

All studies included in this review defined MLTC as a dichotomous variable based on counts of individual diseases or conditions. 84 studies (83%) used the presence of two or more conditions in the same individual as the cut-off for MLTC (2, 3, 10, 51, 82, 84, 86-89, 91, 94-97, 99, 101, 103, 105-111, 113-115, 117-119, 122-143, 146, 148, 151, 152, 155, 156, 161, 163, 167-170, 174, 176-182, 184-186, 188-190, 192, 193). 14 studies (14%) used the presence of two or more conditions, in addition to other thresholds of three, four and five or more conditions in order capture 'complex' or 'severe' MLTC, or to assess the impact of total number of conditions included in the definition on estimates of prevalence (68, 71, 90, 104, 116, 147, 149, 164-166, 171-173, 191). Two studies (2%) used three or more conditions in the same individual as the cut-off for MLTC (93, 175), and one study (1%) used three or more conditions in three or more separate organ systems to define MLTC (187).

2.3.5 Methodology used to guide operationalisation of MLTC

36 studies (36%) did not describe the methodology used by the study team to select the individual health conditions used in the operationalisation of MLTC (68, 82, 84, 86-89, 91, 96,

103, 113, 118, 125-128, 130, 132, 136, 138, 140, 142, 146, 148, 152, 153, 165, 166, 168, 174, 177, 178, 184, 186, 187, 189). 18 studies (18%) were secondary analyses of survey data, and therefore were limited to the health conditions included in the survey (85, 90, 94, 110, 114, 117, 122, 133, 134, 137, 139, 162, 163, 169, 172, 176, 181, 188, 192), and 3 studies (3%) used the health conditions included in the Disease Burden Morbidity Assessment questionnaire (71, 171, 175). 22 studies (22%) based their choice of health conditions included in the operationalisation of MLTC on conditions recommended in systematic reviews of the literature or on conditions previously included in existing MLTC studies (2, 3, 93, 97, 99, 101, 104, 105, 107, 115, 119, 124, 129, 143, 149, 161, 167, 170, 173, 182, 190, 193). 16 studies (16%) based their choice of health conditions used in the operationalisation of MLTC on conditions thought to be highly prevalent or clinically important by the study teams, or on the recommendations within strategic frameworks, local policy or public health guidance (83, 94, 95, 106, 109, 116, 123, 135, 151, 156, 163, 175, 179, 180, 185, 191). 5 studies (5%) based their choice of health conditions included in the operationalisation of MLTC on a combination of conditions recommended in systematic reviews of the literature and what was thought to be highly prevalent or clinically important by study teams (10, 111, 147, 155, 164). 1 study (1%) based their choice of health conditions on which ones were likely to have objective evidence (e.g. blood pressure measurement) recorded in the medical records (174).

2.3.6 Individual health conditions used in operationalisation of MLTC

Across all studies a total of 345 health conditions were identified as having been used within various operationalisations of MLTC. The twenty most commonly included health conditions within the studies reviewed are shown in Table 2.3.

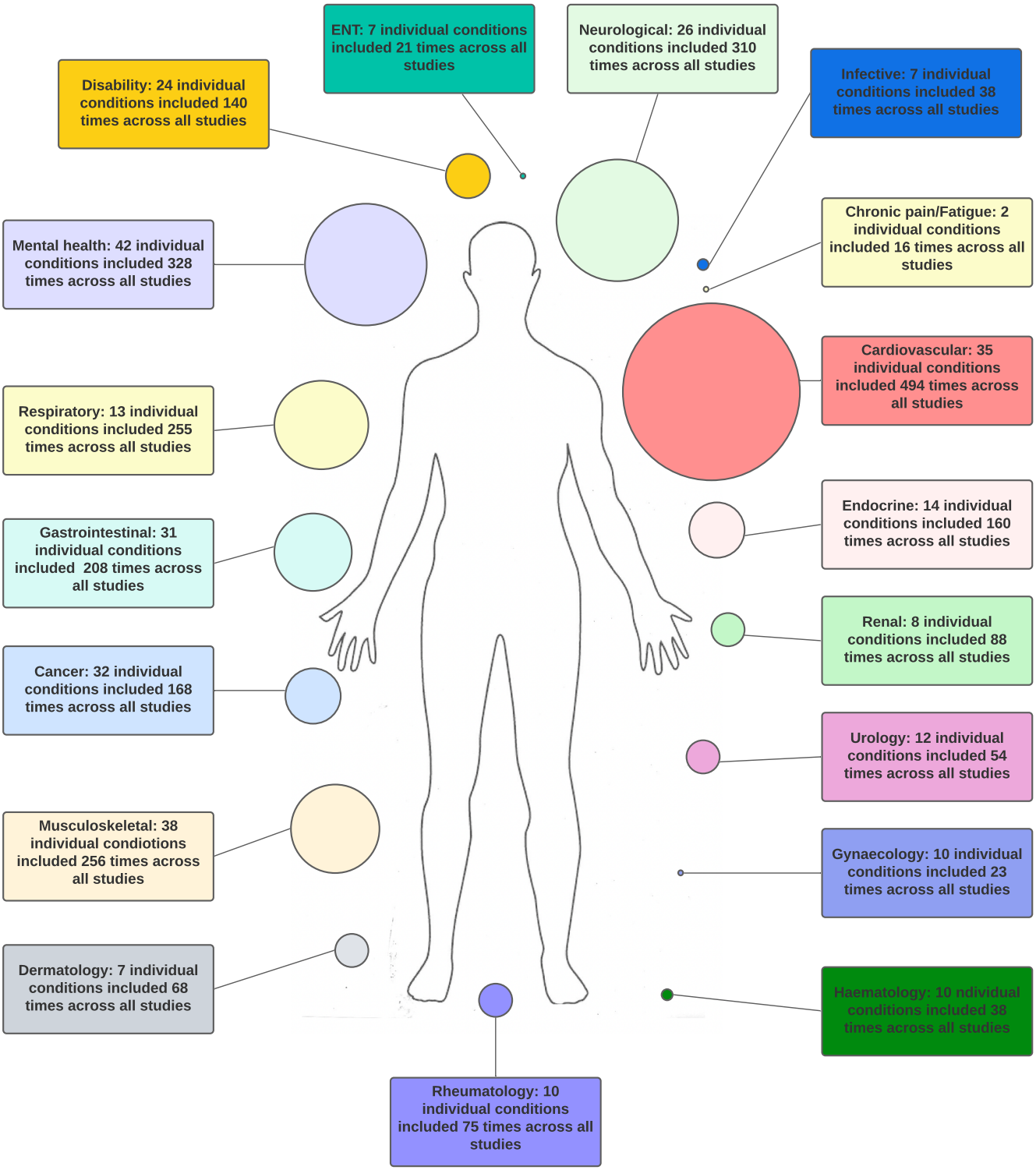
Table 2.3. The 20 most commonly used individual health conditions in population based prevalence studies on MLTC inclusive of women of reproductive age

Rank	Condition	Number of studies that have included individual condition, n (%)
1	Diabetes	100 (99%)
2	Hypertension	90 (89%)
3	Coronary heart disease	89 (88%)
4=	Stroke	84 (83%)
4=	Cancer	84 (83%)
5	Asthma	82 (81%)
6	Arthritis	72 (71%)
7	Chronic Obstructive Pulmonary Disease	65 (64%)
8	Depression	62 (61%)
9	Kidney disease	50 (50%)
10	Heart failure	47 (47%)
11	Osteoporosis	44 (44%)
12	Anxiety	42 (42%)
13=	Dementia	38 (38%)
13=	High cholesterol	38 (38%)
14	Myocardial Infarction	35 (35%)
15	Bronchitis	34 (34%)
16=	Schizophrenia	31 (31%)
16=	Back or neck pain	31 (31%)
17=	Thyroid disorder	30 (30%)
17=	Rheumatoid arthritis	30 (30%)
18	Liver disease	29 (29%)
19=	Epilepsy	27 (27%)
19=	Obesity	27 (27%)
19=	Parkinson’s disease	27 (27%)
20=	Migraine	26 (26%)
20=	Emphysema	26 (26%)

The number of health conditions included in the operationalisation of MLTC for each study ranged from 5 conditions up to 114 conditions.

The health conditions included across all studies were organised into 18 distinct morbidity categories (Neurological; Infective; Chronic pain/Fatigue; Cardiovascular; Endocrine; Renal; Urology; Gynaecology; Haematology; Rheumatology; Dermatology; Musculoskeletal; Cancer; Gastrointestinal; Respiratory; Mental health; Disability; Ear/Nose/Throat), with a further miscellaneous category used for conditions that could not be assigned to one of the other categories. The number of health conditions included within each morbidity category, and the number of times those conditions were include across all studies is shown in Figure 2.4.

Figure 2.4. Schematic representation of morbidity categories including the number of health conditions within each category and the number of times those conditions were included across all studies.



There was considerable variability observed when comparing the morbidity categories with respect to both the range of health conditions included within each category, and the number of times the different health conditions were included across all studies.

2.3.7 Further observations made during categorisation and mapping of health conditions

During the process of categorising and mapping the individual health conditions chosen for inclusion across the studies the following observations were made relating to the management of the included health conditions by study teams.

2.3.7.1 Condition overlap

This is the inclusion of a number of health conditions that have been counted individually to identify MLTC, however, these conditions could either be part of the same health condition or represent a severe manifestation or a complication of an index health condition. Examples of condition overlap were the inclusion of 'Coronary Heart Disease, Myocardial Infarction, Heart failure' as separate conditions, 'Chronic Obstructive Pulmonary Disease, Emphysema, Chronic Bronchitis' as separate conditions, 'Schizophrenia or Bipolar disorder, Psychosis' as separate conditions and 'Arthritis, Joint pain, Chronic Pain' as separate conditions. Condition overlap was observed in 51 studies (51%) (2, 3, 10, 83, 101, 105, 106, 108, 110, 111, 123, 137, 143, 147, 149, 156, 165, 167, 171, 173, 184, 185).

2.3.7.2 Indeterminate conditions

This is the description of health conditions in such a way as it is not clear which health condition or conditions are identified within the grouping. Examples of indeterminate conditions were 'Kidney Disease', 'Circulatory Conditions', 'Respiratory Disease', 'Mental Health Condition' and 'Thyroid Disorder'. Indeterminate conditions were observed in 70 studies (69%) (3, 68, 71, 84, 85, 91, 93-95, 99, 101, 103-111, 114, 115, 118, 119, 123-129, 132, 133, 136-140, 143, 146-149, 152, 155, 161, 164-171, 174-182, 184-188, 190, 191).

2.3.7.3 Condition aggregation

This is the grouping together of several individual health conditions and treating the grouped conditions as a single entity. Examples of condition aggregation were 'Chronic obstructive pulmonary disease/Asthma', 'Depression/Bipolar disorder/Schizophrenia' and 'Osteoarthritis/Rheumatoid arthritis'. Condition aggregation was observed in 45 studies (45%) (2, 3, 10, 68, 71, 84, 86, 89, 90, 96, 97, 101, 105-107, 109, 111, 113-115, 123, 124, 126, 129, 130, 135, 137-139, 148, 155, 156, 162-164, 167, 172, 174, 176, 180, 186-189, 192, 193).

2.3.8 Information reported about the characteristics of the study population

The social and demographic characteristics and information relating to the wider determinants of health collected across all studies is shown in Table 2.4.

Table 2.4. Information collected by studies relating to participant characteristics and factors relevant to wider determinants of health

Component of social and demographic characteristics reported by study	Number of studies reporting component		Study references
	n	%	
Age	100	99	(2, 3, 10, 68, 71, 82-91, 93-97, 99, 101, 103-111, 113-119, 122-125, 127, 128, 130-143, 146, 147, 149, 151, 153, 155, 156, 161-182, 184-187, 189-194)
Sex	98	97	(2, 3, 10, 68, 71, 82-91, 93-97, 99, 101, 103-111, 113-119, 122-128, 130-143, 146, 147, 149, 151, 153, 155, 161-182, 184-187, 189-194)
Standardised measure of socioeconomic status or other indicator of socioeconomic status including income, occupation, employment status, benefit recipient status or educational attainment	74	73	(3, 10, 68, 71, 82-91, 93, 95-97, 101, 103-106, 108, 110, 111, 113, 114, 117-119, 122, 125-131, 133, 135, 139-142, 146-149, 151, 152, 155, 162, 164, 165, 167-172, 174, 176-179, 181, 182, 186, 187, 189-191, 193)
Ethnicity or information about country of origin or migrant status	26	26	(82, 87, 88, 90, 97, 105, 113-119, 122, 134, 143, 146, 147, 149, 162, 165, 168, 172, 173, 182, 192)
Health behaviours such as smoking status, alcohol consumption, diet, physical activity or body mass index	32	32	(86, 88, 93, 95, 101, 103, 104, 113, 114, 117, 118, 126-131, 141, 147, 149, 152, 153, 155, 168, 172, 174, 178, 179, 181, 189-191)
Housing and living environment or area of living classification e.g. rural or urban	28	28	(71, 83, 86, 88, 97, 101, 104, 114, 122, 123, 125, 127, 128, 130, 139, 141, 142, 148, 155, 162, 164, 169, 172, 175, 176, 190, 193)
Healthcare use including funding arrangements for accessing healthcare e.g. use of private or insurance based models	33	33	(71, 82, 85-90, 94, 104, 106-108, 116, 117, 119, 125, 133, 134, 138, 139, 142, 146, 151, 161, 162, 165, 169, 175, 176, 189, 190, 192)
Participation in social and community networks or family structure including marital status and cohabitation	29	29	(84, 87, 88, 90, 93, 96, 97, 114, 115, 118, 119, 122, 125, 126, 130, 140-142, 147, 149, 152, 155, 165, 169, 181, 182, 189, 191, 193)

The majority of studies reported the age (99%) and sex (97%) of study participants. The reporting of other characteristics was observed to have more variation, for example, 73% of studies included information about socioeconomic status, but only 32% and 26% of studies reported information about health-behaviours or ethnicity respectively. Only one study explicitly used a theoretical framework to guide the choice of social and demographic characteristics collected about the study population (104).

2.4 Discussion

2.4.1 Key findings

This systematic review presents an extensive overview of how the existing evidence base for MLTC at a population-level relates to the study of MLTC in pregnancy. Several methodological issues and key knowledge gaps were identified which limit the utility and transferability of the existing literature to understanding and researching MLTC in pregnancy. Four principles have been identified and presented to guide the choice of the definition and operationalisation of MLTC in future research involving pregnant populations.

2.4.2 Summary of narrative synthesis in relation to review objective

The first part of this review explored the methodological processes employed by study teams to define MLTC and to select the individual health conditions included in its operationalisation. The majority of studies (97%) considered MLTC to be the presence of two or more conditions in one individual, which is consistent with both UK clinical guidance (73),

and the recommendations around MLTC research published by NIHR and the Academy of Medical Sciences (22, 72). A further 14% of these studies attempted to define 'complex MLTC' or 'severity' of MLTC with the population identified as having MLTC by using higher order counts of individual conditions. There is no compelling reason why a similar approach to defining MLTC should not be used for research into MLTC in pregnancy.

Just over half of studies reviewed (57%) either did not describe their chosen methodology for operationalising MLTC, or were secondary analyses of survey data and so were limited to the health conditions included in the survey. The extent to which these studies considered the specific health needs pregnant populations in constructing their definition and operationalisation of MLTC is not clear. A further 27% of studies reviewed based their operationalisation on recommendations from systematic reviews or on the individual conditions chosen by previous MLTC studies. While appraisal of the literature is an integral and necessary part of study design, the most cited systematic review used was based on studies exclusively conducted in adults aged 50 years and over (92) and the most commonly cited study did not contain any gynaecological health conditions (10). This potentially limits the applicability of the recommended conditions to adults in younger age groups and women of reproductive age, and represents an important source of bias when considering MLTC and pregnancy.

While the replication of lists of health conditions that have been used in other studies has the potential advantage of facilitating comparison between studies, careful consideration is required to ensure the study population is suitably similar to the index population for which the list was created. None of the studies reviewed explicitly discussed this contention, and

notably none of the studies included in this review were specifically investigating MLTC in pregnant populations or women of reproductive age. The replication of operationalisations that have been used in previous research also has the disadvantage of perpetuating the exclusion of certain health conditions within the study of MLTC. A clear example of this is observed when comparing the representation of conditions included within different morbidity categories. The morbidity category of Cardiovascular contained a large range of health conditions that were frequently chosen for inclusion in the operationalisation of MLTC across all studies. Other morbidity categories contained fewer conditions overall and these conditions were less frequently chosen for inclusion in the operationalisation of MLTC across all studies. It is plausible that some health conditions that are likely to be relevant to women's health or pregnancy outcome may not be well represented or included in previous population based MLTC research. For the aforementioned reasons, the use of a pre-existing operationalisation of MLTC is unlikely to be a suitable methodological choice for MLTC research in pregnant populations.

The remainder of studies reviewed (17%) based their operationalisations of MLTC on estimates of disease prevalence, assessment of clinical importance or on recommendations made within strategic frameworks, local policy or public health guidance. The benefit of this approach is that the operationalisations of MLTC used in these studies are likely to be the most meaningful to the population being studied. While these operationalisations are not necessarily suitable for direct use in pregnant populations, adopting the principle of selecting conditions based on bespoke information about the intended study population should result in the operationalisation of MLTC being both relevant and transferable to clinical practice.

The second part of this review explored the different types and representation of health conditions in the operationalisation of MLTC. Several conditions such as Asthma, Diabetes, Depression, Anxiety and Hypertension were observed to be commonly included in operationalisations of MLTC. These conditions would be expected to be prevalent in women of reproductive age, and should therefore be included the operationalisation of MLTC in pregnant populations. Other conditions that were commonly included in operationalisations such as cardiovascular diseases (e.g. stroke and coronary heart disease) would be expected to have a lower prevalence in women of reproductive age. These conditions, however, have been shown to be important conditions in relation to severe maternal morbidity and maternal mortality and should be considered for inclusion in the operationalisation of MLTC in pregnancy (27, 29, 195, 196). The inclusion of other commonly used conditions such as dementia, osteoporosis, osteoarthritis and chronic obstructive pulmonary disease may be of limited utility in MLTC studies in pregnant populations due to the anticipated low prevalence in women of reproductive age and lack of evidence of association with adverse pregnancy outcomes.

It was also observed that certain types of health conditions such as gynaecological conditions, endocrine conditions, infective conditions, rheumatological conditions and conditions causing pain and fatigue were not commonly included in the operationalisation of MLTC in existing studies. These types of conditions are highly likely to contribute to the burden of morbidity among women of reproductive age (197-202), and may adversely impact pregnancy outcomes (203, 204). The inconsistent and low representation of these conditions in previous MLTC research limits the generalisability of these studies to women of

reproductive age and pregnant populations. The omission of these types of health conditions additionally highlights the concern that the burden of morbidity among women of reproductive age has not been fully appraised in existing MLTC studies.

The use of conditions aggregation, condition overlap and indeterminate conditions was also a commonly observed feature of the studies include in this review. The use of these particular approaches to managing the operationalisation of MLTC poses important methodological considerations for pregnancy research. Regarding indeterminate conditions, it is possible that a large number of different health conditions have been included within the single indeterminate condition. It is difficult to fully evaluate the extent to which the health conditions that have been captured within single indeterminate conditions are relevant to pregnant populations overall, or the outcomes under investigation in the subsequent studies presented in this thesis. The use of condition overlap and condition aggregation is particularly problematic in instances with individual health conditions do not share common biological pathways, risk factors or outcomes. This is pertinent in pregnancy and the postnatal period, where it is well established that individual health conditions can have markedly different clinical trajectories and risk profiles. The use of condition overlap and condition aggregation should be avoided in MLTC research in pregnant populations due to the limitations it would place on the interpretation of any observed associations between MLTC and maternal and perinatal outcomes of interest.

The third part of this review explored what information relating to the characteristics of the study populations were reported within included studies. Overall, a wide variety of characteristics were reported, many of which are likely to be relevant to pregnancy

outcomes (24). Disparities were observed, however, with regard to some key participant characteristics know to be associated with adverse maternal and perinatal outcomes and wider health inequalities (27, 34, 205-208). While almost all studies reviewed reported the age of participants (99%), just under three quarters (73%) reported a measure of socioeconomic status for participants, and less than one third (26%) reported the ethnicity of participants. Similarly, with regard to the reporting of participant characteristics such as smoking status or BMI only 32% of studies reviewed included at least one of these variables. The inconsistencies observed with regard to the reporting of these particular characteristics limits the extent to which the existing literature is transferable to understanding MLTC in pregnant populations. Another notable observation was that the explicit use of conceptual frameworks to identify relevant participant characteristic variables and to account for them in subsequent analyses was limited. It is becoming increasingly well recognised that inequalities in health outcome and health status are strongly linked to wider determinants of health (209, 210). In particular for pregnancy, wider determinants that contribute to deprivation, structural and cultural biases or social complexity and vulnerability are likely to be important to fully understanding maternal and perinatal outcomes for women with MLTC (28).

2.4.3 Strengths and limitations

The strengths of this systematic review are as follows:

1. This study has used narrative synthesis to review and synthesise the methodological choices used by multiple population-based prevalence studies of MLTC. This approach has allowed the literature to be uniquely considered from the perspective of pregnancy

research, highlighting key knowledge gaps and relevant methodological issues. The final output of this review is a pragmatic list of key principles presented in section 2.4.4 to guide the choice of definition and operationalisation of MLTC in future epidemiological research involving pregnant populations.

2. The search strategy for this systematic review was co-designed with a librarian and multiple iterations of the strategy were tested to ensure the appropriate balance between sensitivity and specificity was achieved prior to the final searches being undertaken in four large bibliographic databases. This approach has ensured that a large number of studies meeting the eligibility criteria have been identified from the searches, and it is unlikely that any relevant literature within the bibliographic databases has been overlooked. Further to this, additional search strategies were employed (e.g. references of systematic reviews and citation searching in web of science) to ensure that all potentially relevant literature was captured. This lends support to the robustness of the findings of the narrative synthesis.
3. The methods for data synthesis used in this systematic review are based on established peer-reviewed guidance and reported in accordance with this. This means that the methodological processes are reproducible, and the relationships between the study-level data presented and the conclusions of the narrative synthesis are transparent.

The limitations of this systematic review are as follows:

1. This study focuses on appraising the literature for existing population-based prevalence studies of MLTC. This was a pragmatic choice, as it was reasoned that a necessary part of the methodology of these studies would be to define and operationalise MLTC. As a result, the studies included in this review are exclusively

either cross-sectional or cohort studies published in peer-reviewed English language journals. Studies that have employed other research designs or methods, those published in languages other than English or those published in grey literature may have defined and operationalised MLTC in different ways to the studies included in this review. There is a possibility that the inclusion of these other sources of literature in this review may have led to different conclusions being drawn from the synthesis.

2. The literature searches for this review were undertaken once in 2020 and again in 2022 immediately prior to finalising the health conditions to be included in the epidemiology of MLTC in pregnancy study presented in chapter 4. The identification of additional studies in the 2022 searches did not materially alter the findings of the synthesis overall. The searches were not repeated again as the purpose of this review was to inform the design of the studies presented in the subsequent chapters of this thesis, rather than to summate all the published literature on MLTC in women of reproductive age to date. It is possible that since the last search was undertaken, new literature has been published that would have altered the findings of this synthesis. In particular, one study of the epidemiology of MLTC in pregnancy has been published since the last searches were undertaken and would have met the inclusion criteria for this review (211). Notably, however the health conditions used to operationalise MLTC in this study demonstrated features of condition overlap and condition aggregation. Additionally a number of health conditions were included which were identified by this review as being of limited utility to understating MLTC in pregnancy due having a low prevalence in women of reproductive age or not being known to be associated with adverse maternal and perinatal outcomes. Therefore,

while the study presented by Lee et al. is highly relevant due to it being conducted in a pregnant population, the operationalisation of MLTC used in this study would not have been found to be suitable for the work undertaken for this thesis.

3. This study was only able to consider papers published in the English language, and for pragmatic reasons related to the timeline of the thesis only included published literature. It is possible that the inclusion of grey literature and of studies published in languages other than English may have uncovered different conceptualisations of MLTC potentially altering the overall findings of the narrative synthesis.

2.4.4 Conclusion

It was not possible to identify a pre-existing definition and operationalisation of MLTC from the literature that would be entirely suitable for MLTC research in pregnancy. Based on the findings of this systematic review and narrative synthesis, the following principles should be used to guide the choice of definition and operationalisation of MLTC in future epidemiological research involving pregnant populations:

1. The definition of MLTC should be based on the presence of two or more discrete health conditions within one individual. This is the most common way to define MLTC in population-based prevalence studies and is also consistent with key clinical guidance.
2. The health conditions included in the operationalisation of MLTC should be chosen based on an association with adverse maternal and perinatal outcomes, and/or prevalent among women of reproductive age, and/or specific to women's health or the longer-term health of women.

3. The health conditions included in the operationalisation of MLTC should be well-defined in order to avoid indeterminate conditions, condition overlap and aggregation of conditions.
4. Information collected about the characteristics of the study population should be important to maternal and perinatal outcomes, and where possible also inclusive of the wider determinants of health that are relevant to pregnancy outcome.

Chapter 3: Data and data management

3.1 Introduction and research objectives

It is increasingly common to use routinely collected data in health research, as it offers a time and cost-effective approach to the creation of large study cohorts (51). These data are however, generally not collected for research purposes, and consequently require significant cleaning and curation before it is possible to use them to answer research questions. This chapter presents an overview of the data sources, the methods used to define and operationalise MLTC, and the approach taken to generating variables for the exposure and outcomes under investigation and the social and demographic characteristics of the study population. The statistical methods used in the analyses of the component studies are described within each separate chapter. This chapter also presents and evaluates the methodological choices made during the derivation of the final study populations from within the datasets.

This chapter addresses research objective 2 of this thesis:
To describe and evaluate the methodological approach and decisions taken to construct a pregnancy cohort from the CPRD pregnancy register and Hospital Episode Statistics Admitted Patient Care (HES APC) dataset with data of suitable quality for undertaking research.

3.2 Data sources and permission for use

3.2.1 Background to the Clinical Practice Research Datalink

The Clinical Practice Research Datalink (CPRD) is a dynamic longitudinal database composed from anonymised electronic health records (EHRs) collected from a network of contributing general practices in the UK (212). CPRD is comprised of two different datasets, CPRD Aurum which contains data contributed by general practices using EMIS software, and CPRD GOLD which contains data contributed by general practices using Vision software. The main dataset used for this research is CPRD GOLD, as at the time of planning this study this was the only dataset which provided a Pregnancy Register. CPRD GOLD includes data for 21 million patients, approximately 3 million of whom are currently registered at a contributing practice in 2022 representing 4.6% of the UK population at the time of data extraction. Previous studies examining the population coverage of CPRD have reported that it is broadly representative of the UK population with respect to age, sex and ethnicity (213, 214). CPRD has previously been used to study a wide range of both acute and longer-term health conditions, including MLTC in the general population (3, 9).

3.2.2 Structure of CPRD GOLD

The CPRD GOLD dataset is comprised of 10 separate data files which contain a wide range of information relating to patient demographics, clinical care processes, prescription records and characteristics of the general practice where the patient is registered for care (215). The structure of CPRD GOLD is shown in Figure 3.1. All patients registered at a practice in CPRD are assigned a unique encrypted patient identifier which allows information in the separate

files within CPRD GOLD relating to the same patient registration to be joined together. The unique encrypted patient identifier also allows the patients within CPRD GOLD to be linked to additional data such as hospitalisations or area deprivation statistics.

Figure 3.1. Schematic representation of structure of CPRD GOLD and associated linked datasets used in the component studies

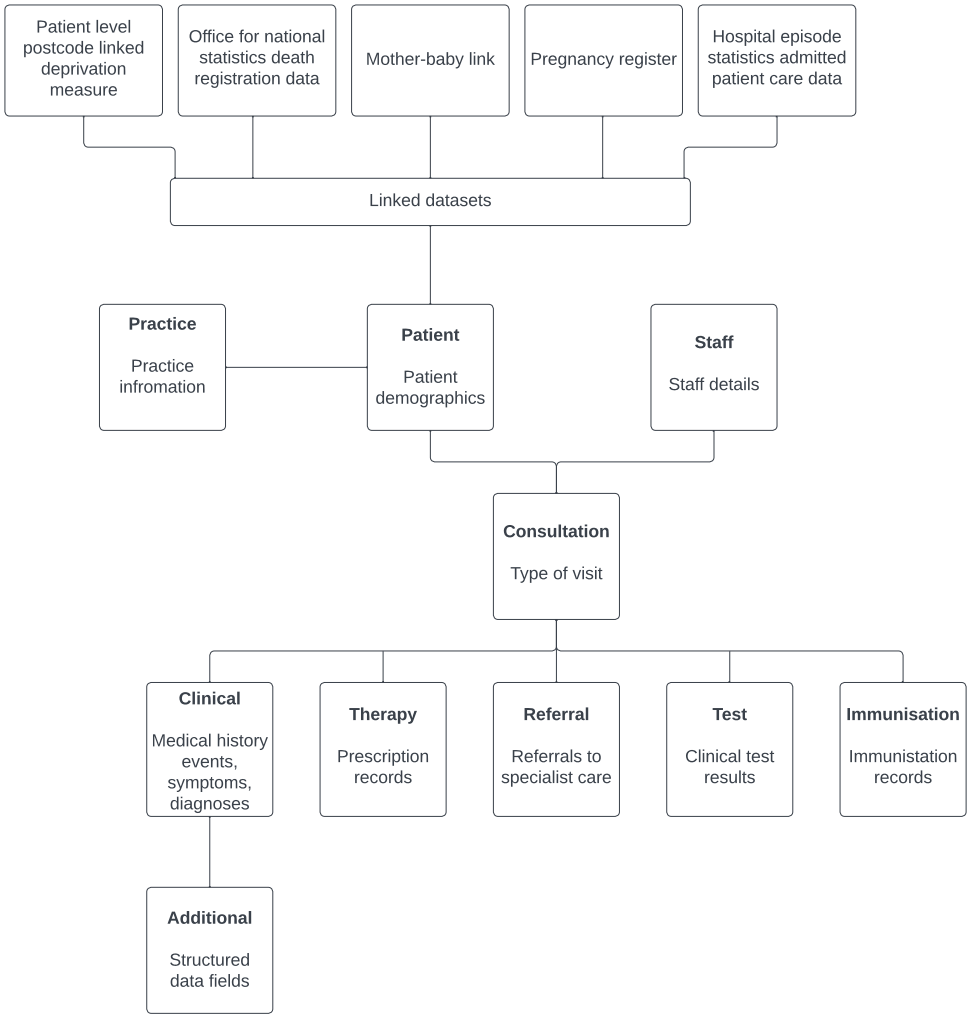


Figure 3.1. adapted from Herrett et al.(212)

3.2.3 Linked data

CPRD can be linked to several other health and area-based datasets which further enhances its utility for health-related research. This linkage is performed by NHS Digital (NHS-E or CPRD as appropriate) prior to the datasets being released to the researcher. The linked data sources used for this research are shown in Figure 3.1 and described below.

1. CPRD Pregnancy Register

The CPRD Pregnancy Register is a dataset generated by CPRD using a bespoke algorithm that identifies pregnancy episodes based on information recorded within the CPRD GOLD dataset (63, 216). Each woman in the pregnancy register can have multiple pregnancy episodes, and each pregnancy episode has its own unique identifier. Information relating to the pregnancy episode is stored as separate fields in a single line of data. This information includes derived dates for pregnancy trimesters, the outcome of the pregnancy episode, maternal age at the time of birth and whether there are linked primary care records to a baby born at the end of the pregnancy episode.

2. CPRD Mother-baby link

The CPRD Mother-Baby link is a dataset generated by CPRD using a bespoke algorithm that identifies mother-baby pairs based on information in the maternal clinical record and the CPRD practice-specific family number (217). Information contained within the mother-baby link can be used to identify relevant CPRD Gold primary care records relating to babies born to women in the pregnancy register and to link babies to Office for National Statistics (ONS) death registration data (218).

3. Hospital Episode Statistics Admitted Patient Care

The Hospital Episode Statistics Admitted Patient Care dataset (HES APC) is derived from administrative data recorded in English NHS hospitals relating to hospital admissions to secondary care (219).The dataset contains demographic information, dates of admission and discharge, and codes relating to diagnoses made and procedures undertaken during the admission episode. It also contains information specifically relating to any periods of critical care provided during an admission episode, and information relating to maternity care if the hospital admission is associated with the delivery of a baby. The coding system used within HES APC is different to the coding system used within CPRD. Within HES APC diagnoses of health conditions are coded using ICD-10 codes and procedures and operations performed during hospital admissions are coded using OPCS-4 codes.

4. Patient postcode linked deprivation measures

The Index of Multiple Deprivation (IMD) is a commonly used relative measure of socioeconomic deprivation. The IMD is a composite score derived from seven domains indicating different elements of material deprivation such as employment status or barriers to housing and services. It is based on the 2019 English Indices of Deprivation which are calculated based on regional areas defined by the lower layer super output (LSOA) level. In CPRD two levels of IMD are available; patient (based on the patient's postcode) or practice (based on the practice's postcode) (220). For the studies presented in this thesis, patient level IMD was used, and was available for patients registered at English practices that had consented to linkage.

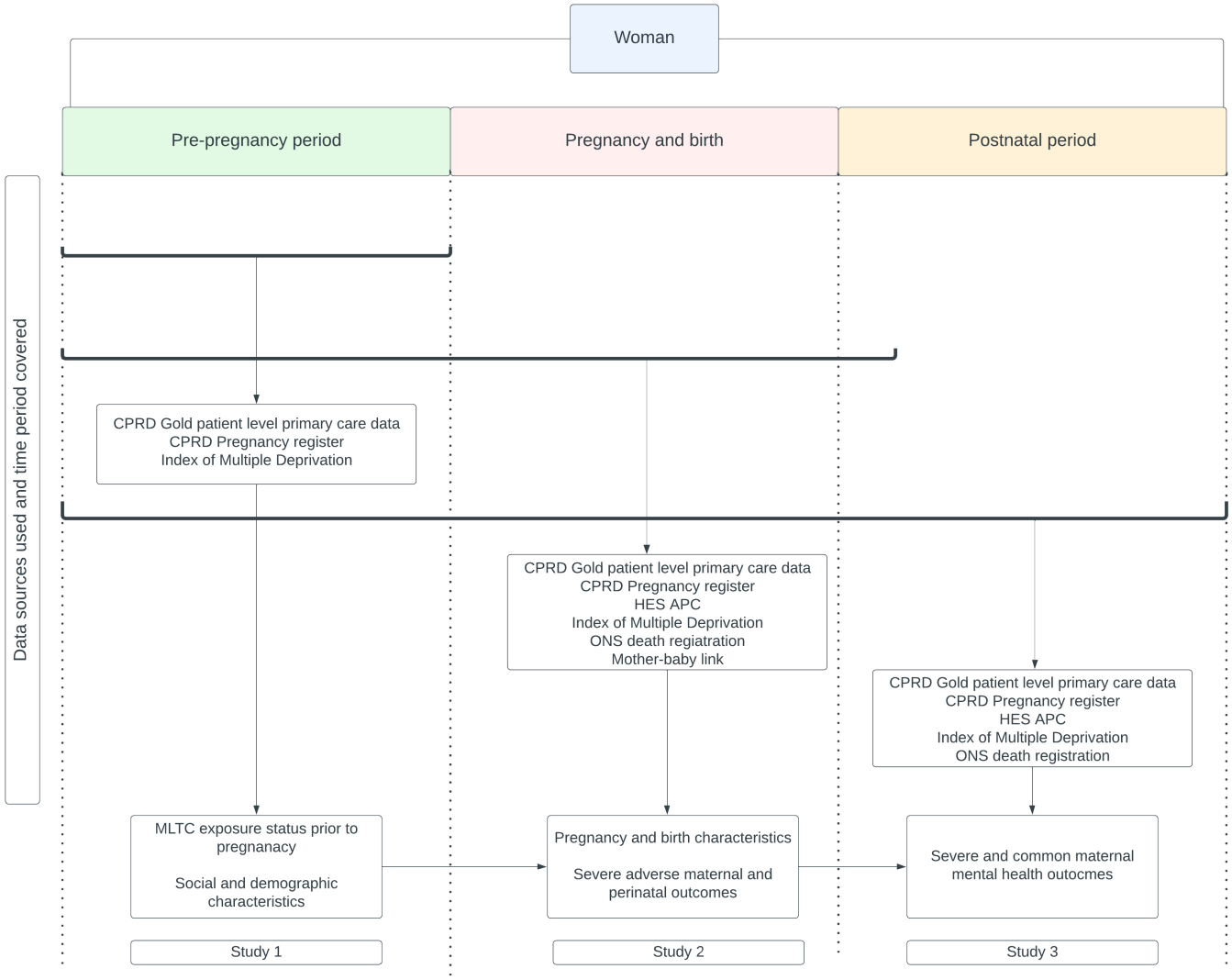
5 Office for National Statistics (ONS) death registration data

The certification and registration of death is a legal requirement in the UK. Information taken from death registration such as the date of death and cause of death is collated by the ONS for England and Wales. Linkage between ONS death registration data and CPRD GOLD is available from 1998 onwards for patients who are registered at English practices that have consented to linkage (218).

3.2.4 Use of data within component studies

The findings of three component studies to this thesis are presented in chapters 4, 5 and 6. For each woman included in the study information relating to three separate time periods (preconception, pregnancy and birth, and postnatal) was collected using the data sources described above. The schematic diagram presented in Figure 3.2 illustrates which data sources and the relevant time frames that were used to enable the three component studies of this thesis to be carried out.

Figure 3.2. Schematic representation of the time frames and data sources contributing to each component study in this thesis



3.2.5 Permission for data use

The use of the CPRD GOLD dataset and linkage to the datasets detailed above for the component studies in this thesis was approved by the CRPD Independent Scientific Advisory Panel (ISAC) on the 25th of March 2020 (ISAC protocol number 20_047A). Overarching ethics approval for the use of CPRD data in research is provided by the Health Research Authority (HRA) (221). The CPRD GOLD primary care data was extracted for use by the Nuffield Department of Population Health CPRD fob-holder on the 17th of May 2022 using the CPRD Gold January 2022 dataset. Patient data eligible for this extraction was identified by CPRD based on women within the pregnancy register with a pregnancy start date within the study period. The linked datasets (Pregnancy register, Mother baby link, HES APC, IMD, ONS deaths) were provided by CPRD on the 9th of June 2022 using the most up-to-date linkage datasets available at the time the request for linked data was submitted (linkage set 22/CPRD Gold January 22 dataset).

3.3 Exposure under investigation

3.3.1 Definition of MLTC

The main exposure of interest was MLTC which was defined as the woman having any combination of two or more physical health, mental health or chronic infectious conditions prior to the start of the pregnancy. As shown in chapter 2, this definition was the most common way to define MLTC in previous population-based prevalence studies and is also consistent with key clinical and research guidance (22, 72, 73). In addition to this, MLTC was also conceptualised according to type and complexity. Women with two or more physical

health conditions were considered to have physical health MLTC, women with two or more mental health conditions were considered to have mental health MLTC, and women with at least one physical and one mental health condition were considered to have mixed MLTC. Women who had three or more health conditions prior to the start of pregnancy were considered to have complex MLTC. For ease of reference, these definitions are shown in Table 3.1.

Table 3.1. Definitions of MLTC used in all subsequent analyses

MTLC	any combination of two or more physical health, mental health or chronic infectious conditions prior to the start of the pregnancy
Physical health MTLC	two or more physical health conditions prior to the start of the pregnancy
Mental health MTLC	two or more mental health conditions prior to the start of the pregnancy
Mixed MTLC	at least one physical and one mental health condition prior to the start of the pregnancy
Complex MTLC	three or more health conditions prior to the start of pregnancy

3.3.2 Use of CPRD to study pre-existing health conditions

In the CPRD dataset, whenever a patient receives healthcare from a professional working in primary care, the details of that consultation are recorded in the patient's clinical record using a using a defined thesaurus of clinical terms and descriptors (read terms) which are uniquely coded (read codes, stored within CPRD as medical codes). In addition to this any medication prescribed within primary care is recorded using a unique coding system

(product codes), and physiological parameters such as blood pressure readings or test results are stored within a bespoke structured data field (entity type data). Information within the clinical record can also be supplemented to include details of diagnoses and procedures from secondary care (via the HES APC data), and relevant past medical history from before the patient was registered at the practice (from clinical records transferred between practices). It is therefore possible to search the CPRD dataset for a pre-defined list of relevant medical codes, product codes or entity type data to identify health conditions of interest. All information in the clinical record is given an 'event date' which is date associated with the clinical event e.g. a diagnosis of diabetes, as recorded by the clinician. This makes it possible for the timings of different health-related events to be mapped across the patient's clinical record.

3.3.3 Selection of health conditions of interest (operationalisation of MLTC)

As reported following the systematic review presented in chapter 2, it was not possible to identify a pre-existing list of health conditions that was suitable for use to study MLTC in pregnancy. For this reason a bespoke list was created. A multi-professional advisory panel consisting of obstetricians, obstetric physicians, anaesthetists, midwives, general practitioners, a representative from the charity Birth Companions and researchers with expertise in CPRD was convened. The purpose of this group was to provide guidance as to which health conditions should be included in this study, and this approach was chosen in order to support the construction of a list that is both clinically meaningful and suitable for use with CPRD.

A structured review of guidelines relevant to pregnancy, MBRRACE-UK reports and UKOSS studies was undertaken to identify a long-list of pre-existing health conditions that were relevant to pregnancy outcome. Conditions thought to be important causes of morbidity among women of reproductive age or important to the longer-term health of women were also identified. Members of the advisory panel met on the 18th January 2021 and were asked to review the long list. Health conditions that were suitable for inclusion were required to be:

1. Known to impact maternal and perinatal outcomes, and/or prevalent among women of reproductive age, and/or specific to women's health or the longer-term health of women.
2. Possible to study using primary care data (excluded conditions that were very rare, or where the diagnosis and management was exclusively undertaken in secondary care).

The advisory panel were also asked to comment on how conditions should be organised, how the severity of the condition could be determined, and whether any conditions should be considered for inclusion that were not on the long-list. Following the advisory panel meeting, a total of 53 discrete health conditions were identified as being relevant to MLTC in pregnancy and suitable for investigation using CPRD. These were grouped into appropriate categories based on a body-systems classification approach and are shown in Figure 3.3. Health conditions that were considered important, but for which it was not possible to use CPRD to accurately study the condition are also listed.

Figure 3.3. Schematic representation of individual health conditions included in the study, and those conditions identified as important but not suitable for inclusion

3.3.4 Construction of code lists for chosen health conditions

Previously published studies that have used CPRD, alongside code list repositories maintained by the University of Manchester (222), University of Keele (223) and London School of Hygiene and Tropical Medicine (224) were searched to identify whether code lists for the chosen health conditions existed. If a pre-existing code list was identified, the validity of the code list was assessed. Code lists were only considered for use in this study if they were externally validated through comparison with patient health records, or clinically validated through the input of a general practitioner in the creation of the code list. If multiple pre-existing code lists were identified for the same condition, a judgement was made as to which code list was most appropriate for use when considering the definition of the condition under investigation. If potentially relevant codes were identified through the comparison of multiple code lists, but not present on the final chosen code list, then these codes were added in to augment the code list following discussion with a general practitioner. Additionally, the CPRD GOLD Code Browser tool was used to undertake a key word search of the CPRD GOLD Medical Dictionary to identify any relevant new codes that may have been added to the CPRD GOLD Medical Dictionary since the creation of the code list. If no suitable pre-existing code lists were identified, then code lists were created de novo based on the approach described by Watson et al (225). The creation of new code lists was done collaboratively with two general practitioners (SH and BMG).

The provenance of the final code lists used in this study are detailed in appendix B (Table B1). If code lists were created de novo for use in this work, the constituent medical codes,

product codes, product names, read code and read terms used to identify those health conditions in the data set are included in appendix B (Table B2).

3.3.5 Determination of exposure status for individual health conditions

For each included health condition, a pre-defined set of rules was constructed to govern how evidence in the clinical record and temporal parameters should be used in order to determine whether the woman was deemed to have the health condition prior to the start of the pregnancy. These rules were defined through consultation with the advisory panel and through careful consideration of what is currently known about the natural progression of the health condition and its impact on maternal and perinatal outcomes. Overall the exposure status of any given health condition was based on either the health condition being active in the preconception period (12 months prior to the start of pregnancy), or the woman ever having been diagnosed with the health condition. The rationale for how each included health condition was assigned an exposure status is included in appendix B (Table B1). Generally conditions that were required to be active in the preconception period were those that were either treatable with lifestyle modifications, those where mild disease would not be expected to impact on pregnancy outcomes, or those associated with periods of disease quiescence. Examples of these conditions include asthma, migraine and hypertension. Conditions where exposure status was based on the woman ever having been diagnosed were those that were considered to require lifelong management or treatment, those where risk to pregnancy outcome is elevated irrespective of disease activity status, or those where the condition was expected to cause persistent challenges to the individual throughout their lifetime. Examples of these conditions include congenital structural heart disease, inflammatory bowel disease

and diabetes. The estimated start date of each pregnancy was used as the time-point against which the exposure status was measured.

Within the list of health conditions under investigation, there are a number of conditions that have the potential to overlap with another health condition on the list. This occurs because one health condition represents a severe form or progression of an index health condition, or because two separate health conditions share common symptoms or clinical presentations. It is important to ensure that health conditions that overlap are not counted as separate conditions, which would lead to an over-estimation in the prevalence of MLTC. To address this, all health conditions that have the potential to overlap were identified and pre-defined set of rules was constructed to govern the management of this. A Table detailing how the exposure status for each health condition was defined, and the specific rules used to manage condition overlap are included in appendix B (Table B3).

The primary purpose of information recoded within EHRs, such as those from which CPRD is constructed, is to facilitate patient care rather than to collect data for research purposes. The existence of both diagnostic and symptom codes within the read code framework provides necessary flexibility for clinicians to document clinical encounters in a way that is meaningful and accurate. This does however mean that there is limited standardisation of the ways in which information about diagnoses are recorded within the dataset. In this work, diagnostic codes were considered more reliable indicators of health status than symptom codes, which are often imprecise or could be used to describe multiple different conditions. For this reason symptom codes were for the most part excluded from the code lists used. This should improve the specificity of the code lists in identifying the health

conditions of interest and adds assurance to the identification of true cases. This approach does, however, make the assumption that the absence of a medical or product code recorded within the woman's EHR equates to her not having that condition. It is not possible to identify individuals for whom information about their health condition has been recorded without using diagnostic codes. It is also not possible to identify individuals for whom information about their health condition has been recoded in other formats within the EHR e.g. as free text notes or clinical letters from secondary care that are not coded within the primary care records. This caveat around the use of code lists to identify event data within the EHRs also applies to the ascertainment of outcome events described in the following sections.

3.4 Outcomes under investigation

3.4.1 Severe adverse maternal and perinatal outcomes

The outcomes included in the study investigating the association between MLTC and severe adverse maternal and perinatal outcomes presented in chapter 5 were maternal death, severe maternal morbidity, stillbirth and neonatal death. A description of these outcomes including how the variables were constructed from the dataset is detailed in Table 3.2.

Table 3.2. Description of variable and its construction and use for severe adverse maternal and perinatal outcomes

Severe adverse maternal and perinatal outcome variables	Description of variable and use	Construction of variable
Maternal death	Definition: **The death of a woman during pregnancy or up to one year after the end of pregnancy** Variable use: A case of maternal death was considered to have occurred if the recorded death date was between the start date of pregnancy and up to 42 days after the end of pregnancy (early maternal death) or between 42 days and up to one year after the end of pregnancy (late maternal death).	Women who had died were identified from the date of death field in the CPRD patient file. Additional cases were ascertained through ONS death registration data for women who were eligible for linkage to this dataset. If a woman had a date of death recorded in CPRD and a date of death recorded in the ONS dataset, the ONS date was used as this was found to be the more accurate record in a validation study by Gallagher et al. (226).
Severe maternal morbidity	Definition: **A life-threatening event occurring during pregnancy or up to 42 days after the end of pregnancy.** Variable use: Women were considered to have experienced an event consistent with severe maternal morbidity if they had any relevant ICD-10 or OPCS-4 code recorded in the HES APC diagnostic or procedure file between the start of the pregnancy and up to 42 days after the end of the pregnancy.	A composite indicator for severe maternal morbidity was constructed based on the English Maternal Morbidity Outcome Indicator (EMMOI) published by Nair et al. (227). The EMMOI uses ICD-10 and OPCS-4 codes to identify events consistent with severe maternal morbidity, and has been validated for use in HES APC. Codes from the EMMOI were reviewed using the OPCS-4 and ICD-10 data dictionaries, and in conjunction with input from the supervisory team. The output of this review is detailed in appendix B (Table B4). Irrelevant or poorly defined codes were excluded and any additional new relevant codes were identified and included. MBRRACE-UK reports were additionally used to identify conditions that represent important causes of morbidity and mortality in the UK that were not included in the original EMMOI, and relevant codes for these conditions were identified from the OPCS-4 and ICD-10 data dictionaries. As the structure and definition of OPCS-4 codes are often changed by NHS digital to reflect updated recommendations for the use of codes by clinical coders, all OPCS-4 codes were tracked across the study period using the Table of coding equivalences and specification published by NHS Digital (228). All codes used to identify cases of severe maternal morbidity are included in appendix B (Table B5).

Table 3.2. (continued) Description of variable and its construction and use for severe adverse maternal and perinatal outcomes

Severe adverse maternal and perinatal outcome variables	Description of variable and use	Construction of variable
Neonatal death	Definition: **The death of a baby born at any time during the pregnancy who lives, even briefly, but dies within four weeks of being born** Variable use: A case of neonatal death was considered to have occurred if the pregnancy ended in a livebirth and the baby's recorded death date was between the end date of the pregnancy and up to 56 days after birth, or the mother had a relevant read code recorded in the clinical record between the end date of the pregnancy and up to 56 days after birth.	Babies who had died were identified from the date of death field in the CPRD patient file within the primary care records of the baby, or through linkage to ONS death registration data. If no primary care records were available for the baby, then medical codes recorded in the mother's primary care records were used to identify cases of neonatal death. Although the definition of neonatal death is a death occurring within 28 days of birth, for the purposes of constructing this variable a 56-day time limit was used. This was to account for small margins of error around the end date of the pregnancy, and delays in recording the date of death in the primary care record. It also accounts for women attending a routine 6-8 week postnatal check where codes relating to neonatal death could feasibly be recorded in the maternal primary care record for the first time. Sensitivity analysis suggested that use of a more conservative time frames (28 days and 42 days) led to plausible cases being missed. All codes used to identify cases of neonatal death are included in appendix B (Table B6).
Stillbirth	Definition: **The death of a baby occurring before or during birth once a pregnancy has reached 24 weeks.** Variable use: A case of stillbirth was considered to have occurred if the birth outcome was recorded as a stillbirth	Birth outcome is coded in both HES APC and CPRD. For 96.31% of pregnancy episodes there was agreement between HES APC and CPRD as to the birth outcome (livebirth or stillbirth). For the remaining 3.69% of pregnancies, the following logic was used to determine the birth outcome: 1. If the outcome was unknown or indeterminate in CPRD, but present in HES APC, then the birth outcome from HES APC was used. 2. If the outcome was missing in HES APC but recorded in CPRD then the birth outcome from CPRD was used. 3. If the outcome information was unknown, indeterminate or missing, or conflicting between both sources, then evidence of record linkage between mother and baby through the mother-baby link was used to determine the outcome. 4. If it was still not possible to determine the birth outcome using the logic above, the birth outcome was coded as missing.

3.4.2 Maternal mental health outcomes

The outcomes included in the study investigating the association between MLTC and severe and common maternal mental health outcomes presented in chapter 6 were acute psychosis, self-harm (including thoughts of self-harm, suicidal ideation and non-fatal suicide attempt) and active common mental health disorders (postnatal depression and/or postnatal anxiety). A description of these outcomes including how the variables were constructed from the dataset is detailed in Table 3.3.

Table 3.3. Description of variable and its construction and use for maternal mental health outcomes

Maternal mental health outcome variables	Description of variable and use	Construction of variable
Severe maternal morbidity: Acute psychosis	Suggested definition: **A disorder characterised by the presence of hallucinations and delusions occurring in the absence of functional or structural pathology** Variable use: Women were considered to have experienced an episode of acute psychosis if at any point between the end of pregnancy and up to one year after giving birth they had a relevant medical code recorded in the clinical record.	Cases of acute psychosis were identified based on the methods described by Hardoon et al. and using the code lists published by Cassell et al. and Olier et al. (3, 229, 230) Additional relevant codes for puerperal psychosis were identified using the CPRD GOLD code browser and included in the final code list.
Severe maternal morbidity: Self-harm or non-fatal suicide attempt, thoughts of self-harm and suicidal ideation	Suggested definition: **Intentional non-fatal self-injury with or without suicidal intent, or thoughts relating to self-harm or suicide.** Variable use: Women were considered to have an episode of self-harm, non-fatal suicide attempt, or thoughts of self-harm or suicidal ideation if at any point between the end of pregnancy and up to one year after giving birth they had a relevant medical code recorded in the clinical record.	Cases of self-harm were identified using the code lists published by Carr et al. and Clements et al.(230, 231). Additional relevant codes for suicidal ideation and thoughts of self-harm were identified using the CPRD GOLD code browser and included in the final code list.
Common mental health disorder: postnatal depression and/or anxiety	Suggested definition: **Common mental health disorders are characterised by low mood or excessive fear or anxiety in the presence of additional core symptoms and not secondary to other causes such as grief, medication or alcohol and drug misuse.** Variable use: Women were considered to have active postnatal depression and/or anxiety if at any point between the end of the pregnancy and up to one year after giving birth they had either a relevant diagnostic code, a relevant symptom code plus a prescription record, or a prescription record plus a past history of a diagnosis of anxiety or depression in the clinical record.	Cases of active postnatal depression and/or anxiety were identified using a triangulation approach that has previously been externally validated in the SAIL databank which contains routinely collected data from Primary Care in Wales (232). A code list published by Tianyi et al. was used (233).

3.5 Covariates of interest

3.5.1 Social and demographic characteristics

The social and demographic covariates included in the three studies presented in chapters 4, 5 and 6 including a description of how the variable was constructed from the dataset is detailed in Table 3.4.

Table 3.4. Description of variable and its construction and use for maternal social and demographic characteristics

Social and demographic characteristic variables	Description of variable and use	Construction of variable
Smoking status	Definition: **The smoking status of the woman prior to the start date of the pregnancy.** Smoking status was categorised as follows: 1. Current smoker 2. Ex-smoker 3. Non-smoker	The smoking status variable was constructed based on the methods described by Arendse et al. using the entity type data for smoking status from the CPRD clinical and additional patient files (234). The most recently documented smoking status within 5 years of the start date of the pregnancy was used to determine the maternal smoking status for that pregnancy.
Maternal age	Definition: **The woman's age at the time of birth.** Maternal age was categorised as follows: 1. 15 to 19 years 2. 20 to 34 years 3. 35 to 39 years 4. 40 to 49 years	The maternal age variable was constructed by categorising the maternal age field in the CPRD pregnancy register.
Ethnicity	Definition: **The ethnic group the woman identifies as belonging to.** Ethnicity was categorised as follows: 1. White or White British 2. Black or Black British 3. Asian or Asian British 4. Mixed 5. Other	The variable for ethnicity was constructed based on the methods described by Mathur et al. and using the code list published by Wright et al. (235, 236). All relevant codes recorded in the CPRD clinical file were identified. If all ethnicity codes were consistent across the woman's primary care record then that ethnic group was used. If a woman had more than one ethnicity recorded, then the most frequently recorded ethnicity was used as the woman's final ethnicity. If the woman had no codes for ethnicity recorded in CPRD, and she was eligible for linkage to HES APC, then the ethnicity recorded in the HES APC patient file was used. The categorisation of ethnicity was consistent with the higher level ethnic groupings used by the Office of National Statistics.
Index of Multiple Deprivation	Definition: **A composite measure of deprivation derived from seven domain indicators based on the woman's postcode**. IMD was categorised according to quintiles of deprivation, with 1 representing the most affluent quintile and 5 representing the most deprived quintile.	Patient level IMD provided as a linked dataset from CPRD for women eligible for linkage (English practices only).

Table 3.4. (continued) Description of variable and its construction and use for maternal social and demographic characteristics

Social and demographic characteristic variables	Description of variable and use	Construction of variable
Body Mass Index	Definition: **The Body Mass Index of the woman prior to the start date of the pregnancy measured in kg/m^2.** BMI was categorised as follows: 1. Underweight = less than 18.5 kg/m^2 2. Healthy weight = 18.5 to 24.9 kg/m^2 3. Overweight = 25 to 29.9 kg/m^2 4. Obese = over 30 kg/m^2	The variable for BMI was constructed based on the methods described by Bhaskaran et al. and Nicholson et al. using the code list published by Nicholson et al. (237, 238). Any recording of an adult height measurement, weight measurement or BMI were identified from the clinical and additional patient files using entity type data for height, weight, and BMI. Height and weight measurements were used to calculate the woman's BMI using the most recently recorded weight within 5 years of the start of the pregnancy. Any weight measurements recorded during a pregnancy and up to 3 months after giving birth were not used as these were judged to not represent a stable measurement of the woman's weight. If the woman did not have a height or weight measurement recorded, but did have a BMI value recorded within 5 years of the start of the pregnancy then this was used. If there was no information recorded for height, weight or BMI as entity type data, then relevant medical codes for BMI were identified from the clinical file, with the most recently recorded read code within 5 years of the start of the pregnancy used.

3.5.2 Pregnancy and birth characteristics

The pregnancy and birth covariates included in the study presented in chapter 5 including a description of how the variable was constructed from the dataset is detailed in Table 3.5.

Table 3.5. Description of variable and its construction and use for pregnancy and birth characteristics

Pregnancy and birth characteristic variables	Description of variable and use	Construction of variable
Anaesthetic intervention at the time of birth	Definition: **The type of anaesthetic used during birth**. Anaesthetic intervention was categorised as follows: 1. No anaesthetic or local anaesthetic only 2. Regional anaesthetic (Epidural or spinal) 3. General anaesthetic	The anaesthetic intervention variable was constructed using the pre-labour, delivery, and post-labour anaesthetic fields in HES APC maternity file. Additionally, OPCS-4 codes for anaesthetic interventions were identified from the HES APC procedure files. A code was considered relevant if it occurred within 7 days wither side of the end date of the pregnancy. If a woman had more than one type of anaesthetic intervention, the one judged to be more likely to cause or be associated with adverse outcomes was used. A general anaesthetic was considered to be associated with a higher risk profile than a regional, and a regional to be associated with a higher risk file than a local anaesthetic. All codes used to identify anaesthetic interventions are included in appendix B (Table B7).
Mode of birth	Definition: **The method by which the baby is delivered.** Mode of birth was categorised as follows: 1. Spontaneous vaginal birth 2. Assisted vaginal birth including breech vaginal birth 3. Emergency caesarean birth 4. Elective caesarean birth	The mode of birth variable was constructed by collapsing the method of delivery field in the HES APC maternity file.
Small for gestational age (SGA) and extremely small for gestational age (eSGA)	Definition: **A baby born with a birth weight less that the 10th centile (small for gestational age) or less than the 3rd centile (extremely small for gestational age) based on the sex of the baby and the gestation at birth.**	The small and extremely small for gestational age variable was constructed using the birthweight and sex of baby fields in the HES APC maternity file. The UK-WHO neonatal and infant close monitoring growth charts were used to identify birthweight thresholds consistent with small and extremely small for gestational age based on the sex and gestation of the baby at birth (239).

Table 3.5. (continued) Description of variable and its construction and use for pregnancy and birth characteristics

Pregnancy and birth characteristic variables	Description of variable and use	Construction of variable
Obstetric condition in current pregnancy	Definition: **The diagnosis of any one or more of anaemia, gestational hypertension, pre-eclampsia, obstetric cholestasis or gestational diabetes in the current pregnancy**.	Code lists for gestational hypertension, pre-eclampsia, obstetric cholestasis and gestational diabetes were created using the CPRD GOLD code browser and the ICD-10 data dictionary. A woman was considered to have a diagnosis of an obstetric condition in the current pregnancy if there was a relevant code in the CPRD clinical file (medical code) or HES APC diagnoses file (ICD-10 code) between 20+0 weeks gestation and up to two weeks after the end date of the pregnancy. This timeframe was chosen to allow for information communicated to the GP from secondary care following the birth of the baby e.g. through a discharge summary, to be recorded in the mother's clinical record. Additionally, records of haemoglobin concentration were identified from entity type data for full blood count measurement in the clinical and additional patient files. A haemoglobin measurement of less than 105g/L in the second or third trimester of pregnancy was considered consistent with a diagnosis of antenatal anaemia (240). All codes used to identify obstetric conditions in the current pregnancy are included in appendix B (Table B7).
Gestation at delivery	Definition: **The gestational length of the pregnancy at the time of birth.** Gestation at delivery was categorised as follows: 1. Birth at 37+0 weeks gestation and above was considered term. 2. Birth at 36+6 weeks gestation and below was considered preterm	The start and end dates of the pregnancy episode recorded in the CPRD pregnancy register were used to calculate the gestational length of the pregnancy at the time of birth.
Maternal admission to critical care	**Definition: Admission to adult critical care (high dependency or intensive care) due to a requirement for more detailed observation, intervention or organ support that could not be provided through ordinary ward care (241)**	The maternal admission to critical care variable was constructed from information about augmented periods of care within the HES APC critical care file. Episodes of critical care were counted if the episode start date occurred at any point during the pregnancy or up to 42 days after the end of the pregnancy.
Gestational age at booking	Definition: **The gestational age of the pregnancy at the time of the first antenatal appointment with a midwife**. Gestational age at booking was categorised as follows: 1. First antenatal assessment <10+0 weeks gestation 2. First antenatal assessment ≥ 10+0 weeks gestation	The gestational age at booking variable was constructed from the gestation at first antenatal assessment field in the HES APC maternity file. If the first antenatal assessment occurred at >10+0 weeks gestation, then this was considered 'late booking' in accordance with NICE guidance on the provision of antenatal care (46).

Table 3.5. (continued) Description of variable and its construction and use for pregnancy and birth characteristics

Pregnancy and birth characteristic variables	Description of variable and use	Construction of variable
Onset labour method	Definition: **The method by which the process of labour begins.** Onset of labour method was categorised as follows: 1. Spontaneous onset labour 2. Induction of labour (surgical or medical)	The onset of labour method variable was constructed using the method to initiate labour field in the HES APC maternity file. If the mode of birth was recorded as elective caesarean section, then the onset of labour method variable was not used.
Parity and previous caesarean section	Definition: **Parity was considered as the number of times a woman had given birth to a baby at greater than 24+0 completed weeks gestation irrespective of the outcome of the pregnancy.** Categories of parity: 1. Nulliparous (No previous births at >=24+0) 2. Multiparous (One or more previous births at >=24+0)	All pregnancies over 24+0 completed weeks gestation within the pregnancy register were identified. A look-back approach was utilised to ascertain if the women had any previous pregnancies prior to any pregnancy included in the study. Among multiparous women, any record of a previous caesarean birth was identified using information on mode of birth recorded in HES APC maternity file.

3.6 Derivation of the study population for chapter 4

3.6.1 Study population

A total of 422,091 pregnancies to 331,517 women were included in the study investigating the epidemiology of MLTC in pregnancy presented in chapter 4. The study population consists of women who:

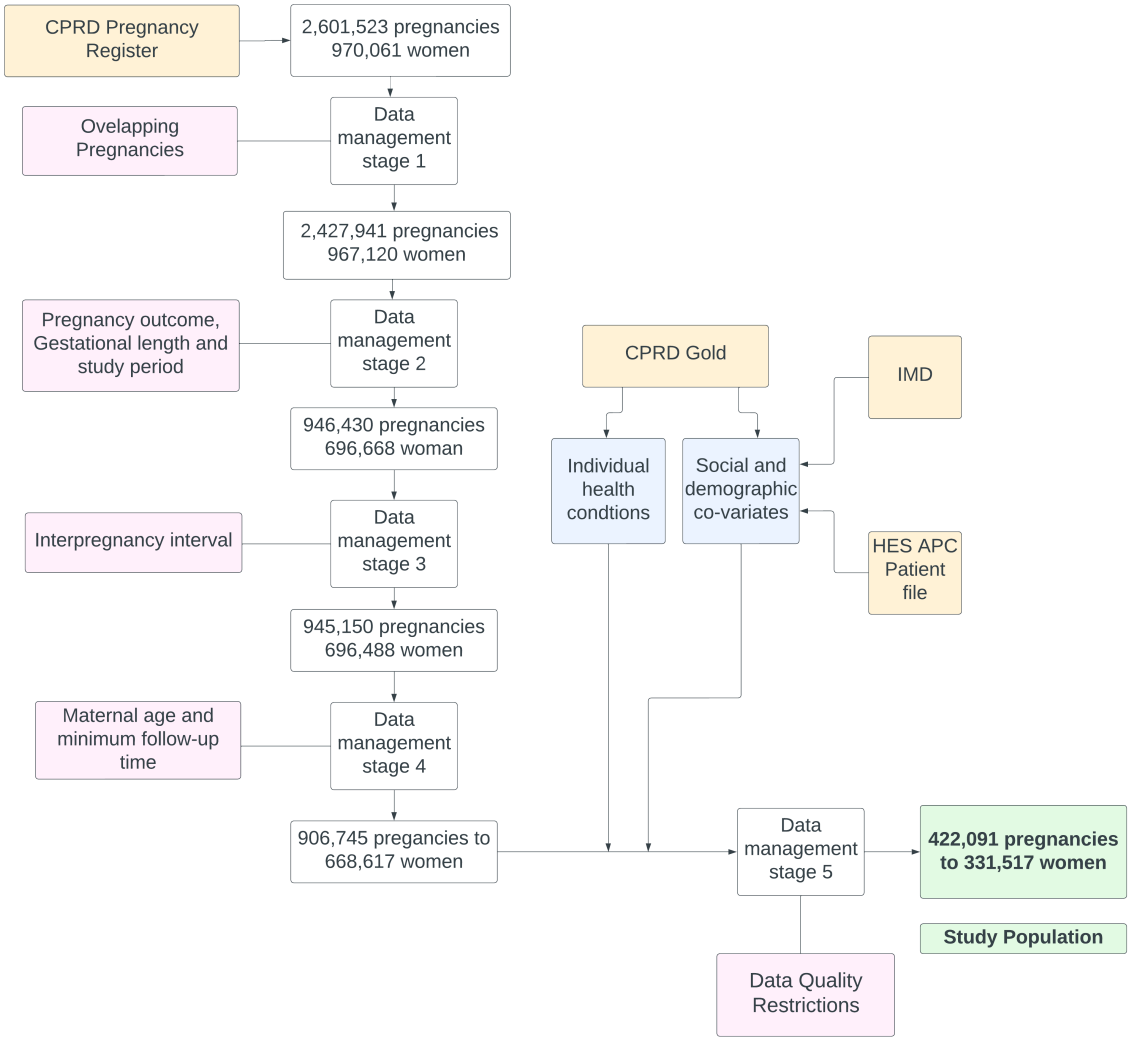
a) Were aged between 15 and 49 years old at the time of pregnancy.
b) Had a pregnancy with an estimated start date between the 1st of January 2007 and the 31st of December 2017.
c) Had a pregnancy that was a minimum gestational length of 22+0 weeks and resulted in either a late fetal loss, stillbirth or livebirth.
d) Had pregnancy data that was research quality (woman is registered for at least one year and practice is up-to-standard for at least one year prior to the estimated start date of the pregnancy).
e) Remained actively registered with a CPRD contributing practice with a last collection date for data that is a minimum of 56 days following the estimated end date of the pregnancy.

The purpose of this section is to describe how the final study population was derived from the CPRD pregnancy register, including the methodological decisions underpinning the inclusion and exclusion criteria applied.

3.6.2 Description of the data and overview of data cleaning and management

The initial pregnancy register dataset provided by CPRD consisted of a total of 2,601,523 pregnancy episodes among 970,061 women based on the woman having at least one pregnancy episode with an estimated start date within the study period (1st of January 2007 and the 31st of December 2017). In the first instance, four stages of data management were undertaken resulting in 906,745 pregnancies to 668,617 women eligible to remain in the study. Following this, data files for the exposure status of individual health conditions and the social and demographic characteristic variables were merged with the pregnancy register. A final stage of data cleaning was undertaken to apply data quality parameters to the dataset thus identifying all pregnancies and women eligible to be included in the final study population. Each pregnancy within the dataset was a single line of data with all information about the exposure status of MLTC, general practice and maternal characteristics relevant to that pregnancy included within it. A summary of this process is detailed in Figure 3.4. The first four stages of data management are described in detail below (sections 3.6.3 to 3.6.7), and the fifth stage of data management is described in detail in the following section about data quality considerations (section 3.7).

Figure 3.4. Flow diagram illustrating the stages of data management undertaken to identify the final study population for chapter 4 (study of the epidemiology of MLTC in pregnancy)



3.6.3 Overlapping pregnancy episodes (Data management stage 1)

The CPRD pregnancy register algorithm intentionally uses all relevant information relating to pregnancy within the woman's primary care records with the aim of identifying all periods in time when a woman may be pregnant. This approach seeks to minimise the potential bias introduced from the exclusion of pregnancies with unknown outcomes, or those which do not fit chronologically within designated pregnancy episodes (66). A key criticism of previous attempts to identify pregnancy episodes within EHRs has been the removal of these pregnancies, which may lead to the exclusion of pregnancies with complications, or pregnancies to women with complex pregnancy histories (242, 243). An inevitable consequence of this approach, however, is that the pregnancy register contains pregnancy episodes to the same women that overlap within the same time-period and cannot therefore both be a 'true' pregnancy.

For the purposes of data cleaning, pregnancy episodes were defined as overlapping if the time-period during which the woman was pregnant, for two or more pregnancies, overlapped by at least one day. Overlapping pregnancies were identified and categorised according to the information contained within the pregnancy register regarding the pregnancy outcome, estimated length of pregnancy, linkage to primary care records of a baby, date of earliest antenatal record and the estimated end date of the pregnancy. The choice of which pregnancy episode to retain among a group of overlapping pregnancy episodes was determined using a pre-defined set of hierarchical rules. The aim was to retain the pregnancy episode associated with the most robust evidence of being the authentic pregnancy episode to remain within the study cohort.

A flow diagram detailing stage 1 of data management (management of overlapping pregnancy episodes) is included in appendix B (Figure B1).

3.6.4 Pregnancy outcome and gestational length (Data management stage 2)

The outcome of a pregnancy episode (livebirth, stillbirth, or early pregnancy loss) in the pregnancy register is determined using different types of information within the woman's primary care records e.g. entity type data for birth outcome or birth record for a baby linked through the mother-baby link. For pregnancies with a livebirth or stillbirth outcome, a validation study of the pregnancy register algorithm conducted by Minassian et al. reported that 84.9% of pregnancies with a livebirth or stillbirth outcome could be matched to a delivery episode in HES APC, but that the proportion of early pregnancy losses that could be matched to a record of pregnancy loss in HES APC was much lower (37.4%) (63). This may reflect the possibility that early pregnancy loss is more likely to be self-managed at home or in the community, rather than requiring admission to secondary care. It may also reflect the possibility that the estimation of the start and end dates for early pregnancy losses are less robust than for pregnancies of more advanced gestations. This could be caused by early pregnancy losses having fewer clinical records associated with them, or by non-contemporaneous recording of early pregnancy loss resulting in pregnancy episodes that are not in the correct chronological order. As the measurement of the exposure status of MLTC was reliant on evidence from the woman's primary care record prior to the start date of the pregnancy, ensuring that pregnancies included in the cohort were likely to be ones with the

most robust estimations of the start and end dates of the pregnancy was paramount. For this reason, pregnancies less than 22+0 weeks gestation were excluded from the cohort.

The pregnancy register also contains a number of pregnancy episodes with uncertain outcomes, for which it was not possible to assign a definitive pregnancy outcome from the information contained within the woman's clinical record. These pregnancy episodes are retained in the Pregnancy Register, and the optimal handling of them is left to the discretion of the researcher. A recent study by Campbell et al. used additional information from linked secondary care and digital imaging datasets to investigate the underlying aetiology of uncertain pregnancy episodes (66). This study reported that pregnancy episodes with an unknown outcome were highly likely to be genuine and contemporaneous pregnancies verified by outcome data being available in the linked datasets. For this reason, pregnancy episodes with uncertain outcomes above 22+0 weeks gestation were retained for possible inclusion in the cohort due to the likelihood of being able to match these pregnancies to a delivery episode in HES APC.

3.6.5 Study period (Data management stage 2)

Pregnancy episodes were retained for inclusion in the cohort if the estimated start date of the pregnancy was between the 1st of January 2007 and the 31st of December 2017. A ten-year study period was chosen to allow for temporal trends in MLTC to be assessed and to allow for enough eligible pregnancies to be included in the final study population to allow for rare maternal and perinatal outcome events to be studied.

A flow diagram detailing stage 2 of data management (identification of the study population based on pregnancy outcome, gestational length and study period parameters) is included in appendix B (Figure B2).

3.6.6 Inter-pregnancy interval (Data management stage 3)

For women with more than one pregnancy episode in the pregnancy register, the inter-pregnancy interval between successive pregnancies was calculated as the difference in days between the end date of one pregnancy and start date of the next pregnancy. An improbable inter-pregnancy interval was defined as less than 28 days between two successive pregnancy episodes belonging to the same woman. This cut off was chosen as the shortest time interval between pregnancies where conception would be physiologically possible. Similarly to the management of overlapping pregnancy episodes, a pre-defined set of hierarchical rules was used to guide the choice of which pregnancy to retain in the cohort. A flow diagram detailing stage 3 of data management (management of pregnancy episodes with improbable inter-pregnancy interval) is included in appendix B (Figure B3)

3.6.7 Maternal age (Data management stage 4)

Pregnancy episodes were retained for inclusion in the cohort if the maternal age was between 15 and 49 years. This age range is consistent with the WHO definition of reproductive age in women, and consistent with previous studies examining epidemiology and outcomes in pregnant populations.

3.6.8 Minimum follow-up time (Data management stage 4)

Pregnancy episodes were retained for inclusion in the final study population if the woman remained registered with her primary care practice for a minimum of 56 days following the end date of the pregnancy, and the last collection date for the practice occurred at least 56 days after the end date of the pregnancy. This time frame was chosen to allow for all relevant event data for the study of the association between MLTC and severe adverse maternal and perinatal outcomes presented in chapter 5 to be captured. Women who did not have the minimum amount of follow-up time because they died were identified and retained for inclusion in the cohort.

A flow diagram detailing stage 4 of data management (identification of study population using maternal age and minimum follow-up time parameters) is included in appendix B (Figure B4).

Following the stages of data management described above, 906,745 pregnancies to 668,617 women remained in the cohort prior to the application of data quality restrictions.

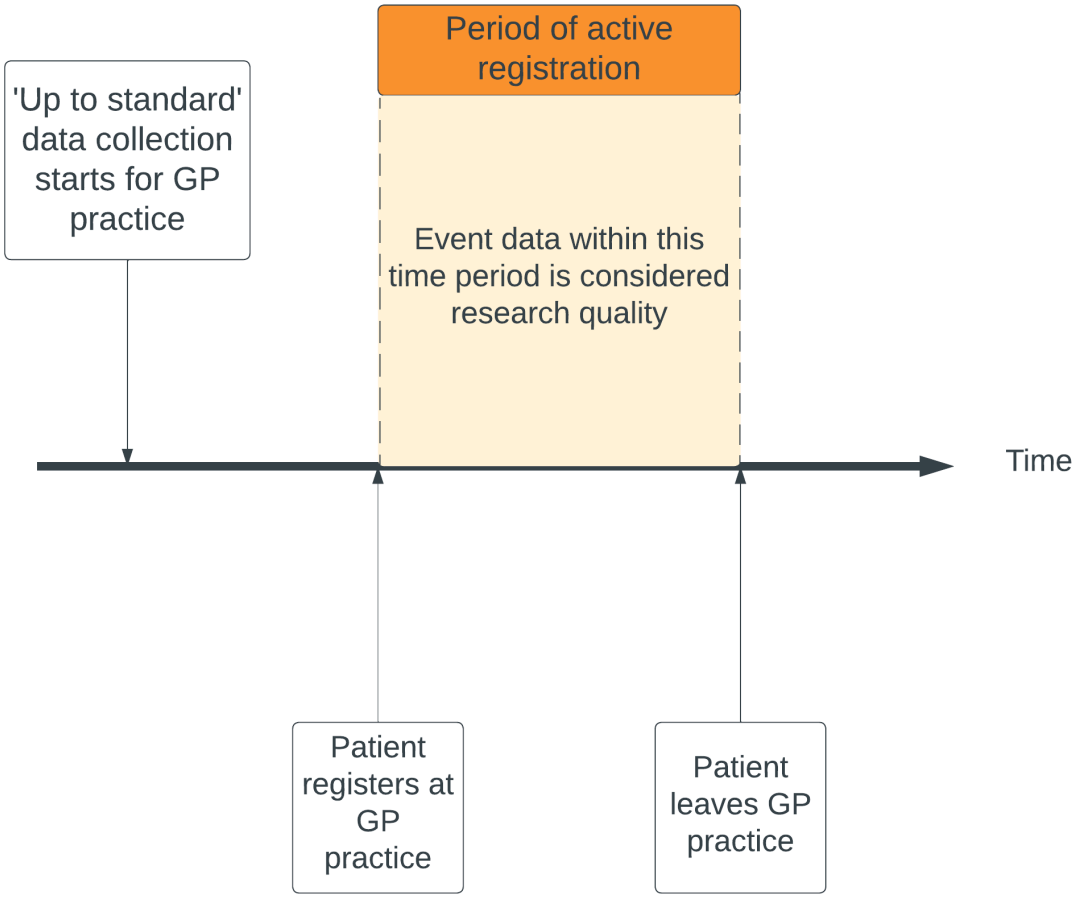
3.7 Data quality considerations

3.7.1 Data quality in CPRD GOLD

The dynamic and longitudinal nature of CPRD GOLD means that the quality of the data within the dataset changes over time for each practice and, potentially, each patient. There are two parameters within CPRD GOLD that relate to data quality; the date at which the

practice data is deemed to be of research quality (up-to-standard date) and the date the patient's current period of registration with the practice began (current registration date). The diagram shown in Figure 3.5 illustrates the use of up-to-standard and current registration to identify the time-period during which event data is considered research quality.

Figure 3.5. Schematic representation of identification of event data considered research quality in CPRD GOLD



CPRD recommend that only event data (read codes and prescription codes) that is considered to be of research quality is used in studies, however, in practice data quality restrictions have been applied in a variety of different ways in previously published studies.

3.7.2 Data quality in CPRD pregnancy register

In addition to the data quality restrictions described above, the validation of the pregnancy register was undertaken using pregnancy episodes that were considered to be research quality (63). Research quality was defined as pregnancy episodes for which the practice was contributing research quality data and the woman was registered with the GP for at least 12 months before the start of the pregnancy. The diagram shown in Figure 3.6 illustrate the use of data quality restrictions (up-to-standard and current registration) to identify whether a pregnancy episode is considered research quality.

Figure 3.6. Schematic representation of identification of research quality pregnancies in CPRD Pregnancy register

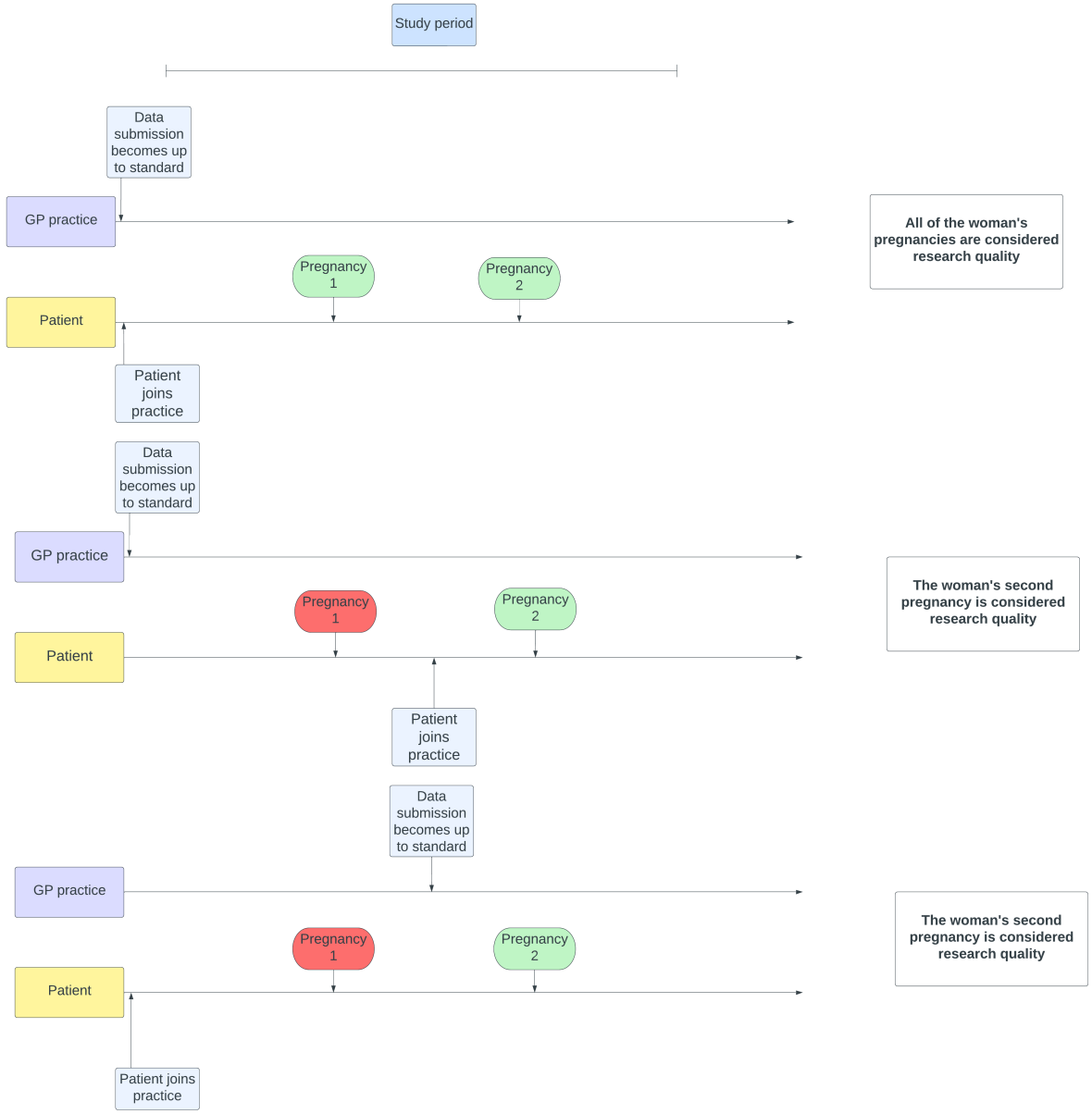
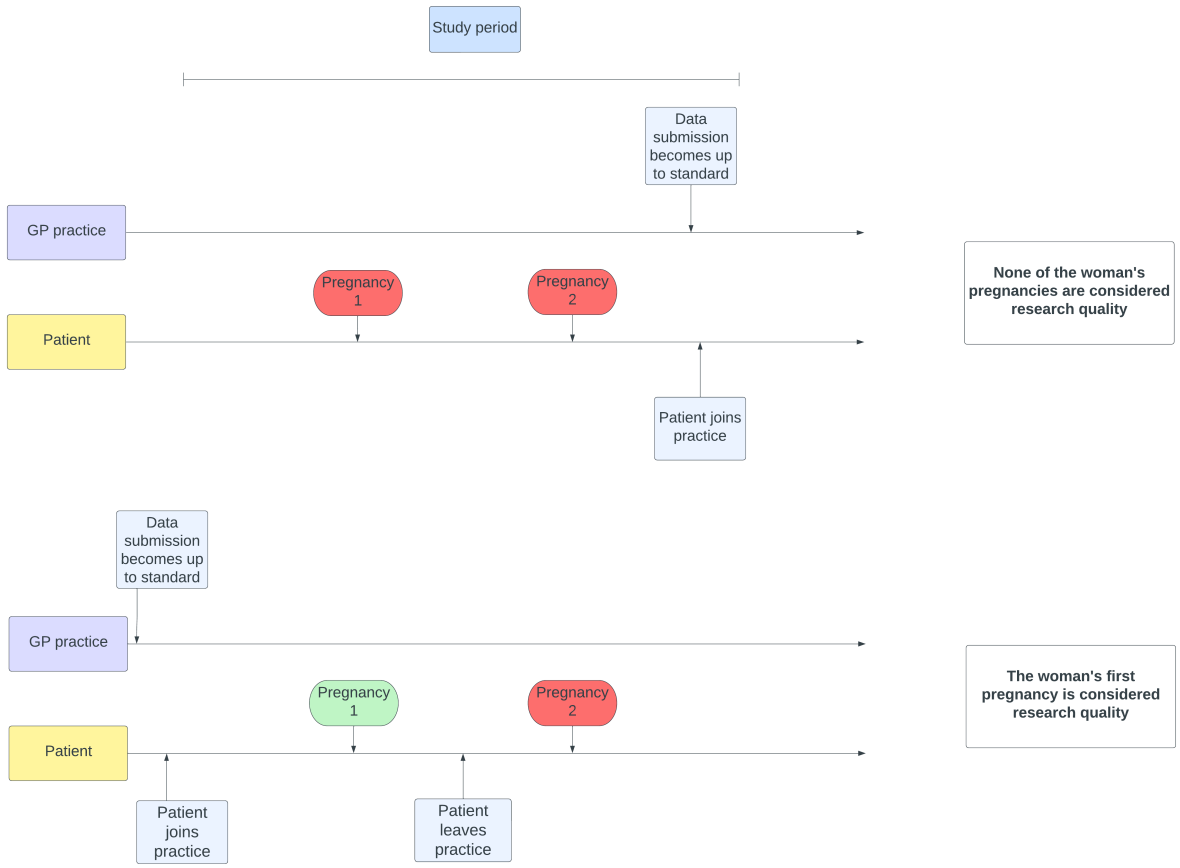
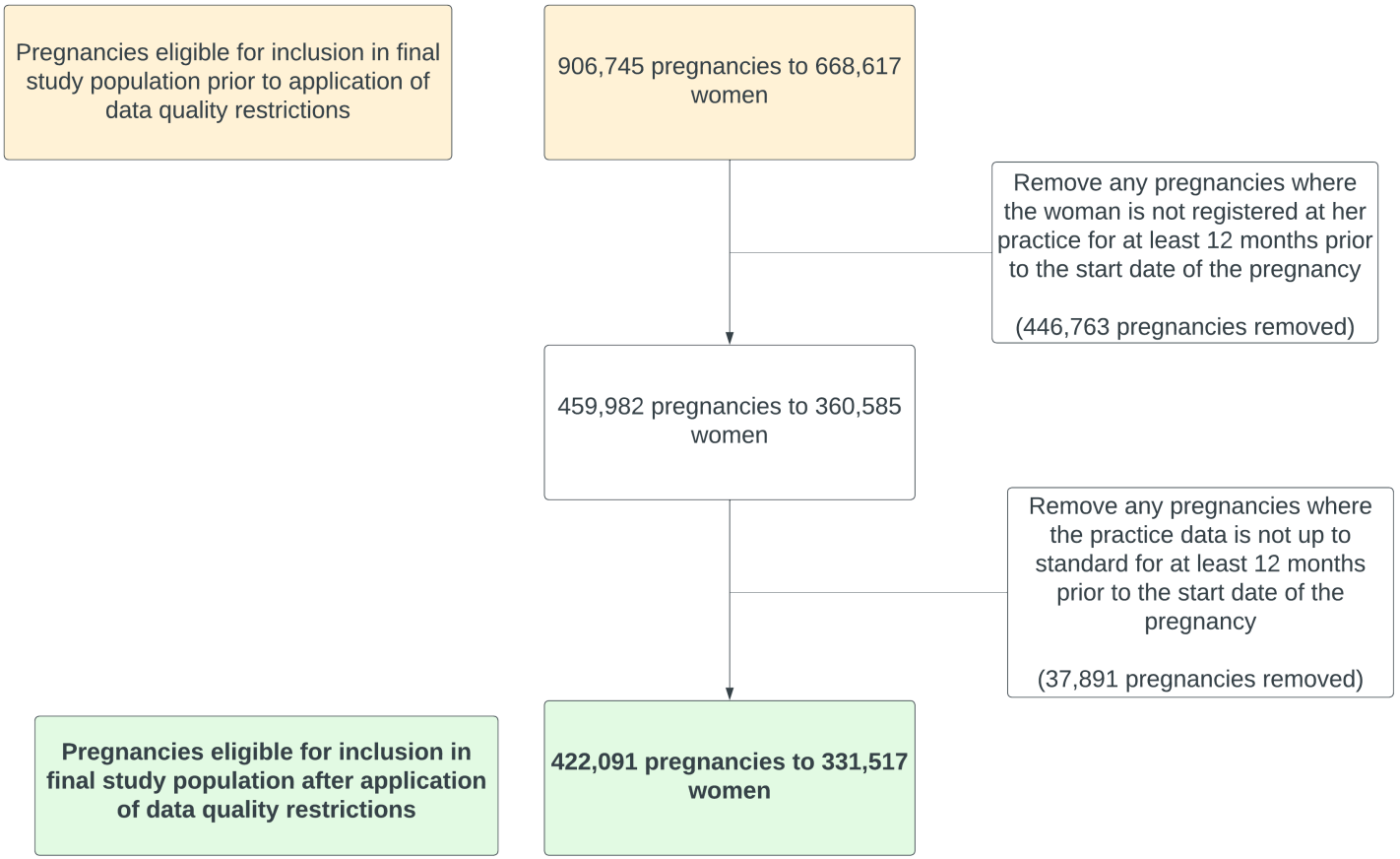


Figure 3.6. (continued) Schematic representation of identification of research quality pregnancies in CPRD Pregnancy register



The flow diagram shown in Figure 3.7 illustrates the changes in the study population following the application of data quality restrictions to identify pregnancies considered research quality.

Figure 3.7. Flow diagram illustrating the application of data quality restrictions identifying research quality pregnancies eligible for inclusion in the final study population.



As illustrated application of data quality restrictions leads to the exclusion of 484,654 (53.5%) of pregnancies that otherwise meet the inclusion criteria for the study population. Overall 337,100 (50.4%) of women had no pregnancies in the study period considered research quality, 279,282 (41.8%) of women had only research quality pregnancies, and 52,235 (7.8%) of women had a mixture of research quality and non-research quality pregnancies in the study period. In order to better define, understand and justify the use of data quality restrictions the following analyses were undertaken:

a) Comparison of temporal and regional differences between research quality and non-research quality pregnancies
b) Comparison of exposure status for individual health conditions and prevalence of MLTC between research quality and non-research quality pregnancies
c) Comparison of social and demographic characteristics between research quality and non-research quality pregnancies

These analyses are described and discussed in the following sections (3.5.3 – 3.5.6.).

3.7.3 Temporal and regional differences in research quality

The proportion of pregnancies that are considered research quality based on year of study entry and by region is shown in Tables 3.6 and 3.7 respectively.

Table 3.6. Proportions of research quality and non-research quality pregnancies by year of study

Year of study	Non-research quality pregnancies		Research quality pregnancies	
	n pregnancies/n total for year of study entry	%	n pregnancies/n total for year of study entry	%
2007	69677/115046	60.6	45369/115046	39.4
2008	64709/110672	58.5	45963/110672	41.5
2009	60756/107400	56.6	46644/107400	43.4
2010	57356/103398	55.5	46042/103398	44.5
2011	52585/97913	53.7	45328/97913	46.3
2012	45469/87787	51.8	42318/87787	48.2
2013	38462/77383	49.7	38921/77383	50.3
2014	31975/65789	48.6	33814/65789	51.4
2015	25764/54649	47.1	28885/54649	52.9
2016	20861/46382	45.0	25521/46382	55.0
2017	17040/40326	42.3	23286/40326	57.7

Table 3.7. Proportions of research quality and non-research quality pregnancies by geographical region of primary care practice

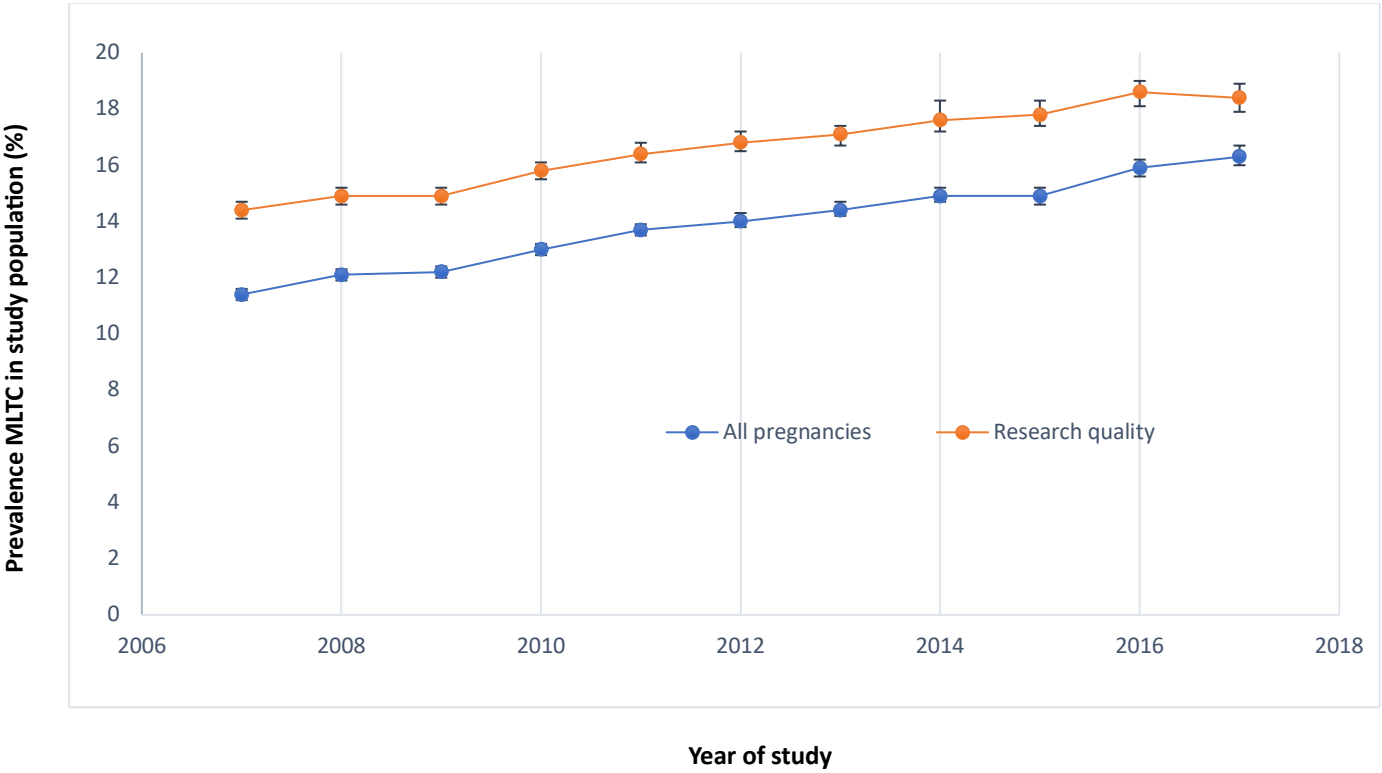
Region of practice	Non-research quality pregnancies		Research quality pregnancies	
	n pregnancies/n total for region	%	n pregnancies/n total for region	%
England	286348/521377	54.9	234989/521377	45.1
North East	2946/7937	37.1	4991/7937	62.9
North West	33244/71702	46.4	38458/71702	53.6
Yorkshire	4121/9739	42.3	5618/9739	57.7
East Midlands	4424/10090	43.9	5666/10090	56.2
West Midlands	30551/60491	50.5	29940/60491	49.5
East of England	25931/47120	55.0	21189/47120	45.0
London	69182/99240	69.7	30058/99240	30.3
South East	89824/162348	55.3	72524/162348	44.7
South West	26165/52710	49.6	26545/52710	50.4
Wales	75841/135886	55.8	60045/135886	44.2
Scotland	109726/207327	52.9	97601/207327	47.1
Northern Ireland	12699/42155	30.1	29456/42155	69.9

The proportion of pregnancies considered research quality increased across the study period. In 2007 39.4% of pregnancies were considered research quality compared to 57.7% in 2017. There are also differences observed in the proportion of pregnancies considered research quality by geographical area. Within England, two regions (West Midlands and South West) have a roughly equitable split between the proportions of pregnancies considered research quality and those considered non-research quality. Four regions (North East, North West, Yorkshire and the Humber and East Midlands) had a higher proportion of research quality pregnancies compared to non-research quality pregnancies and three regions (East of England, London and South East) had a lower proportion of research quality compared to non- research quality pregnancies. By devolved nation within the UK, the proportions of research quality and non-research quality pregnancies was split roughly equitably in Scotland. Northern Ireland had a higher proportion of research quality pregnancies, while Wales and England had marginally lower proportions of research quality pregnancies overall.

3.7.4 Exposure status and prevalence of MLTC

The prevalence of MLTC was estimated for each year of the study for all pregnancies and for those considered research quality. This is shown in Figure 3.8.

Figure 3.8. Graph of the prevalence of MLTC by year of study for all pregnancies (prior to the application of data quality restrictions) and for pregnancies considered research quality (after the application of data quality restrictions)



The prevalence of MLTC was observed to be higher when the cohort was restricted to research quality pregnancies overall, and for each year of the study. The prevalence of all health conditions included in the study was compared between all pregnancies in the cohort, and those considered research and non-research quality, and is included in appendix B (Table B8). For 12 health conditions (22.6%) there was no significant difference in prevalence between the groups, for 12 conditions (22.6%) there was a lower prevalence of the conditions among research quality pregnancies, and for 29 conditions (54.7%) there was a higher prevalence of the conditions among research quality pregnancies.

3.7.5 Social and demographic characteristics

The distribution social and demographic characteristics for all pregnancies in the cohort, and for non-research and research quality pregnancies is shown in Table 3.8.

Table 3.8. Social and demographic characteristics of all pregnancies (prior to the application of data quality restrictions) and for non-research quality pregnancies (ineligible for final study population) and research quality pregnancies (eligible for final study population)

Social and demographic characteristics	All pregnancies in cohort (total n=906745)		Non-research quality pregnancies (total n=484652)		Research quality pregnancies (total n=422091)	
	n/total n with data	%	n/total n with data	%	n/total n with data	%
Maternal Age						
Less than 20 years	53979/906745	6.0	35755/484652	7.4	18224/422091	4.3
20- 34 years	678090/906745	74.8	371381/484652	76.6	306709/422091	72.7
35-39 years	141345/906745	15.6	63350/484652	13.1	77995/422091	18.5
More than 40 years	33329/906745	3.7	14166/484652	2.9	19163/422091	4.5
Smoking status						
Non-smoker	355429/610696	58.2	122595/210663	58.2	232873/400033	58.2
Ex-Smoker	100054/610696	16.4	33338/210663	15.8	66716/400033	16.7
Current smoker	155213/610696	25.4	54733/210663	26.0	100480/400033	25.1
Missing (as a proportion of total n)	*296049/906745*	*32.7*	*273991/484652*	*56.5*	*22058/422091*	*5.2*
BMI category						
Underweight	19025/470936	4.0	7842/165399	4.7	11183/305537	3.7
Healthy Weight	244489/470936	51.9	91102/165399	55.1	153387/305537	50.2
Overweight	118451/470936	25.2	39011/165399	23.6	79440/305537	26.0
Obese	88971/470936	18.9	27444/165399	16.6	61527/305537	20.1
Missing (as a proportion of total n)	*435809/906745*	*48.1*	*319255/484654*	*65.9*	*116554/422091*	*27.6*

Table 3.8. (continued) Social and demographic characteristics of all pregnancies (prior to the application of data quality restrictions) and for non-research quality pregnancies (ineligible for final study population) and research quality pregnancies (eligible for final study population)

Social and demographic characteristics	All pregnancies in cohort (total n=906745)		Non-research quality pregnancies (total n=484652)		Research quality pregnancies (total n=422091)	
	n/total n with data	%	n/total n with data	%	n/total n with data	%
Ethnicity						
White	595103/700203	85.0	330506/403092	82.0	264597/297111	89.1
Black/Black British	27266/700203	3.9	19863/403092	4.9	7403/297111	2.5
Asian/Asian British	47129/700203	6.7	31155/403092	7.7	15974/297111	5.4
Mixed	9540/700203	1.4	6524/403092	1.6	3016/297111	1.0
Other	21165/700203	3.0	15044/403092	3.7	6121/297111	2.1
Missing (as a proportion of total n)	206542/906745	22.8	81562/4884654	16.8	124980/422091	29.6
IMD Quintile *						
1 (Most affluent)	84619/404286	20.9	47557/220490	21.6	37062/183587	20.2
2	77349/404286	19.1	41538/220490	18.8	35811/183587	19.5
3	79938/404286	19.8	43027/220490	19.5	26911/183587	20.1
4	80919/404286	20.0	45058/220490	20.4	35861/183587	19.5
5 (Most deprived)	81461/404286	20.2	43249/220490	19.6	38212/183587	20.8
Missing (as a proportion of total n)	*117091/521377*	*22.5*	*65959/286388*	*23.0*	*51132/234989*	*21.8*

** IMD quintile only available for patients registered at English practices, total n =521,377*

There were no differences in the distribution of IMD quintile following the application of data quality restrictions. The proportions of current, ex and non-smokers were similar among research-quality and non-research quality pregnancies, however the amount of missing data was substantially reduced by the application of data quality restrictions. Pregnancies to women with research-quality data had higher proportions of women over the age of 35, and lower proportions of women under the age of 20. Pregnancies to women with research quality data had higher proportions of women of White ethnicity, and lower proportions of women from minority ethnic backgrounds. Pregnancies to women with research quality data had higher proportions of women who were overweight or obese compared to those who were classified as normal weight or underweight. The proportion of missing data was reduced for BMI, but increased for ethnicity following the application of data quality restrictions.

3.7.6 Discussion of implications of applying data quality restrictions

The application of data quality restrictions substantially reduced the size of the study population, as 53.4% of pregnancies did not meet the data quality criteria (patient is registered with practice for a minimum of 12 months prior to the start date of the pregnancy, and the practice is contributing up-to-standard quality data for a minimum of 12 months prior to the start date of the pregnancy). This has potential implications for the statistical power of the subsequent studies, which is a particularly important consideration given that all the proposed outcomes under investigation apart from common perinatal mental health disorders are rare. The application of data quality restrictions and subsequent reduction in the study population could plausibly result in a finding of no difference in effect

between the groups under investigation. It should be noted, however, that the size of the study population, even after the application of data quality restrictions is much larger than could be feasibly recruited through traditional prospective cohort methods.

Considerations around study size and power, need to be balanced however, by consideration for the accuracy with which the exposure status of MLTC can be determined. It was observed that the prevalence of MLTC was higher when the cohort was restricted to research quality pregnancies overall, and for each year of the study. The comparison of research and non-research quality pregnancies also revealed differences in the prevalence of the component individual health conditions. In particular, for 54.7% of health conditions, the prevalence was found to be higher for research quality pregnancies. It is possible that these differences in prevalence are driven by underlying differences in the characteristics of the population who have research quality pregnancies. It is, however, notable that all conditions that required evidence of active management/a prescription record in the preconception period, or where the identification of a case was dependent on entity type data for test results showed an increase prevalence when the cohort was restricted to research quality pregnancies only. An example of this is the identification of asthma for which the prevalence in research quality pregnancies was 7.5% compared to the prevalence in non-research quality pregnancies which was 2.5% (p-value for differences in proportion=<0.001). This raises the possibility that differences in the prevalence of some health conditions are driven by data quality, with pregnancies that are non-research quality being less likely to have accurate and timely information recorded in the clinical records. This has the potential to introduce misclassification bias if all pregnancies in the cohort are included in the final study population. The application of data quality restrictions would allow for the most accurate

ascertainment of exposure status and therefore a more robust assessment of the association between the exposure and outcomes under investigation.

Differences in the distribution of social and demographic characteristics of women with pregnancies with research quality data and those without were observed following the application of data quality restrictions. Overall women with research quality pregnancy data were more likely to be older and were more likely to be of white ethnicity compared to women with non-research quality pregnancy data. Women with research quality pregnancy data also appeared to be marginally more likely to be overweight or obese rather than being classified as having a normal BMI at the start of pregnancy compared to women with non-research quality pregnancy data. Data about birth characteristics collated by the Office for National Statistics and NHS Digital show a trend towards increasing rates of maternal obesity and advancing maternal age among the maternity population across the time period of this study (244, 245). Although an increase in the proportions of pregnancies with research quality data was seen across the study period, due to the decreasing coverage of CPRD GOLD pregnancy register across the same timeframe an oversampling of pregnancies from the latter part of the study period has not occurred. This means that it is less likely that differences in the distribution of maternal characteristics is merely reflective of demographic changes in the maternity population overall, and may indeed be driven by data quality restrictions being more likely to select certain maternal characteristics.

The application of data quality restrictions also appears to impact the regional representativeness of the final study population, with some areas of the UK observed to have a much lower proportion of pregnancies eligible for inclusion in the final study

population. This was particularly stark for London region, where only 30.3% of pregnancies were eligible to remain in the cohort following the application of data quality restrictions, despite this region contributing approximately 1 in 10 pregnancies to the whole cohort overall. Overall, the application of data quality restrictions will result in differential distribution of the demographic characteristics of the study population, and in a higher proportion of pregnancies from certain regions of the UK being excluded from the study population. The differential distribution of maternal characteristics and impact on regional representativeness represent selection biases, which have the potential to reduce the generalisability of the findings of the component studies to the wider maternity population.

There was no difference observed in the distribution of IMD quintile or smoking status for women with available data comparing those with research quality pregnancy data to those without, however missing data for smoking status was markedly reduced following the application of data quality restrictions. With regard to IMD quintile, comparison with nationally available data shows that the distribution of IMD quintile in the study population appears to differ to the distribution in the maternity population nationally (246). In particular, the proportion of women in the most affluent quintile is higher, and the proportion of women in the most deprived quintile is lower in the study population. While valid inferences can still be obtained from studies with non-representative population samples, cautious interpretation of results is required. Lack of representativeness within study populations can result in both over or under estimation of the associations between the exposure and the outcome. Severe adverse maternal and perinatal outcomes have consistently been shown to be more likely among women experiencing socioeconomic deprivation and those from minority ethnic backgrounds. The under-representation of

women from minority ethnic groups and the over-representation of women from higher socioeconomic backgrounds within the study population could plausibly result in an under-estimation of the association between MLTC and the outcomes under investigation.

3.8 Derivation of the study population for chapters 5 and 6

3.8.1 Study population

A total of 146,306 pregnancies to 121,211 women were included in the studies investigating the association between MLTC and severe adverse maternal and perinatal outcomes presented in chapter 5, and the association between MLTC and severe and common maternal mental health outcomes presented in chapter 6. The study population consists of women who:

a) Were aged between 15 and 49 years old at the time of pregnancy.
b) Had a pregnancy with an estimated start date between the 1st of January 2007 and the 31st of December 2017.
c) Had a pregnancy that was a minimum gestational length of 22+0 weeks and resulted in either a late fetal loss, stillbirth or livebirth.
d) Had pregnancy data that was research quality (woman is registered for at least one year and practice is up-to-standard for at least one year prior to the estimated start date of the pregnancy).
e) Remained actively registered with a CPRD contributing practice with a last collection date for data that is a minimum of 56 days following the estimated end date of the pregnancy.

f) Had a pregnancy in CPRD pregnancy register that could be matched and validated with a delivery record in HES APC.

The purpose of this section is to describe the process of identifying the final study population included in the work presented in chapters 5 and 6.

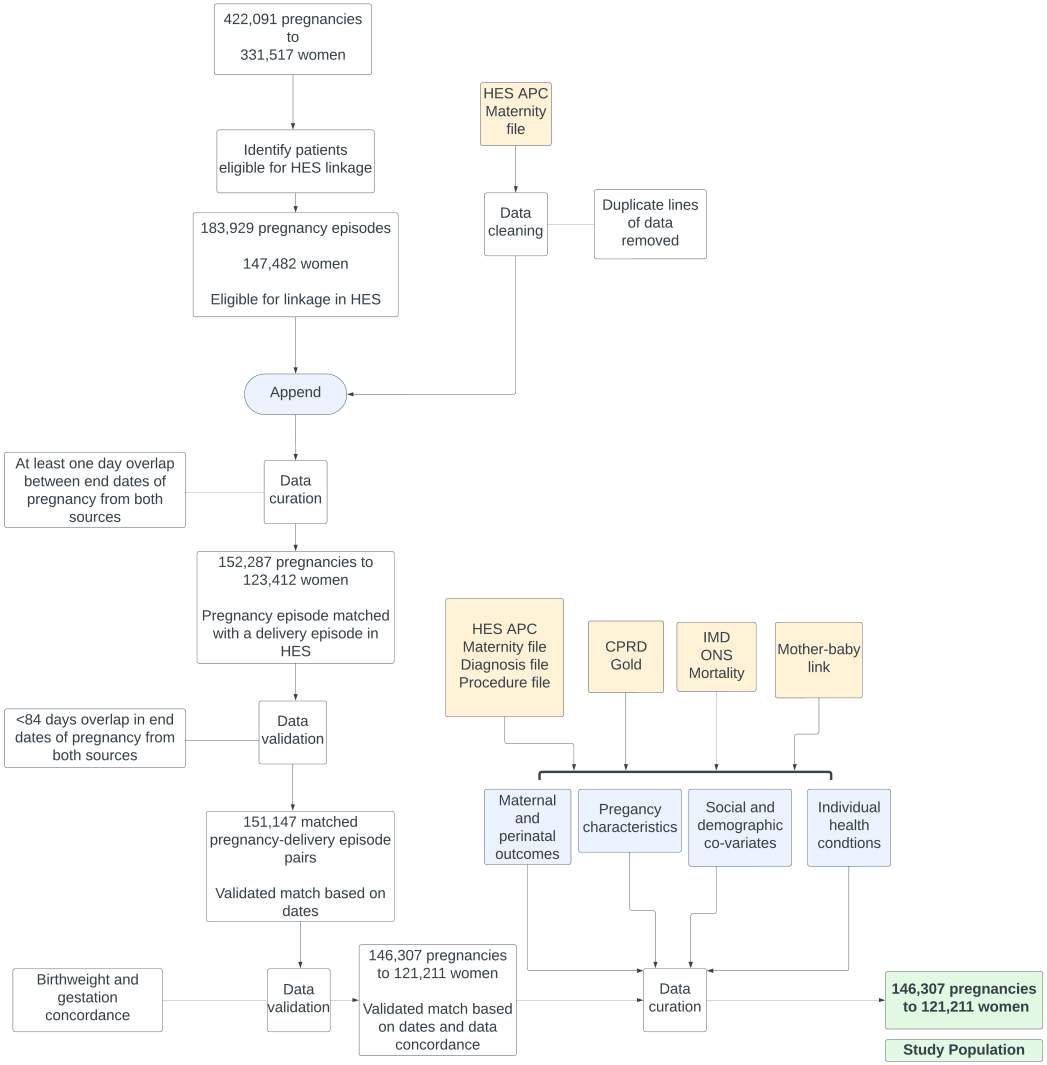
3.8.2 Description of the data and overview of data cleaning and management

From among the final study population included in the epidemiology of MLTC in pregnancy study presented in chapter 4, a total of 183,929 pregnancies to 147,482 women were eligible for linkage to the HES APC dataset. These were patients from English practices where the practice had consented to the linkage.

The final study population was restricted to women from English practices who had a pregnancy that could be matched and validated with a delivery record in HES APC. For the study presented in chapter 5, this was necessary because linkage to ONS mortality data used to construct the outcome variables for maternal and neonatal death was only available for women from England, and data about birth outcome and severe maternal morbidity events was only present in HES APC. For the study presented in chapter 6, a sensitivity analysis showed diagnostic codes for self-harm events and postpartum psychosis were only present in HES APC and not recorded within the primary care records for 26% and 35% of women respectively. The use of the wider cohort including pregnancies without HES APC linkage, would plausibly result in under ascertainment of the severe maternal mental health morbidity outcome events.

Preliminary cleaning of the HES APC maternity file was undertaken to remove lines of data that were exact duplicates for the same patient. Following this the HES APC maternity file was appended to the file containing the cohort of pregnancies from CPRD that were eligible for linkage. A further two stages of data cleaning and validation were undertaken to identify matched pregnancy-delivery episode pairs that were eligible for inclusion in the final study population. Once these were identified, the files for pregnancy and birth characteristics and the maternal and perinatal outcomes were merged in. The data were then organised so each pregnancy was a single line of data with all information about pregnancy, delivery, exposure status of MLTC, maternal characteristics, and maternal and perinatal outcomes relevant to that pregnancy included within it. A summary of this process is detailed in Figure 3.9. The data cleaning and validation used to identify pregnancies and delivery episodes eligible for inclusion in the final study population is described in detail in the following sections (sections 3.8.3 to 3.8.5)

Figure 3.9. Flow diagram illustrating the stages of data cleaning and management undertaken to identify the final study population for chapters 5 and 6

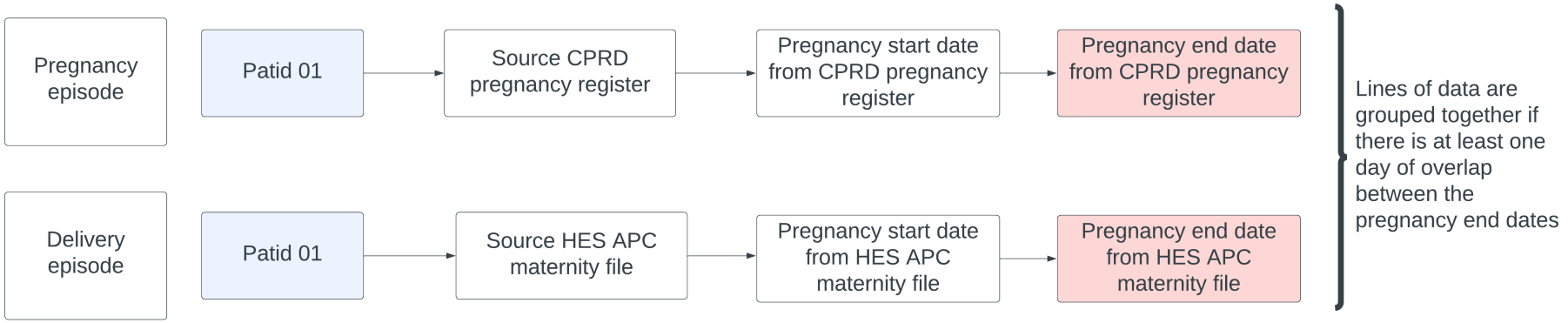


3.8.3 Identification of matched pregnancy-delivery episode pairs

The HES APC maternity file does not include a data field for the date of birth of the baby, and for this reason proxy dates for the start and end of pregnancy were calculated. For the estimated end date of the pregnancy the start date of the episode of care plus 14 days was used. This is because it was assumed reasonable that if a woman was admitted to hospital for the birth of her baby (spontaneous labour, induction of labour, elective caesarean birth) or with a pregnancy complication necessitating delivery, that birth would likely occur within two weeks of admission. For the estimated start date of the pregnancy the start date of the episode of care minus 301 days was used. This is because it was assumed reasonable that for most women, pregnancy would not last longer than 43 completed weeks of gestation. These estimated dates were deliberately generous to try and maximise the possibility of matching a pregnancy from CPRD with a corresponding delivery episode in HES APC.

Pregnancies episodes from CPRD and delivery episodes from HES APC belonging to the same woman were identified through the unique encrypted patient identifier. Pregnancy episodes and delivery episodes were then sorted in chronological order, and the start date and end date for the pregnancy was used to identify and group together any CPRD pregnancy episodes and HES APC delivery episodes which overlapped by at least one day. This is represented diagrammatically in Figure 3.10.

Figure 3.10. Schematic representation of identification of matched pregnancy-delivery episode pairs from within CPRD pregnancy register and HES APC maternity file



If a CPRD pregnancy episode did not overlap with any HES APC delivery episode then these pregnancies were excluded from the cohort. If a CPRD pregnancy episode overlapped with one HES APC delivery episode then these matched pregnancy-delivery episode pairs were retained in the cohort for validation. If a CPRD pregnancy episode overlapped with more than one HES APC delivery episode then the data underwent further inspection. If it was likely that the HES APC delivery episodes were multiple lines of duplicate data and actually represented one baby born at the end of a singleton pregnancy then the data was de-duplicated and these matched pregnancy-delivery episode pairs were retained in the cohort for validation. If it was likely that the multiple HES APC delivery episodes represented the birth of separate babies from a multiple pregnancy these matched pregnancy-delivery episodes were excluded from the cohort. At the end of this stage of the process, 152,287 pregnancies were matched to a single delivery episode in HES APC.

3.8.4 Assessment of quality of matching process

Following on from this, the quality of the matching process was explored by assessing the number of days difference between the end date of the pregnancy episode for CPRD and the proxy end date of the pregnancy from HES APC for matched pregnancy-delivery episode pairs. Based on the validation methods used by Minassian et al., if the dates from the two sources were less than 84 days apart then the matched pregnancy-delivery episode pairs were retained for inclusion in the cohort (63). If they were greater than 84 days apart then they were excluded from the cohort. Overall, 151,147 (99.5%) of matched pregnancy-delivery episode pairs were retained for inclusion in the cohort following this stage of validation.

3.8.5 Assessment of concordance of information between CPRD and HES APC

The concordance of the birthweight (measured in grams) and the gestational age (measured completed weeks) recorded within the HES APC delivery episode was assessed first. The records were identified as concordant if the birthweight in HES APC was plausible for the gestational age based on upper and lower limits of birthweight by sex and gestation according to the UK-WHO neonatal and infant close monitoring growth charts (239). The gestational age recorded within the delivery episode was then compared to the gestational age recorded within the CPRD pregnancy episode and the records were identified as fully concordant if the gestational age from both sources correlated. A total of 119,346 (79%) of matched pregnancy-delivery episode pairs were fully concordant across all three sources of data assessed. If either the birthweight or gestational age in HES APC was missing, whichever piece of data was present was compared to the gestational age in the CPRD pregnancy register and were identified as concordant if they correlated. A further 26,961 (18%) matched pregnancy-delivery episode pairs were identified as concordant based on correlation of data in the presence of a single piece of missing data. Matched pregnancy-delivery episode pairs for which there was discordance across the three data sources assessed were not retained for inclusion in the cohort. A summary of the validation of the quality of matching process is detailed in appendix B (Figure B5). In total 146,307 (96.8%) of matched pregnancy-delivery pairs were identified as eligible to remain in the study population based on an assessment of the quality of the matching process using concordance of information between CPRD pregnancy register and HES APC.

3.8.6 Discussion of the implications of the validation of matching process

A total of 183,929 pregnancies from the study population for the epidemiology of MLTC study were eligible for HES APC linkage, and of these 152,287 pregnancies could be successfully matched to a delivery episode in the HES APC dataset. Following this, two additional stages of validation were undertaken; an assessment of the quality of the matching process and assessment of the concordance of the information between CPRD pregnancy register and HES APC. These additional validation stages were deemed necessary as the outcomes under investigation in the studies presented in chapters 5 and 6 are tightly time bound as their occurrence is specifically related to pregnancy and the period after birth. To be able to robustly assess the association between MLTC and the outcomes under investigation, it is therefore imperative to ascertain whether the outcomes have occurred within the correct pre-specified time frames. This requires that we have as high a degree of certainty as possible that the dates for the start and end of pregnancy are accurate, and that the pregnancy is matched to the correct delivery episode in HES APC.

Only a small proportion of matched pregnancy-delivery episode pairs were excluded from the final study population because they did not meet the validation criteria of having less than 84 days difference between the end dates of the pregnancy from both sources. Of the matched pregnancy-delivery episode pairs that were validated based on dates, 4840 (3.2%) further were excluded from the cohort as the quality of the match between CPRD and HES APC could not be assured. A recent study investigating the validity of linkage between the HES APC maternity and neonatal datasets with National birth registration data found that records within HES APC that had missing or unreliable data were more likely to be from

preterm births (247). Of all pregnancies that were matched to a delivery episode in HES APC, 10,877 (7.4%) were classified a preterm births and 141,410 (92.86%) were classified as term births. Following the validation and quality assurance of matching process, 98.7% of term births (139,651 pregnancies) were retained in the final study population, but only 61% of preterm births (6056 pregnancies) were retained. This raises the possibility that the validation and quality assurance processes has resulted in preterm births being more likely to be excluded from the final study population. Preterm birth is recognised as a leading risk factor for neonatal death (248), and is also more likely to be associated with obstetric-specific conditions such as pre-eclampsia and the need for interventions in the peripartum period (45). The under ascertainment of preterm births could plausibly result in a lower-than-expected rate of severe adverse outcomes in the study population, particularly for neonatal death.

3.9 Conclusion

There are many methodological considerations arising from the extensive data cleaning and curation required to derive a study population from the routinely collected data sources used in this thesis. The characteristics of the study population, the regional representativeness, the amount of missing data and the measurement of the exposure status are all impacted by the application of data quality restrictions and the process of validating matched pregnancy-delivery episode pairs. All these factors represent important sources of bias that could affect observed effect sizes, study robustness and generalisability.

Overall, the application of data quality restrictions introduces selection bias for certain maternal characteristics and regional representativeness but reduces misclassification bias of exposure status. Prioritising the minimisation of misclassification bias would allow for the most accurate ascertainment of exposure status and assessment of the association between exposure and outcomes under investigations. For this reason, the application of data quality restrictions is used as part of the identification of pregnancies eligible for inclusion in the final study population. The validation of the matching process identified and removed pregnancy-delivery episode pairs with poor quality or discordant data. This should act to improve the robustness of the assessment of the association between the exposure and the outcomes under investigation. The apparent disproportionate loss of preterm births from the study population as a consequence of the validation of the matching process, however, will require cautious consideration during the analysis of the subsequent studies.

Chapter 4: Investigating the epidemiology of MLTC in pregnancy in the UK

4.1 Introduction and research objectives

MLTC is an increasingly prevalent health phenomenon and is known to be associated with excess risk across several important adverse health outcomes including a higher likelihood of disability, functional impairment, low quality of life and premature mortality. The systematic review presented in chapter 2 demonstrated notable gaps in our current understanding of the epidemiology of MLTC in pregnancy. This is in part due to a paucity of studies that have specifically focussed on pregnant populations, and in part due to the exclusion of relevant health conditions in previous population-based research. There are important consequences to the lack of robust epidemiological information about MLTC in pregnancy. First, the recognition of MLTC as an important health concern for pregnant women and subsequent priority setting of resource allocation cannot occur. Second, the implications of MLTC for maternal and perinatal health cannot be comprehensively delineated. Third, planning of future maternity care provision to meet the needs of women with MLTC cannot happen effectively.

This chapter addresses research objective 3 of this thesis:

To describe the epidemiology of MLTC in pregnancy in the UK across a ten-year period.

4.2 Methods

4.2.1 Data sources

The primary data sources used in this study were CPRD GOLD and CPRD Pregnancy Register. Additional linkage between CPRD Pregnancy register and the 2019 Index of Multiple Deprivation and the HES APC was used to provide information about socioeconomic status and ethnicity.

A detailed description of the data sources used in this study can be found in chapter 3 (section 3.2).

4.2.2 Study population

The study population consisted of women who:

a) Were aged between 15 and 49 years old at the time of pregnancy.
b) Had a pregnancy with an estimated start date between the 1st of January 2007 and the 31st of December 2017.
c) Had a pregnancy that was a minimum gestational length of 22+0 weeks and resulted in either a late fetal loss, stillbirth or livebirth.
d) Had pregnancy data that was research quality (woman is registered for at least one year and practice is up-to-standard for at least one year prior to the estimated start date of the pregnancy).
e) Remained actively registered with a CPRD contributing practice with a last collection date for data that is a minimum of 56 days following the estimated end date of the pregnancy.

A detailed description of the derivation of the study population, including the application of inclusion and exclusion criteria can be found in chapter 3 (sections 3.6 and 3.7).

4.2.3 Exposure under investigation

The main exposure under investigation was MLTC which was defined as a woman having any combination of two or more long-term physical health, mental health or infectious conditions prior to the start of pregnancy. MLTC was also considered by type and complexity. Women with two or more physical health conditions were considered to have physical health MLTC, women with two or more mental health conditions were considered to have mental health MLTC, and women with at least one physical and one mental health condition were considered to have mixed MLTC. Women who had three or more health conditions prior to the start of pregnancy were considered to have complex MLTC.

A detailed description of the measurement of exposure status can be found in chapter 3 (section 3.3).

4.2.4 Social and demographic characteristics

Information about maternal age, ethnicity, smoking status, BMI and socioeconomic status was extracted from the EHRs for all women in the study population. Variables indicating maternal age, smoking status and BMI were derived on a per pregnancy basis using the estimated start date of the pregnancy, and socioeconomic status and ethnicity were derived on a per woman basis.

A detailed description of the derivation of the social and demographic variables can be found in chapter 3 (section 3.5.1).

4.2.5 Statistical analyses

The prevalence of MLTC with 95% confidence interval was estimated for the entire study population, and by geographic region and year of study period. Any trend in prevalence over time was assessed using the Cochrane-Armitage test for trend. To account for the influence of differences in the age-structure of the population by region and across the study period, crude prevalence rates were directly standardised for maternal age using the population age structure in the South-East region and in 2007 of the study respectively as the reference population.

Descriptive statistics (numbers and proportions) were used to describe the social and demographic characteristics of the entire study population and based on MLTC status including by type and complexity. Differences between pregnancies with MLTC and those without were assessed using a chi-squared test for differences in proportions. Descriptive statistics (numbers and proportions) were used to describe the composition of MLTC by type and complexity. The ten most common combinations of health condition based on body system aggregation were described for physical health, mental health and mixed MLTC for women with two health conditions using proportions.

To account for women having more than one pregnancy within the study period, a per woman analysis was undertaken using the woman's first pregnancy in the study period to describe the social and demographic characteristics of the study population.

All results were considered to be statistically significant at the 5% confidence level, and all analyses were conducted in StataMP version 17 (Statacorp, College station, USA).

4.3. Results

4.3.1 Population characteristics

A total of 422,091 pregnancy episodes to 331,517 women were included in this study. Of these 68,972 (16.3%) were pregnancies among women with MLTC (MLTC women) and 353,119 (83.7%) were pregnancies among women without MLTC (non-MLTC women). The social and demographic characteristics of the study population are shown in Table 4.1. Comparison of the social and demographic characteristics of the study population based on MLTC status (undertaken as per pregnancy analysis inclusive of all pregnancy episodes in the study period) revealed differences between pregnancies among MLTC women and pregnancies among non-MLTC women. Overall MLTC women were more likely to be older, have a raised BMI ≥30kg/m^2, be of white ethnicity, be living in socioeconomic deprivation or be a current or ex-smoker compared to non-MLTC women.

There were no substantive differences in the observed patterns for social and demographic characteristics of the study population based on a per woman analysis including only the woman's first pregnancy episode in the dataset as shown in appendix C (Table C1).

Table 4.1. Social and demographic characteristics of the study population presented as a per pregnancy analysis by MLTC status

Social and demographic characteristics	Pregnancies to all women in the study population total n=422091		Pregnancies among non-MLTC women total n=353119		Pregnancies among MLTC women total n=68972		Chi-squared test for differences in proportion**
	n/total n with data	%	n/total n with data	%	n/total n with data	%	
Maternal Age							
Less than 20 years	18224/422091	4.3	17119/353119	4.9	1105/68972	1.6	<0.001
20- 34 years	306709/422091	72.7	258044/353119	73.1	48655/68972	70.6	
35-39 years	77995/422091	18.5	63257/353119	17.9	14738/68972	21.4	
More than 40 years	19163/422091	4.5	14699/353119	4.2	4464/68972	6.5	
Smoking status							
Current smoker	100480/400033	25.1	78024/333204	23.4	22456/66829	33.6	<0.001
Ex-Smoker	66716/400033	16.7	52994/333204	15.9	13722/66829	20.5	
Non-smoker	232837/400033	58.2	202186/333204	60.7	30651/66829	45.9	
Missing (as a proportion of total n)	*22058/422091*	*5.2*	*19915/353119*	*5.6*	*2143/68972*	*3.1*	
BMI category							
Underweight	11183/305537	3.7	9184/250564	3.7	1999/54937	3.6	<0.001
Healthy Weight	153387/305537	50.2	129952/250564	51.9	23435/54937	42.6	
Overweight	79440/305537	26.0	65254/250564	26.0	14186/54937	25.8	
Obese	61527/305537	20.1	46174/250564	18.4	15353/54937	27.9	
Missing (as a proportion of total n)	*116554/422091*	*27.6*	*102555/353119*	*29.0*	*13999/68972*	*20.3*	
Ethnicity							
White	264597/297111	89.1	218085/247474	88.1	46512/49637	93.7	<0.001
Black/Black British	7403/297111	2.5	6756/247474	2.7	647/49637	0.9	
Asian/Asian British	15974/297111	5.4	14386/247474	5.8	1588/49637	2.3	
Mixed	3016/297111	1.0	2609/247474	1.1	407/49637	0.6	
Other	6121/297111	2.1	5638/247474	2.3	483/49637	0.7	
Missing (as a proportion of total n)	*124980/422091*	*29.6*	*105645/353119*	*29.9*	*19335/68972*	*28.0*	

Table 4.1. (continued) Social and demographic characteristics of the study population presented as a per pregnancy analysis by MLTC status

Social and demographic characteristics	**Pregnancies to all women in the study population** total n=422091		**Pregnancies among non-MLTC women** total n=353119		**Pregnancies among MLTC women** total n=68972		Chi-squared test for differences in proportion**
	n/total n with data	%	n/total n with data	%	n/total n with data	%	
IMD Quintile*							
1 (Most affluent)	37062/183857	20.2	31589/153315	20.6	5473/30542	17.9	<0.001
2	35811/183857	19.5	30129/153315	19.7	5682/30542	18.6	
3	36911/183857	20.1	30762/153315	20.1	6149/30542	20.1	
4	35861/183857	19.5	29694/153315	19.4	6167/30542	20.2	
5 (Most deprived)	38212/183857	20.8	31141/153315	20.3	7071/30542	23.2	
Missing (as a proportion of total n)	*51132/234989*	*21.8*	*42970/196285*	*21.9*	*8162/38704*	*21.1*	

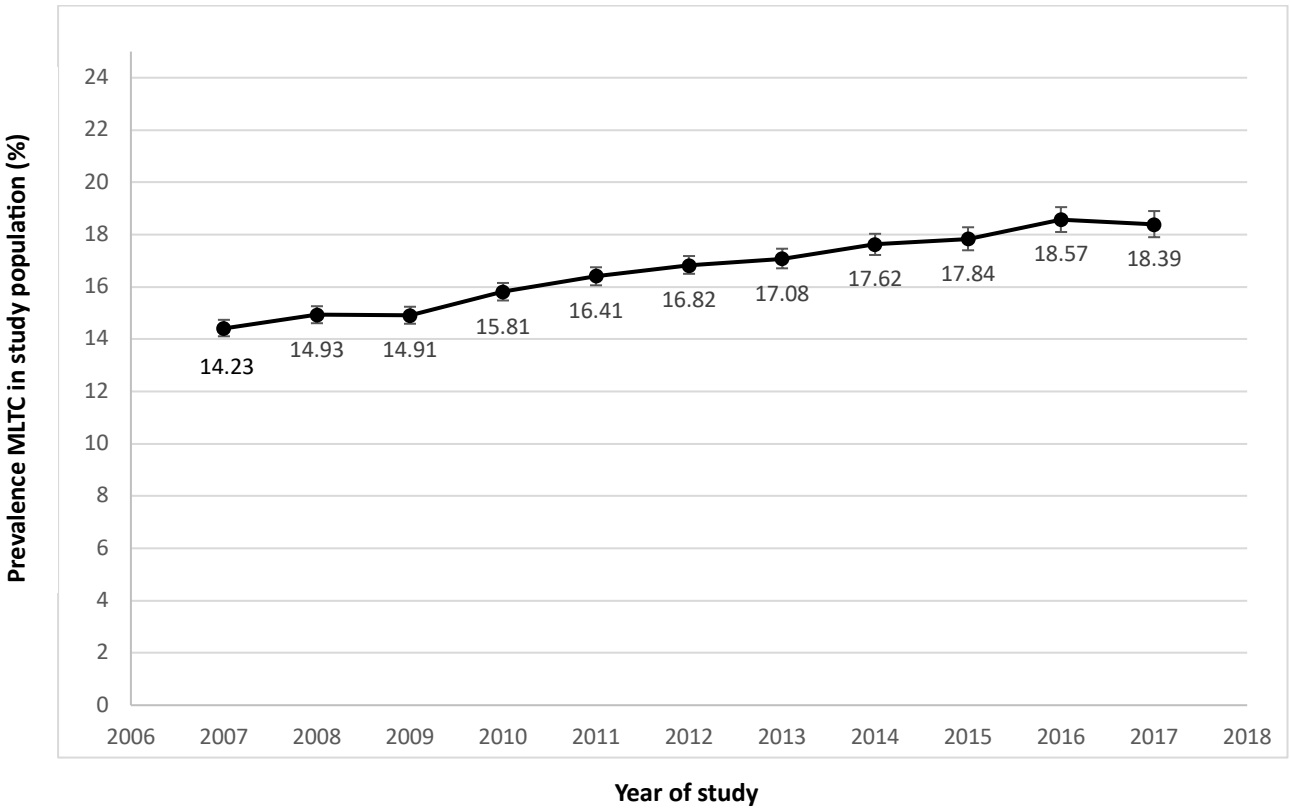
** IMD quintile only available for patients registered at English practices, total n =234,989.*

*** Comparison of pregnancies among non-MLTC women and pregnancies among MLTC women.*

4.3.2 Temporal and geographic trends:

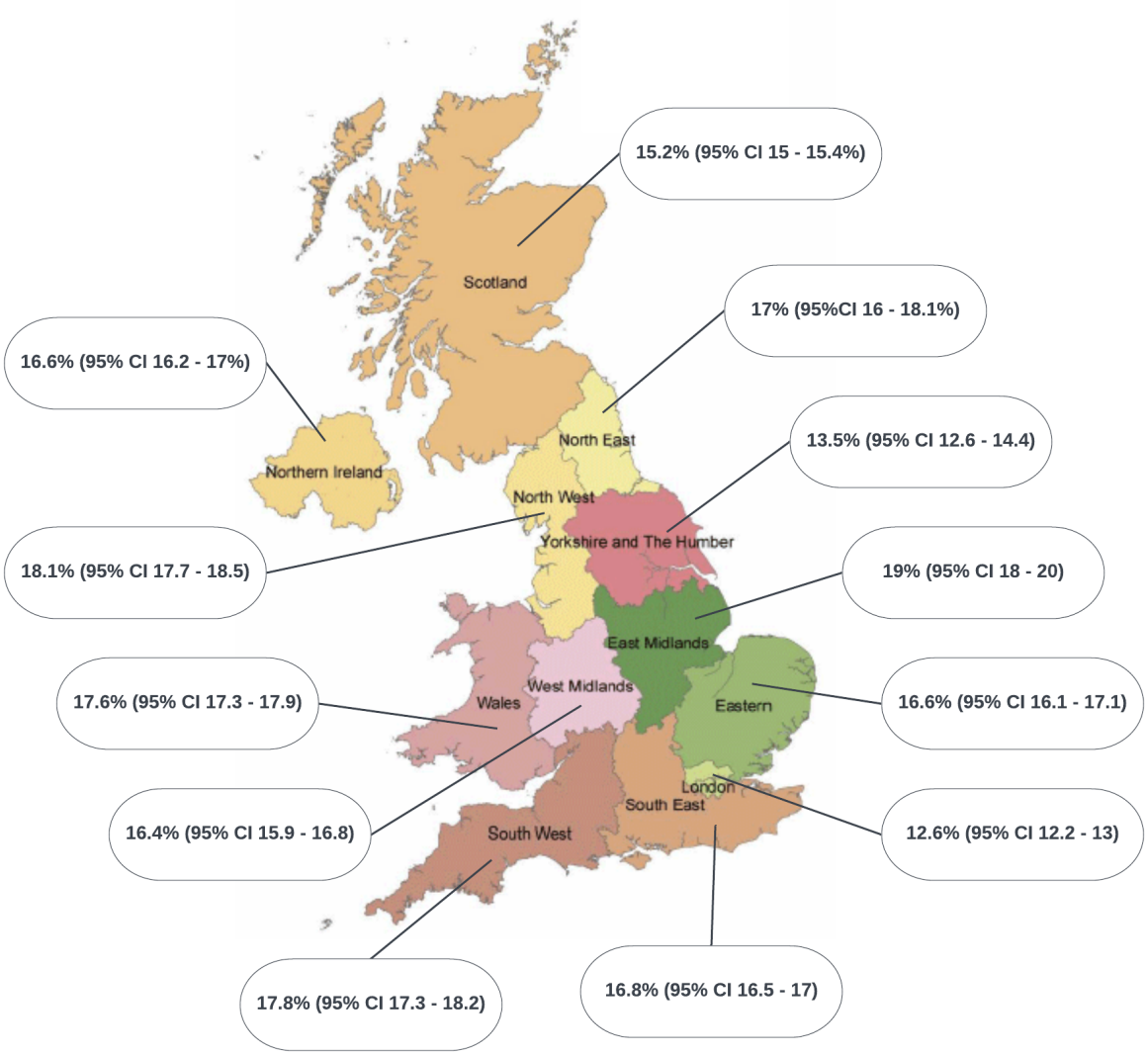
The prevalence of MLTC across the study period for all pregnancies based on the start date of the pregnancy is shown in Figure 4.1.

Figure 4.1. Graph showing the prevalence of MLTC by year of study



Overall, there was a statistically significant increase in the prevalence of MLTC across the study period (test for trend p-value=<0.001). Direct standardisation for maternal age did not substantially alter the observed prevalence by year, or the trend towards an increased prevalence in the latter years of the study period as shown in appendix C (Table C2). The prevalence of MLTC by geographic region of the contributing practice for all pregnancies in the study is shown in Figure 4.2.

Figure 4.2 Schematic illustration of the prevalence of MLTC in pregnancy by graphic region of primary care practice



It can be seen that some geographic regions (Yorkshire and the Humber, London and Scotland) appear to have a lower prevalence of MLTC pregnancies compared to all other regions within the UK. This observation remained consistent, even after direct standardisation of the regional prevalence rate for maternal age as shown in appendix C (Table C3).

4.3.3 Composition of MLTC

The social and demographic characteristics of the study population by type and complexity of MLTC are shown in Tables 4.2 and 4.3. For complex MLTC, a gradient was observed across all the social and demographic characteristics included in the study apart from ethnicity. Overall, the proportions of women who were older, had a raised BMI ≥30kg/m^2, were socioeconomically deprived or current or ex-smokers were higher among those with complex MLTC compared to MLTC consisting of 2 conditions only, or pregnancies to non-MLTC women. Pregnancies among women with physical health MLTC and mixed MLTC contained a higher proportion of older mothers and those with a raised BMI ≥30kg/m^2 compared to pregnancies among women with mental health MLTC and pregnancies among non-MLTC women. Those with mental health MLTC or mixed MLTC were more likely to be current or ex-smokers, more likely to be of white ethnicity, and more likely to be socioeconomically deprived compared to pregnancies among women with physical health MLTC or pregnancies among non-MLTC women.

Table 4.2. Social and demographic characteristics of the study population presented as a per pregnancy analysis by type of MLTC

Social and demographic characteristics	Pregnancies to all women in the study population total n=422091		Pregnancies among non-MLTC women total n=353119		Pregnancies among women with physical health MLTC total n=10218		Pregnancies among women with mental health MLTC total n=21482		Pregnancies among women with mixed MLTC total n=37272		Chi-squared test for differences in proportion**
	n/ total n with data	%	n/ total n with data	%	n/ total n with data	%	n/ total n with data	%	n/ total n with data	%	
Maternal Age											
Less than 20 years	18224/422091	4.3	17119/353119	4.9	279/10218	2.7	265/21482	1.2	561/37272	1.5	<0.001
20- 34 years	306709/422091	72.7	258044/353119	73.1	6672/10218	65.3	14759/21482	73.4	26234/37272	70.4	
35-39 years	77995/422091	18.5	63257/353119	17.9	2467/10218	24.1	4256/21482	19.8	8015/37272	21.5	
More than 40 years	19163/422091	4.5	14699/353119	4.2	800/10218	7.8	1202/21482	5.6	2462/37272	6.6	
Smoking status											
Current smoker	100480/400033	25.1	78024/333204	23.4	1980/9902	20	7774/20671	37.6	12702/36256	35.0	<0.001
Ex-Smoker	66716/400033	16.7	52994/333204	15.9	1733/9902	17.5	4282/20671	20.7	7707/36256	21.3	
Non-smoker	232837/400033	58.2	202186/333204	60.7	6189/9902	62.5	8615/20671	41.7	15847/36256	43.7	
Missing (as a proportion of total n)	*22058/422091*	*5.2*	*19915/353119*	*5.6*	*316/10218*	*3.1*	*811/21482*	*3.8*	*1016/37272*	*2.7*	
BMI category											
Underweight	11183/305537	3.7	9184/250564	3.7	191/8421	2.3	820/16259	5.0	988/30293	3.3	<0.001
Healthy Weight	153387/305537	50.2	129952/250564	51.9	3250/8421	38.6	8044/16259	49.5	12141/30293	40.1	
Overweight	79440/305537	26.0	65254/250564	26.0	2322/8421	27.6	3987/16259	24.5	7877/30293	26.0	
Obese	61527/305537	20.1	46174/250564	18.4	2658/8421	31.6	3408/16259	21.0	9287/30293	30.7	
Missing (as a proportion of total n)	*116554/422091*	*27.6*	*102555/353119*	*29.0*	*1797/10218*	*17.6*	*5223/21482*	*24.3*	*6979/37272*	*18.7*	
Ethnicity											
White	264597/297111	89.1	218015/147474	88.1	6245/7350	85.0	14979/15579	96.2	25288/26708	94.7	<0.001
Black/Black British	7403/297111	2.5	6756/147474	2.7	219/7350	3.0	127/15579	0.8	301/26708	1.1	
Asian/Asian British	15974/297111	5.4	14386/147474	5.8	681/7350	9.3	245/15579	1.6	662/26708	2.5	
Mixed	3016/297111	1.0	2609/147474	1.1	67/7350	0.9	126/15579	0.8	214/26708	0.8	
Other	6121/297111	2.1	5638/147474	2.3	138/7350	1.9	102/15579	0.7	243/26708	0.9	
Missing (as a proportion of total n)	*124980/422091*	*29.6*	*205645/353119*	*29.9*	*2868/10218*	*28.1*	*5903/21482*	*27.5*	*10564/37272*	*28.3*	

Table 4.2. (continued) Social and demographic characteristics of the study population presented as a per pregnancy analysis by type of MLTC

Social and demographic characteristics	Pregnancies to all women in the study population total n=422091		Pregnancies among non-MLTC women total n=353119		Pregnancies among women with physical health MLTC total n=10218		Pregnancies among women with mental health MLTC total n=21482		Pregnancies among women with mixed MLTC total n=37272		Chi-squared test for differences in proportion**
	n/ total n with data	%	n/ total n with data	%	n/ total n with data	%	n/ total n with data	%	n/ total n with data	%	
IMD Quintile*											
1 (Most affluent)	37062/183857	20.2	31589/153315	20.6	953/4481	21.3	1706/9722	17.6	2814/16339	17.2	<0.001
2	35811/183857	19.5	30129/153315	19.7	923/4481	20.6	1777/9722	18.3	2982/16339	18.3	
3	36911/183857	20.1	30762/153315	20.1	893/4481	19.9	1982/9722	20.4	3274/16339	20.0	
4	35861/183857	19.5	29694/153315	19.4	843/4481	18.8	1990/9722	20.5	3334/16339	20.4	
5 (Most deprived)	38212/183857	20.8	31141/153315	20.3	869/4481	19.4	2267/9722	23.3	3935/16339	24.1	
*Missing (as a proportion of total n)**	*51132/234989*	*21.8*	*42970/196285*	*21.9*	*1172/5653*	*20.7*	*2591/12313*	*21.0*	*4399/20738*	*21.2*	

** IMD quintile only available for patients registered at English practices, total n =234,989.*

*** Comparison of pregnancies among non-MLTC women and pregnancies among MLTC women by MLTC type*

Table 4.3. Social and demographic characteristics of the study population presented as a per pregnancy analysis by complexity of MLTC

Social and demographic characteristics	Pregnancies to all women in the study population total n=422091		Pregnancies among non-MLTC women total n=353119		Pregnancies among women with MLTC consisting of 2 conditions total n=47730		Pregnancies among women with MLTC consisting of 3+ conditions total n=21242		Chi-squared test for differences in proportion**
	n/ total n with data	%	n/ total n with data	%	n/ total n with data	%	n/ total n with data	%	
Maternal Age									
Less than 20 years	18224/422091	4.3	17119/353119	4.8	888/47730	1.9	217/21242	1.0	<0.001
20- 34 years	306709/422091	72.7	258044/353119	73.1	34062/47730	71.4	14603/21242	68.8	
35-39 years	77995/422091	18.5	63257/353119	17.9	9893/47730	20.7	4845/21242	22.8	
More than 40 years	19163/422091	4.5	14699/353119	4.2	14699/47730	6.1	1577/21242	7.4	
Smoking status									
Current smoker	100480/400033	25.1	78024/333204	23.4	21956/46153	47.6	7505/20676	36.3	<0.001
Ex-Smoker	66716/400033	16.7	52994/333204	15.9	9246/46153	20.0	4476/20676	21.7	
Non-smoker	232837/400033	58.2	202186/333204	60.7	14951/46153	32.4	8695/20676	42.1	
Missing (as a proportion of total n)	*22058/422091*	*5.2*	*19915/353119*	*5.6*	*1577/47730*	*3.3*	*566/21242*	*2.7*	
BMI category									
Underweight	11183/305537	3.7	9184/250564	3.7	1396/37321	3.7	603/17652	3.4	<0.001
Healthy Weight	153387/305537	50.2	129952/250564	51.9	16610/37321	44.5	6825/17652	38.7	
Overweight	79440/305537	26	65254/250564	26.0	9764/37321	26.2	4422/17652	25.1	
Obese	61527/305537	20.1	46174/250564	18.4	9551/37321	25.6	5802/17652	32.9	
Missing (as a proportion of total n)	*116554/422091*	*27.6*	*102555/353119*	*29.0*	*10409/47730*	*21.8*	*3590/21242*	*6.9*	
Ethnicity									
White	264597/297111	89.1	218015/147474	88.1	32059/34311	93.4	14453/15326	94.3	<0.001
Black/Black British	7403/297111	2.5	6756/147474	2.7	470/34311	1.4	177/15326	1.2	
Asian/Asian British	15974/297111	5.4	14386/147474	5.8	1156/34311	3.4	432/15326	2.8	
Mixed	3016/297111	1.0	2609/147474	1.1	274/34311	0.8	133/15326	0.9	
Other	6121/297111	2.1	5638/147474	2.3	352/34311	1.0	131/15326	0.9	
Missing (as a proportion of total n)	*124980/422091*	*29.6*	*205645/353119*	*29.9*	*13419/47730*	*28.1*	*5916/21242*	*27.9*	

Table 4.3. (continued) Social and demographic characteristics of the study population presented as a per pregnancy analysis by complexity of MLTC

Social and demographic characteristics	Pregnancies to all women in the study population total n=422091		Pregnancies among non-MLTC women total n=353119		Pregnancies among women with MLTC consisting of 2 conditions total n=47730		Pregnancies among women with MLTC consisting of 3+ conditions total n=21242		Chi-squared test for differences in proportion**
	n/ total n with data	%	n/ total n with data	%	n/ total n with data	%	n/ total n with data	%	
IMD Quintile*									
1 (Most affluent)	37062/183857	20.2	31589/153315	20.6	3903/21215	18.4	1570/9327	16.8	<0.001
2	35811/183857	19.5	30129/153315	19.7	4031/21215	19.0	1651/9327	17.7	
3	36911/183857	20.1	30762/153315	20.1	4224/21215	19.9	1925/9327	20.6	
4	35861/183857	19.5	29694/153315	19.4	4270/21215	20.1	1897/9327	20.3	
5 (Most deprived)	38212/183857	20.8	31141/153315	20.3	4787/21215	22.6	2284/9327	24.5	
*Missing (as a proportion of total n)**	*51132/234989*	*21.8*	*42970/196285*	*21.9*	*5741/26956*	*21.3*	*2421/11748*	*20.6*	

** IMD quintile only available for patients registered at English practices, total n =234989.*

*** Comparison of pregnancies among non-MLTC women and pregnancies among MLTC women by MLTC complexity.*

The ten most common combinations of health conditions based on body system aggregation for each type of MLTC are shown in Figures 4.3, 4.4 and 4.5 for pregnancies among women with MLTC consisting of 2 conditions. Among pregnancies to women with physical health MLTC, combinations of co-morbid gynaecological, endocrine, respiratory and pain/fatigue conditions accounted for the majority of the burden of physical health MLTC. Among pregnancies to women with mixed MLTC, mental health conditions that were comorbid with respiratory, endocrine, gynaecological and pain/fatigue conditions accounted for the majority of the burden of mixed MLTC. Among pregnancies to women with mental health MLTC, co-morbid anxiety and depression accounted for the substantial burden of disease in this group.

Figure 4.3 Schematic representation of the ten most common combinations of health conditions by body system aggregation contributing to physical health MLTC comprised of 2 conditions

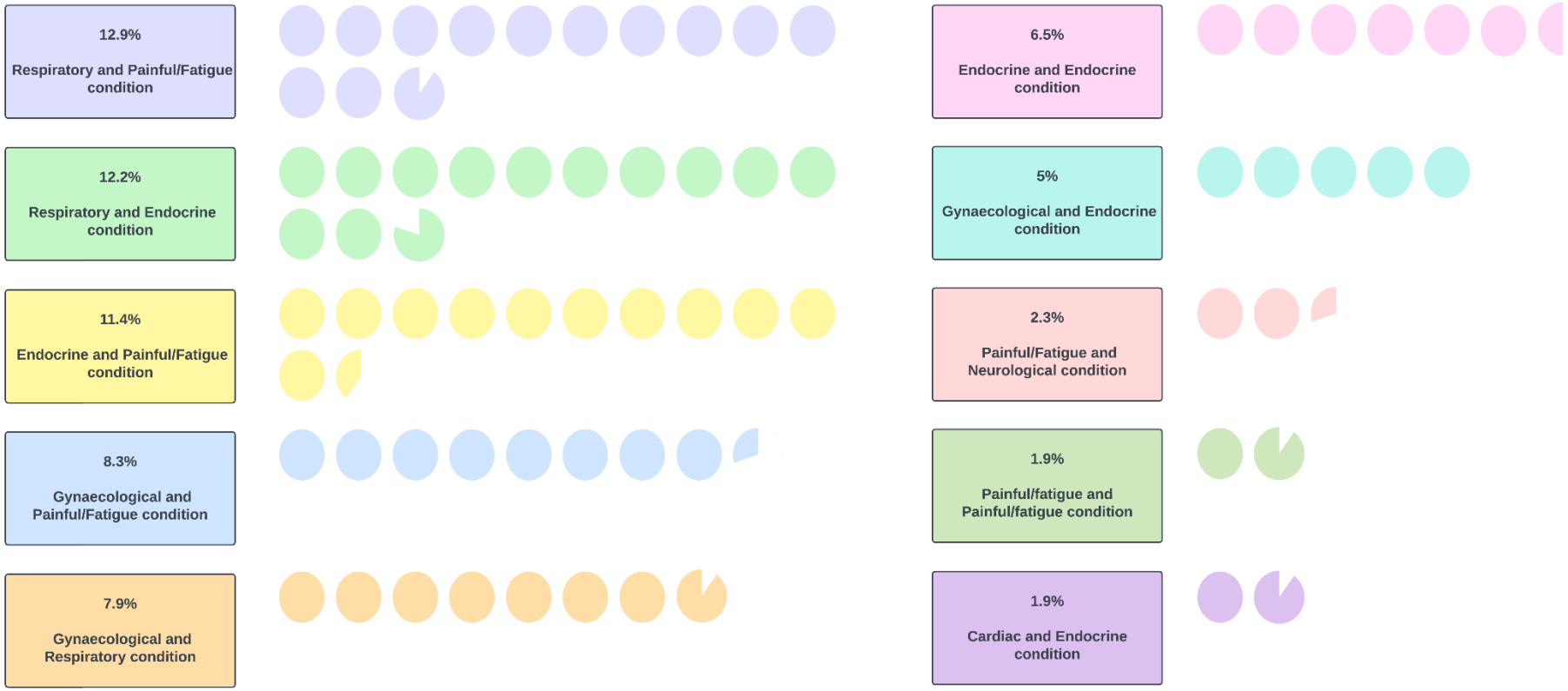


Figure 4.4 Schematic representation of the ten most common combinations of health conditions by diagnosis contributing to mental health MLTC comprised of 2 conditions

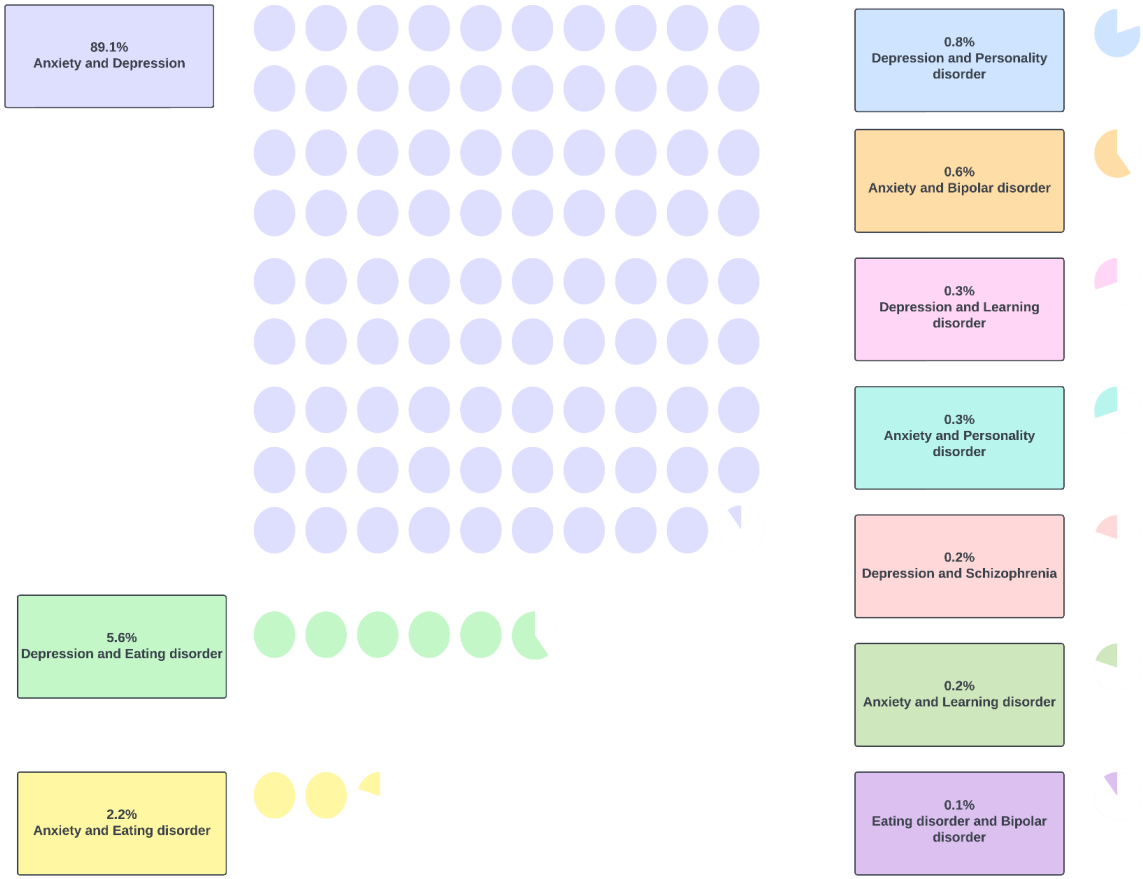
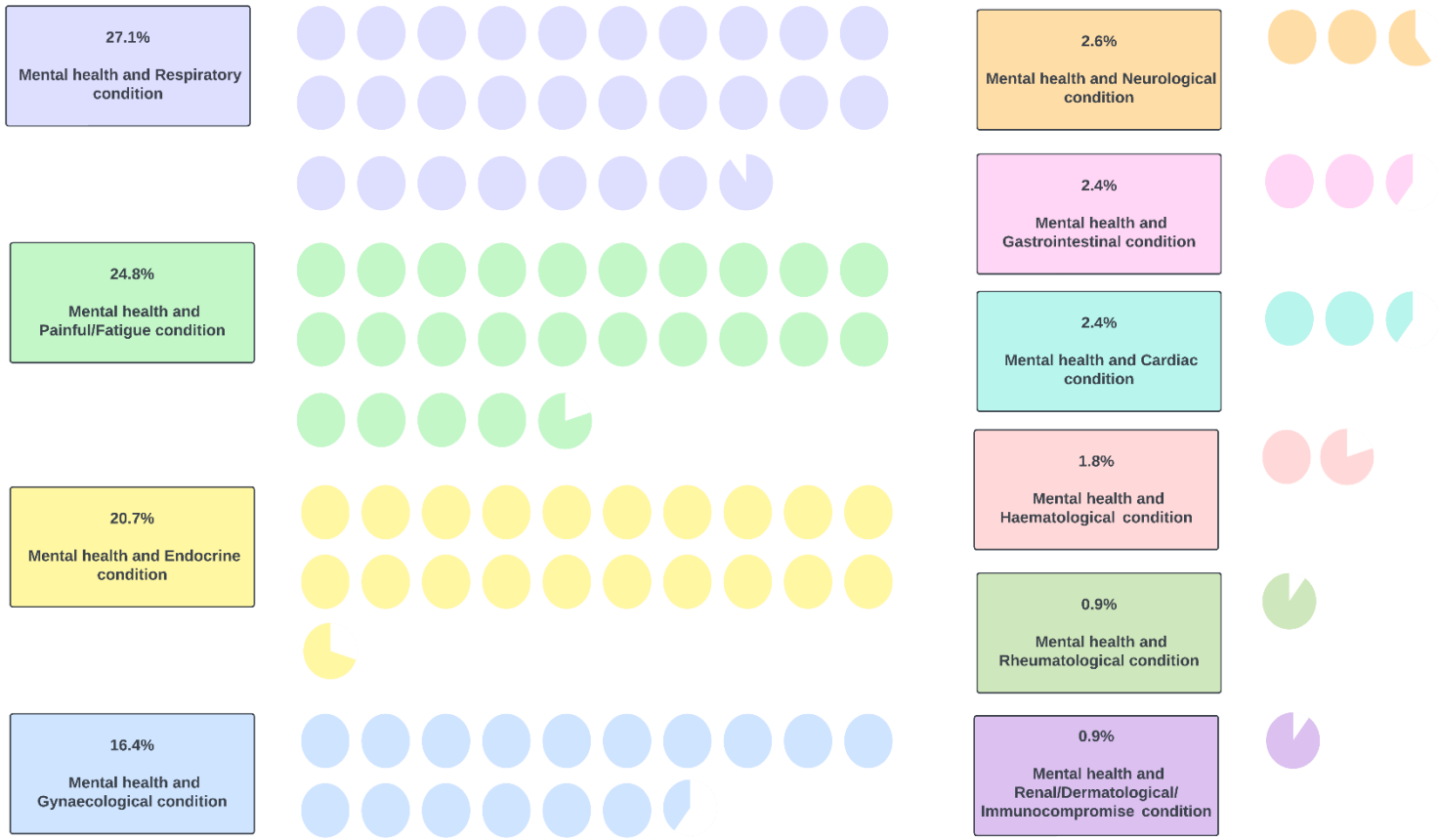


Figure 4.5. Schematic representation of the ten most common combinations of health conditions by body system aggregation contributing to mixed MLTC comprised of 2 conditions



The composition of MLTC based on type and complexity is shown in Figures 4.6 and 4.7. The most common type of MLTC in the study population was mixed MLTC (54% of pregnancies among women with MLTC), followed by mental health MLTC (31.2% pregnancies among women with MLTC), with the least common type of MLTC being physical health MLTC (14.8% of pregnancies among women with MLTC). Exploration of complexity of MLTC within type of MLTC revealed differences in the burden of complex MLTC between the groups. A higher proportion of pregnancies were considered to have complex MLTC for women with mixed MLTC (49% of pregnancies among women with mixed MLTC) compared to women with physical health MLTC (14% of pregnancies among women with physical health MLTC) or mental health MLTC (6% of pregnancies among women with mental health MLTC). For pregnancies to women with complex MLTC, the majority of pregnancies were from mixed MLTC (87% of pregnancies among women with complex MLTC) followed by physical health MLTC (7% of pregnancies among women with MLTC) and mental health MLTC (6% of pregnancies among women with MLTC).

Figure 4.6 Schematic representation of the proportional contribution of different types of MLTC within the study population, and within type of MLTC the proportional contribution of complexity of MLTC

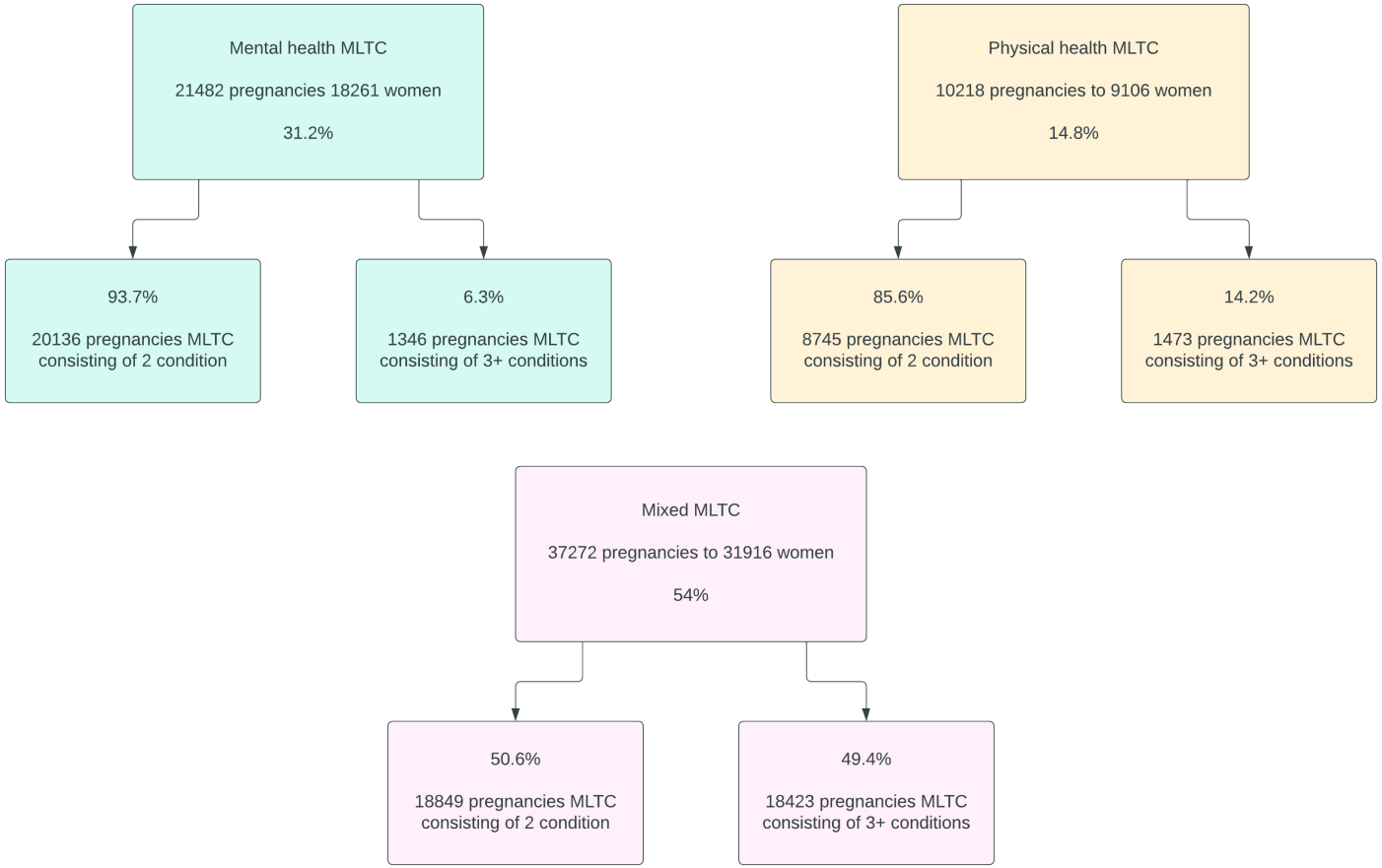
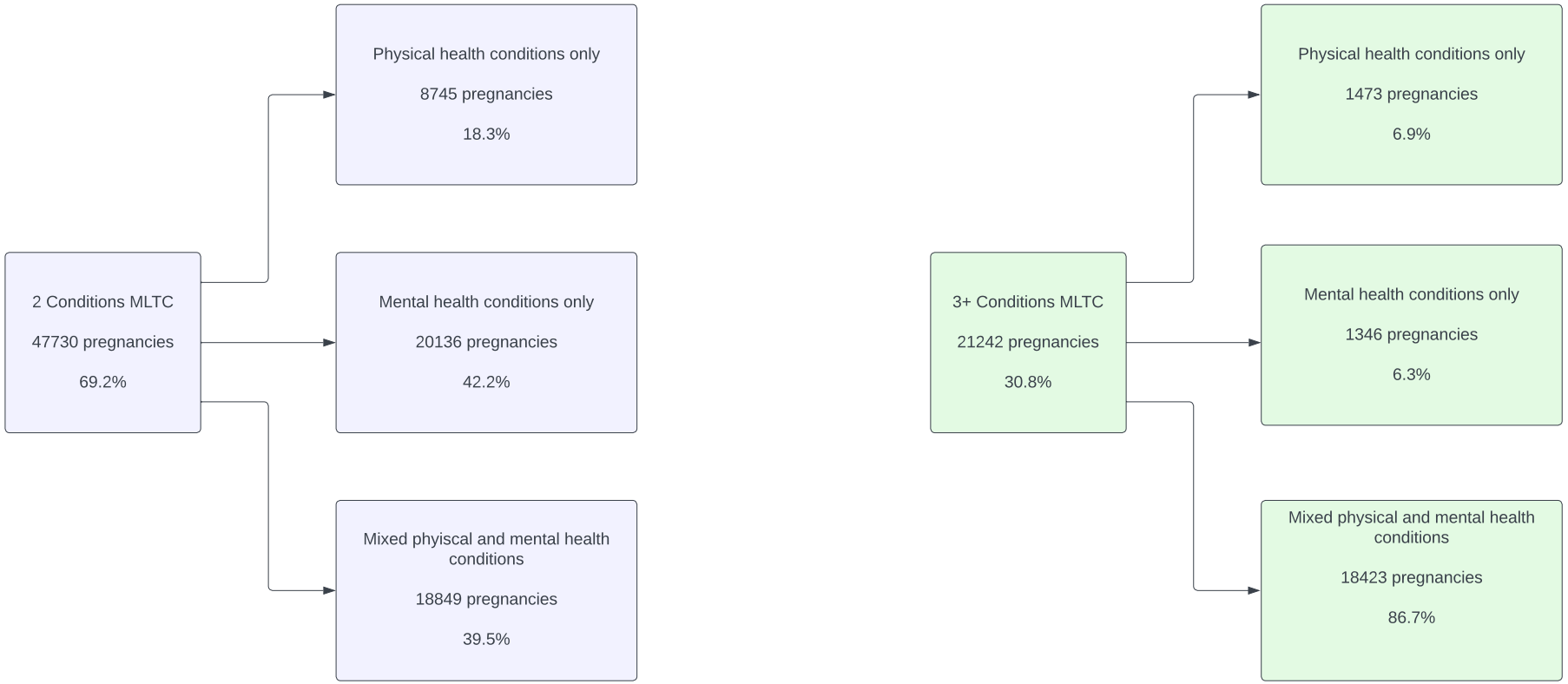


Figure 4.7 Schematic representation of the proportional distribution of complexity of MLTC, and within complexity of MLTC the proportional contribution of physical and mental health conditions



4.4 Discussion

4.4.1 Contribution to knowledge:

The work presented in this chapter represents the largest study of the epidemiology of MLTC in pregnancy to date. The use of a bespoke list of health conditions selected with specific regard to their importance to both pregnancy outcome and women's reproductive health has revealed important patterns of MLTC among younger women not previously described in the literature.

4.4.2 Interpretation of findings and comparison to literature:

4.4.2.1 Prevalence of MLTC

This study reports an overall prevalence of MLTC of 16.3%, showing it to be a common health concern among pregnant women. There is generally a wide variation in the reported prevalence of MLTC in previous population-based studies (70, 249). This likely reflects differences in both the populations being studied, and the health conditions included in the definition and operationalisation of MLTC (70, 249). A recent study by Cassell et al. used CPRD GOLD to study the epidemiology of MLTC in the general adult population of the UK (3). This study showed a prevalence of MLTC of 6.9% among adults aged 25-34 years and 12.1% among adults aged 35-44 years, which are lower than the estimated prevalence reported in this work. Another study by Barnett et al. from 2012 used Scottish Primary Care data to study the epidemiology of MLTC in the general adult population in Scotland (10). This study showed a prevalence of 11.3% among adults aged 25-44 years, which again is a lower

estimate than that obtained in this work. It is important to note that these results are not disaggregated by sex (with MLTC generally reported to be higher in women than men (2)), and that the operationalisation of MLTC in this study did not include gynaecological conditions which were shown to represent a substantial contribution to disease burden in this work. Conversely, a study by Lee et al. that used three Primary Care datasets from the UK to describe the epidemiology of MLTC in pregnancy estimated the prevalence of MLTC to be 44.2% in CPRD (211). Despite the work by Lee et al. and the work presented in this thesis both ostensibly being conducted in pregnant populations using similar data sources, there are important differences between the studies that may account for the observed disparity in the results. First, the population studied by Lee et al. included pregnancies of any outcome including those ending in miscarriage, ectopic or termination of pregnancy, and we cannot discount there may differences regarding MLTC in these pregnancies compared to those ending in a livebirth or stillbirth. Second, as discussed in chapter 2 (section 2.3.8) the health conditions studied by Lee et al. demonstrated features of overlap, and included conditions such as Allergic Rhinitis which is very common, and was not included in this study due to the lack of plausible evidence of its importance to pregnancy outcome. Both these factors would arguably contribute to higher estimates of the prevalence of MLTC than that reported in this work.

4.4.2.2 Population characteristics

Differences in the social and demographic characteristics of pregnancies among women with MLTC compared to pregnancies among non-MLTC women are reported in this study. The finding of higher proportions of socioeconomic deprivation, smoking, obesity, and older age

among pregnancies to women with MLTC is consistent with observations reported in many other studies in the general adult population (9, 10, 250). It is notable that the prevalence of smoking in the study population is higher than estimates of smoking prevalence for the maternity population in England provided by NHS digital, which was estimated to be 9.1% between 2021-2022 (245). This discrepancy may be reflective of differences in how smoking status was defined and measured in this study compared to the NHS Digital data. Estimates produced by NHS Digital are based on women's self-reported use of tobacco products at the time of birth, whereas in this study smoking status was measured at the start of pregnancy using information recorded within the EHRs. This could plausibly result in a higher estimate of prevalence as is it will not account for women who quit smoking during pregnancy.

Regarding ethnicity, women with MLTC were more likely to be from a white ethnic background than from minority ethnic backgrounds. Studies of chronic conditions, including co-morbidity and MLTC studies predominately in older adults, have previously shown that several conditions are more likely to occur among individuals from minority ethnic backgrounds (251-254), therefore the plausibility of women from White ethnic backgrounds having a higher prevalence of MLTC as shown in this study warrants additional scrutiny. As highlighted above, having a diagnosis of any health condition in this study is contingent on the patient having adequate access to primary care. It has previously been documented that individuals from minority ethnic backgrounds face inequalities accessing primary care resulting from a number of barriers including language, culture, and perceptions of healthcare staff (255-258). It is possible that inequalities in access to primary care may account for the lower observed prevalence of MLTC among women from minority ethnic backgrounds seen in this study. It is also becoming increasingly recognised that individuals

from minority ethnic backgrounds are more likely to experience delays in the diagnosis of some common health conditions, or a lower rate of onward referral to secondary care or specialist services (203, 259-266). If younger women from minority ethnic backgrounds were experiencing delays to diagnosis of certain health conditions, this could conceivably present as a lower prevalence of chronic disease among women from these ethnic groups. This would to some extent be corrected in studies inclusive of older adults, as more time would have elapsed for an individual to receive a diagnosis.

4.4.2.3 Temporal and geographic trends

The prevalence of MLTC was observed to increase across the study period from 14.4% in 2007 to 18.4% in 2017 (p-value for trend in prevalence=<0.001). Several other studies of MLTC in the general adult population that have investigated prevalence trend over time, report similar results to this study regarding an observed increase in the prevalence of MLTC (9, 135, 185). One study in England has previously examined regional variations in the prevalence of MLTC, reporting an increased prevalence of MLTC in northern compared to southern regions of the UK, which is a pattern of regional prevalence not replicated by this study (9). Instead, a lower prevalence of MLTC among three relatively disparate geographical regions of the UK (Scotland, Yorkshire and the Humber, London) was observed, and the plausibility of this requires further examination.

An analysis by the Department of Work and Pensions showed that the proportion of people living in poverty by region in the UK was highest in Northern regions of England and London (267, 268). Socioeconomic deprivation is strongly associated with the development of non-

communicable diseases, and has consistently been reported as a risk factor for MLTC (10, 194, 269). It would therefore be anticipated that regions with higher rates of socioeconomic deprivation would conceivably have higher rates of MLTC. In this study, the identification of cases of MLTC was dependent on the presence of medical and product codes within the clinical records. Inequalities in access to primary care based on socioeconomic status are becoming increasingly well recognised and defined in both the literature and within healthcare policy (270). In particular, an inverse relationship between the number of doctors working in general practice and the health needs of populations living in deprivation has been highlighted as key driver of inequitable access (271-274). This type of barrier may plausibly result in populations from deprived areas facing delays to accessing care and diagnosis(275-277), which would be manifested as an apparent lower prevalence of disease with the method of case ascertainment used in this study.

In addition to this, data published by NHS Digital on hospital accident and emergency activity shows that populations living in the most deprived regions of the UK used emergency care twice as much as populations from less deprived regions (278). While this may reflect an increased severity of underlying health conditions requiring secondary care within these populations, it may also reflect a lack of access to timely primary care services or a preference to use emergency care over primary care (279). As care received within accident and emergency departments is not automatically coded within primary care records, this could contribute to lower case ascertainment for certain health conditions. It is possible that the lower prevalence of MLTC in certain regions of the UK reported in this study is an artefact of access to and use of primary care rather that a reflecting a genuinely lower prevalence rate of MLTC.

4.4.2.4 Composition of MLTC

The commonest groupings of health conditions that contributed to MLTC were mental-health disorders (anxiety and depression), endocrine conditions, respiratory conditions, pain and fatigue conditions, and gynaecological conditions. With the exception of gynaecological conditions, which have not routinely been included in previous work on MLTC, these conditions are consistent with those other large population-based studies have reported as being the commonest contributing conditions to MLTC (3, 10, 106, 194). The estimated prevalence of gynaecological conditions among women of reproductive age is reported to be high (197, 198, 280), and so it is not an unanticipated finding that these conditions would contribute to a substantial burden of disease for women with MLTC.

The predominant group type of MLTC observed in this study was mixed MLTC (54%) consisting of women who had at least one physical health and one mental health condition. Studies by McLean et al, Barnett et al. McRae et al. and Cassell at al. have all reported that physical-mental health comorbidity was most commonly observed among those aged 18 to 44 years, and was also more common among women (3, 10, 250, 269). The estimated prevalence of mixed MLTC in these studies however, is lower than that reported in this study, ranging from between 11 to 40%. The most likely reason for this is the inclusion of gynaecological conditions, polycystic ovarian syndrome and a wider range of pain and fatigue conditions in this study. A recent systematic review and meta-analysis conducted by Zaks et al, demonstrated a high prevalence of co-morbid mental health disorders with gynaecological disorders and polycystic ovarian syndrome, which is consistent with what is

reported in this study (281). The association between comorbid mental health disorders and pain or fatigue conditions has also been previously well described in the literature (282, 283), which again supports the plausibility of the patterns observed in this study. The predominance of mixed MLTC revealed in this study illustrates the importance of including conditions that are common and important to women's health within operationalisations of MLTC.

Among pregnancies with MLTC in this study, 30.8% were classified as having complex MLTC consisting of three or more conditions. This estimated prevalence is similar to studies by Head et al. and McRae et al. who reported estimates of complex MLTC of 30.8% and 27.5% respectively, despite these studies including older adults (9, 250). Complex MLTC has previously been shown to be strongly associated with ageing in the general population (269), so it would have been anticipated that our estimation of the prevalence of complex MLTC would be lower than studies inclusive of older adults. In this study a high proportion of complex MLTC (86.7%) was from the co-morbidity of physical and mental health conditions. This suggests that the comparable estimate for the prevalence of complex MLTC reported in this study may again be driven by our inclusion of a greater number of conditions that are important causes of morbidity among women of reproductive age. Previous studies have potentially underestimated the burden of MLTC and complex MLTC among younger women.

4.4.3 Strengths and limitations

The main strengths of this study are as follows:

1. The information contained within the CPRD dataset originates from UK primary care, in many instances directly from what is recorded by general practitioners in the patient's clinical record as part of the necessary documentation of healthcare provision. This means that although this type of data is not strictly collected for research purposes, it is arguably more granular and better reflective of care provided than datasets comprised only from administrative data. As general practitioners are typically responsible for many aspects of assessment and ongoing management of long-term health conditions including drug prescriptions, these data can provide a detailed and accurate picture of health and disease at the population-level. The use of primary care data additionally allows capture of the entire spectrum of morbidity from MLTC at the population-level, including individuals with less severe manifestations of any given health conditions. A key criticism of studies that have only used secondary care data sources is that only individuals who have the most severe disease phenotype requiring treatment in secondary care are captured. Furthermore, this study was purposefully attentive to ensuring that only relevant and well-defined codes were used to identify the health conditions under investigation. This adds additional assurances as to the robustness of the estimates of the prevalence of MLTC.
2. The population of women eligible for inclusion in this study is large, and the study period covers ten-years of data. This has allowed for the examination of trend across the study period and allowed for the description of sub-groups of MLTC by both type and complexity within the dataset.
3. The health conditions included in this study were specifically chosen for their relevance to both maternal and perinatal health, and women's health including

gynaecological conditions and conditions likely to be prevalent among women of reproductive age. Many of the health conditions included in this study, have not been widely included in previous studies of MLTC. Firstly, this means that the results from this study are likely to be highly relevant to developing our understanding of the implications of MLTC to maternal and perinatal health. Secondly, it has allowed for the description of previously undocumented patterns of morbidity among women of reproductive age.

The main limitations of this study are as follows:

1. The identification of health conditions of interest is dependent on the presence of medical codes or prescription codes in the clinical records. This invariably means that within the study population, only those individuals who are willing and able to access and use primary care will be identified as having the health conditions under investigation. Individuals who are not registered with primary care at all, or who face barriers to the access and use of primary care are not adequately represented through this method of case ascertainment. As described above, only relevant and well-defined medical and product codes were used to identify health conditions within the dataset. This approach was chosen in an attempt to add assurance to the identification of true cases. It cannot be discounted, however, that some health conditions may be more likely to be recorded using non-specific descriptive or symptom codes not included in the code lists. This would likely result in an underestimation of the prevalence of these health conditions overall. It can also not be discounted that certain population groups may be less likely to have definitive diagnostic codes recorded or may face differential delays in diagnosis. This would

likely result in an underestimation of the prevalence of MLTC within these groups. These are additional limitations of this method of case ascertainment, which would result in a misclassification of exposure status. In this instance the most likely direction of effect would be to misclassify women with MLTC as non-MLTC.

2. Extensive data cleaning, management and the application of data quality restrictions was necessary to produce a dataset that was of a suitable standard for use in this research. An inescapable consequence of this process, however, is that women with certain characteristics are more likely to be included in the final study population. This represents a source of selection bias, despite the population-based design of this study. Women of white ethnicity and women who were more affluent appeared to be over-represented within the final study population, when compared to other national estimates of the social and demographic characteristics of the maternity population in England and Wales (246). This has implications for the overall generalisability of the findings, but also raises the question as to whether this study adequately describes the patterns and characteristics of MLTC in pregnancy particularly for women from minority ethnic groups or those living in socioeconomic deprivation.
3. All of the social and demographic characteristics described in this study apart from maternal age and smoking had high proportions of missing data. Data quality and completeness of data are commonly encountered issues with routine data, and high proportions of missing data diminish the ability to robustly interpret inferences about differences in the characteristics of the study population. High proportions of missing data also limited the ability to adequately standardise MLTC prevalence rates for ethnicity and socioeconomic status. These are variables of interest in addition to

maternal age that could plausibly account for the observed differences in prevalence between different geographic regions and across the study period. The mechanism of missingness for these two variables (IMD quintile only available for English patients, and women with HES linkage being more likely to have a recorded ethnicity) was not considered to be amenable to the use of multiple imputation to account for the missing data.

4.4.4 Conclusion

This study shows that MLTC is a highly prevalent health problem among pregnant women and is associated with higher proportions of socioeconomic deprivation, smoking, obesity, and advanced maternal age. The predominant type of MLTC among pregnant women was composed of co-morbid physical and mental health conditions, with mental health MLTC being the second commonest type and physical health MLTC being the least common type. Complex MLTC accounted for just under one-third of all MLTC among pregnant women, and was associated with an increasing gradient of effect across all maternal social and demographic characteristics except ethnicity.

Chapter 5: Investigating the association between MLTC and severe adverse maternal and perinatal outcomes during pregnancy and the immediate postnatal period

5.1 Introduction and research objectives

Maternal death, severe maternal morbidity, stillbirth and neonatal death are all examples of severe adverse outcomes in pregnancy. Although these outcomes are relatively uncommon in high income countries (27, 284, 285), they are of great importance due to their substantial impact on the individuals involved, their families and wider society (243). While events culminating in these outcomes can be unanticipated, studies of mortality and life-threatening morbidity often demonstrate the presence of potentially modifiable factors (31, 33, 41-44). A clear example of this is provided by the most recent MBRRACE-UK report on maternal deaths covering the triennium 2019 to 2021 which showed that for 52% of women who died improvement to the care they received may have made a difference to their outcomes (27). Expanding the evidence base surrounding severe adverse outcomes in pregnancy is therefore integral to developing safer maternity care.

Severe adverse outcomes in pregnancy also represent important causes of health inequality, as rates of these outcomes are not evenly distributed across the maternity population as a whole. It is increasingly established that women who are from minority ethnic backgrounds and women who are living in socioeconomic deprivation experience a disproportional burden of severe adverse outcomes in pregnancy (31, 205, 286-289). Findings from a number of studies have shown that pre-existing health conditions are an important risk

factor for severe maternal morbidity and progression to maternal death (41, 290). Additionally, findings from MBRRACE-UK consistently show that women who have pre-existing health conditions, including multiple conditions appear to be over-represented among those who die in pregnancy or after giving birth. This suggests that MLTC may represent an important driver of inequalities in maternal and perinatal outcome, however, the exact nature or magnitude of this potential association has not previously been adequately quantified.

This chapter addresses research objective 4 of this thesis:
To investigate the association between MLTC in pregnancy and severe adverse maternal and perinatal outcomes in pregnancy and the immediate postpartum period.

5.2 Methods

5.2.1 Data sources

The primary data sources used in this study are CPRD GOLD, CPRD pregnancy register and HES APC dataset. Additional linkage between CPRD pregnancy register and the 2019 Index of Multiple Deprivation, Office of National Statistics Death Registration data and CPRD GOLD primary care records for babies linked to mothers through the Mother-baby link was used to provide information about socioeconomic status, maternal death and neonatal death.
A detailed description of the data sources used in this study can be found in chapter 3 (section 3.2).

5.2.2 Study population

The study population consisted of women who:

a) Were aged between 15 and 49 years old at the time of pregnancy.
b) Had a pregnancy with an estimated start date between the 1st of January 2007 and the 31st of December 2017.
c) Had a pregnancy that was a minimum gestational length of 22+0 weeks and resulted in either a late fetal loss, stillbirth or livebirth.
d) Had pregnancy data that was research quality (woman is registered for at least one year and practice is up-to-standard for at least one year prior to the estimated start date of the pregnancy).
e) Remained actively registered with a CPRD contributing practice with a last collection date for data that is a minimum of 56 days following the estimated end date of the pregnancy.
f) Had a pregnancy in the CPRD pregnancy register that can be matched and validated with a delivery record in the HES APC dataset.

A detailed description of the derivation of the study population, including the application of inclusion and exclusion criteria and the matching and validation of pregnancy records to delivery records can be found in chapter 3 (sections 3.6, 3.7 and 3.8).

5.2.3 Exposure under investigation

The main exposure under investigation was MLTC that was defined as a woman having any combination of two or more long-term physical health, mental health or infectious

conditions prior to the start of pregnancy. MLTC was also considered by type and complexity. Women with two or more physical health conditions were considered to have physical health MLTC, women with two or more mental health conditions were considered to have mental health MLTC, and women with at least one physical and one mental health condition were considered to have mixed MLTC. Women who had three or more health conditions prior to the start of pregnancy were considered to have complex MLTC.

A detailed description of the measurement of exposure status can be found in chapter 3 (section 3.3).

5.2.4 Social and demographic characteristics

Information about maternal age, ethnicity, smoking status, BMI and socioeconomic status was extracted from the EHRs for all women in the study population. Variables indicating maternal age, smoking status and BMI were derived on a per pregnancy basis using the estimated start date of the pregnancy, and socioeconomic status and ethnicity were derived on a per woman basis.

A detailed description of the derivation of the social and demographic variables can be found in chapter 3 (section 3.5.1).

5.2.5 Pregnancy and birth characteristics

Information about gestation at first contact with antenatal care, diagnoses of obstetric co-morbidities in the current pregnancy, gestation at delivery, birthweight and obstetric and

anaesthetic interventions at the time of birth were derived from the EHRs for all women in the study population. All co-variates were measured on a per pregnancy basis.

A detailed description of the derivation of the pregnancy and birth variables can be found in chapter 3 (section 3.5.2).

5.2.6 Outcomes under investigation

The outcomes under investigation in this study were maternal death, severe maternal morbidity (SMM), stillbirth and neonatal death.

A detailed description of the outcome variables and their derivation can be found in chapter 3 (section 3.4.1).

5.2.7 Sample size

The sample size of this study was fixed by the number of pregnancy episodes that met the data quality criteria and could be matched to a validated delivery episode in HES. It was not feasible to set a minimum required sample size prior to the data cleaning and curation. All women who met the inclusion criteria were included in this study, and attempts were made to maximise case ascertainment for all outcomes under investigation. An exploration of the minimum difference in the outcome event rate between MLTC women and non-MLTC women that would be required to generate a significant odds ratio given the size of the study population is presented in Table 5.1.

Table 5.1. Minimum detectable odds ratios for outcome events based on the size of the study population and prevalence of MLTC

Outcome	Approximate event rate and prevalence*	Approximate number of cases assuming no difference in event rate between MLTC and non-MLTC groups	Number of cases and prevalence among MLTC women required to achieve minimum detectable odds ratio	Minimum detectable odds ratio (calculated for 80% power at the 95% confidence level)
Maternal death	10 per 100,000 maternities Prevalence 0.01% (29)	MLTC = 3 cases Non-MLTC = 12 cases	MLTC = 7 cases Prevalence 0.03%	2.9 (95% CI 1.2-7.5)
Severe maternal morbidity	100 per 10,000 maternities Prevalence 1% (284)	MLTC = 242 cases Non-MLTC = 1220 cases	MLTC = 290 cases Prevalence 1.2%	1.2 (95% CI 1.1-1.4)
Stillbirth	4 per 1000 births Prevalence 0.4% (285)	MLTC = 97 cases Non-MLTC = 488 cases	MLTC = 126 cases Prevalence 0.5%	1.3 (95% CI 1.1-1.6)
Neonatal death	2 per 1000 births Prevalence 0.2% (285)	MLTC = 48 cases Non-MLTC = 243 cases	MLTC = 67 cases Prevalence 0.3%	1.4 (95% CI 1.04-1.8)

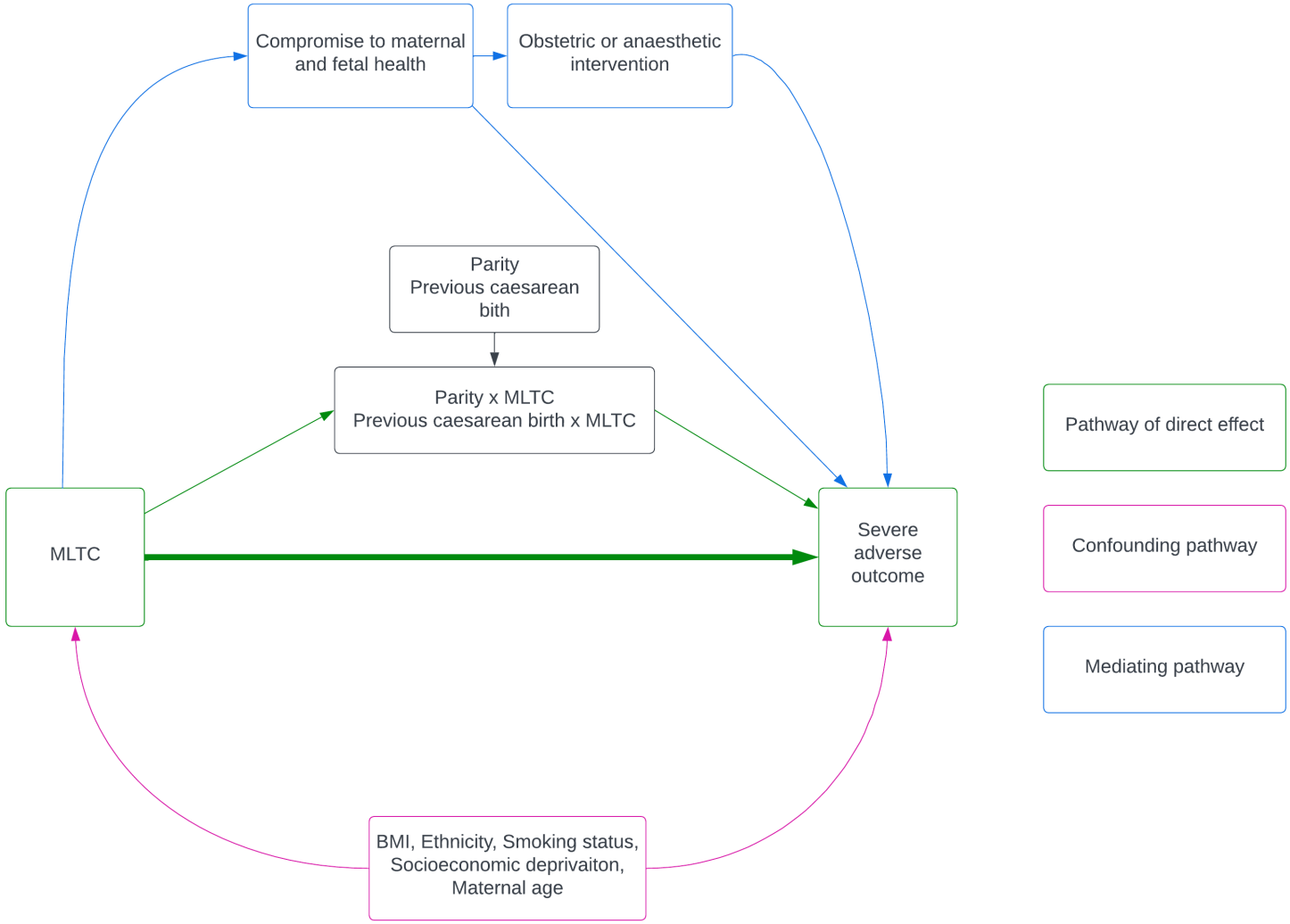
* *Minimum detectable odds ratios based on sample size were calculated prior to data analysis. These calculations were based on estimates of outcome event rates and population prevalence from sources in the published literature.*

Based on the size of the study population and the number of MLTC pregnancies included in the study, an event rate of 30 per 100,000 maternities among MLTC women would be required to generate a minimum detectable odds ratio of 2.9 (95% CI 1.2-7.5) for maternal death. For severe maternal morbidity the minimum detectable odds ratio is 1.2 (95% CI 1.1-1.4) equating to an outcome event prevalence of 1.2% among MLTC women. For stillbirth the minimum detectable odds ratio is 1.3 (95% CI 1.1-1.6) equating to an outcome event prevalence of 0.52% among MLTC women, and for neonatal death the minimum detectable odds ratio is 1.4 (95% CI 1.04-1.8) equating to an outcome event prevalence of 0.28% among MLTC women.

5.2.8 Proposed causal relationship between MLTC and severe adverse outcomes

Directed acyclic graphs (DAGs) were constructed in order to explicitly outline the proposed causal relationship between the exposure and the outcome variables (291). A simplified schematic diagram of the final DAG used to guide the analysis undertaken in this study is presented in Figure 5.1.

Figure 5.1. Directed acyclic graph describing the proposed causal relationship between MLTC and severe adverse outcomes



In this DAG parity for all women, and previous caesarean birth among multiparous women are considered as effect modifiers.

The covariates included in this DAG were selected based on a combination of structured literature review, expert clinical knowledge and the conceptual models presented in chapter 1 (section 1.2, Figure 1.1. and 1.2). The minimum adjustment set to account for confounding identified by the DAG was maternal BMI, socioeconomic status, maternal age, smoking status and ethnicity. Parity for all women, and previous caesarean section among multiparous women were identified as potential effect modifiers. This is from evidence showing differential rates of complicated birth (e.g. requiring assisted or caesarean birth, or birth associated with severe perineal trauma or postpartum haemorrhage) based on parity (292, 293), and increased risk of complications in subsequent pregnancy for women who have a history of caesarean birth (294-296). Factors identified as being on the causal pathway, and that were measurable within the dataset are included in this DAG for illustrative purposes. All DAGs were constructed using the online software DAGitty.

5.2.9 Statistical analysis

Descriptive statistics (numbers and proportions) were used to describe the social and demographic characteristics of the entire study population and by MLTC status. Differences in the characteristics of pregnancies with MLTC and those without was assessed using a chi-squared test for difference in proportions. The rates of all outcomes by MLTC status and for type and complexity of MLTC were calculated using a denominator that was appropriate to the event. For maternal deaths this was per 100,000 maternities, for severe maternal morbidity this was per 10,000 maternities, for stillbirth this was per 1000 births and for neonatal death this was per 1000 live births.

To investigate the association between MLTC (by status, type and complexity) and severe adverse maternal and perinatal outcomes, univariable logistic regression was used to estimate crude odds ratios and 95% confidence intervals. A minimum set of adjustment covariates were identified from the DAG (BMI, maternal age, smoking status, ethnicity and socioeconomic status). Following this, multivariable logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals examining the relative influence of MLTC on the severe adverse maternal and perinatal outcomes after accounting for maternal age, body mass index, ethnicity, socioeconomic status (IMD quintile) and smoking status. Separate models were fitted with maternal age and BMI as either a continuous or a categorical covariate and compared using likelihood ratio testing. There was no statistically significant difference in model fit when either maternal age or BMI was fitted as a continuous covariate, therefore, all covariates were fitted in the models as categorical using the categories shown in Table 5.1. Variables identified as being on the causal pathway are described within the pregnancy and birth characteristics but were not adjusted for in the analysis as the total effect of the exposure of MLTC on the outcomes was of interest.

Multivariable models were only constructed when there were a sufficient number of outcome events to do so. This is based on the commonly used rule that there should be a minimum of 10 outcome events per variable for performing binary logistic regression analysis. For all analyses robust standard errors were used to account for clustering of women who had more than one pregnancy within the study period. Parity and previous caesarean birth among multiparous women were considered as potential effect modifiers of the relationship between MLTC and the severe adverse maternal and perinatal outcomes under investigation. Effect modification was investigated by fitting interaction terms

between MLTC and parity, and MLTC and history of previous caesarean birth among multiparous women only. Divergence between the full model and a model containing the interaction terms was assessed using likelihood ratio testing. As there was no evidence of significant effect modification for either of these parameters (p-value 0.089 for parity, and p-value=0.636 for previous caesarean birth among multiparous women) interaction terms were not included in the full models.

The amount of missing data for each of the covariates included in the models was assessed. The amount of missing data was low for socioeconomic status (0.06% missing), ethnicity (0.85% missing), and smoking status (5.13% missing), but higher for BMI (25.6% missing). All pregnancies were assigned an exposure status based on the information recorded within the woman's EHRs. No pregnancies were missing data for maternal age and 52 pregnancies (0.03%) were missing data for birth outcome. Overall, 137,593 pregnancies (94.0%) have complete data for socioeconomic status, maternal age, ethnicity, and smoking status, and 105,819 pregnancies (72.3%) had complete data for the previously listed covariates in addition to maternal BMI. Due to the higher proportion of missing data for BMI, a complete case analysis for pregnancies with data for all confounding co-variates could therefore plausibly result in a loss of statistical power, which is particularly problematic as all of the outcomes under investigation are rare. For this reason the main models presented (base model A and adjusted model A) are a complete case analysis where data was complete for maternal age, ethnicity, smoking status, and socioeconomic status. This model was adjusted for all confounding covariates apart from BMI. The second model presented (base model B and adjusted model B) is constructed with partially observed covariates imputed through multiple imputation using the chained equations method and was adjusted for all potential

confounders. The number of imputations included within in the model (30 imputations) was determined by the proportion of incomplete cases within the cohort, based on the commonly used rule that the number of imputations should be at least equal to the percentage of incomplete cases (297). Finally, to further explore the impact of missing data, a third model (base model C and adjusted model C) was constructed which is a complete case analysis where data was available for maternal age, ethnicity, smoking status, socioeconomic status and maternal BMI. This model was adjusted for all potential confounders. To account for women having more than one pregnancy in the study period a per woman analysis was undertaken using the woman's first pregnancy in the study period to describe the pregnancy and birth characteristics of the study population by MLTC status, and for the main models presented (base model D and adjusted model D).

To better understand the observed association between MLTC and stillbirth, a supplementary analysis was undertaken. This analysis described and compared the proportions of pregnancies where the woman had given birth by MLTC status across the following gestational time frames:

a. Proportion of births occurring between 22+0 and 27+6 weeks
b. Proportion of births occurring between 22+0 and 31+6 weeks
c. Proportion of births occurring between 22+0 and 36+6 weeks
d. Proportion of births occurring between 22+0 and 38+6 weeks
e. Proportion of births occurring between 22+0 and 40+6 weeks
f. Proportion of births occurring between 22+0 and 41+6 weeks

All results were considered to be statistically significant at the 5% confidence level, and all analyses were conducted in StataMP version 17 (Statacorp, College station, USA). In accordance with CPRD governance requirements, table cells with numbers smaller than five were suppressed to prevent deductive disclosure.

5.3 Results

5.3.1 Population characteristics

A total of 146,307 pregnancies to 121,211 women were included in this study. Of these 24,237 (16.6%) were pregnancies among women with MLTC (MLTC women) and 120,070 (83.4%) were pregnancies to women without MLTC (non-MLTC women). The social and demographic characteristics of the study population are shown in Table 5.2. Similar distributions of social and demographic characteristics were observed in pregnancies among MLTC women and pregnancies among non-MLTC women as those reported in chapter 4 (section 4.3.1, Table 4.1). Overall MLTC women were more likely to be older, have a raised BMI ≥30kg/m^2, be of White ethnicity, be living in socioeconomic deprivation or be a current or ex-smoker compared to non-MLTC women.

There were no significant differences in the social and demographic characteristics of the women who were included in this study, and the women were part of the larger cohort included in the epidemiology of study presented in chapter 4 (section 4.3.1, Table 4.1).

Table 5.2. Social and demographic characteristics of the study population presented as a per pregnancy analysis by MLTC status

Social and demographic characteristics	Pregnancies to all women in the study population total n=146307		Pregnancies among non-MLTC women total n=122070		Pregnancies among MLTC women total n=24237		Chi-squared test for differences in proportion* p-value
	n/total n with data	%	n/total n with data	%	n/total n with data	%	
Maternal Age							
Less than 20 years	6078/146307	4.2	5696/122070	4.7	382/24237	1.6	<0.001
20- 34 years	106209/146307	72.6	89093/122070	73.0	17116/24237	70.6	
35-39 years	27488/146307	18.8	22238/122070	18.2	5250/24237	21.7	
More than 40 years	6532/146307	4.5	5043/122070	4.1	1498/24237	6.1	
Smoking status							
Current smoker	33768/138795	24.3	26249/115286	22.8	7519/23509	46.4	<0.001
Ex-Smoker	24793/138795	17.9	19718/115286	17.1	5075/23509	21.6	
Non-smoker	80234/138795	57.8	69319/115286	60.1	10915/23509	32.0	
Missing (as a proportion of total n)	*7512/146307*	*5.1*	*6784/122070*	*5.6*	*728/24237*	*3.0*	
BMI category							
Underweight	4094/108931	54.8	3371/89267	3.8	723/19664	3.7	<0.001
Healthy Weight	55673/108931	17.0	47147/89267	52.8	8526/19664	43.4	
Overweight	28037/108931	23.1	22927/89267	25.7	5110/19664	26.0	
Obese	21127/108931	19.4	15822/89267	17.7	5305/19664	27.0	
Missing (as a proportion of total n)	*37376/146307*	*25.6*	*32803/122070*	*26.9*	*4573/24237*	*18.9*	
Ethnicity							
White	122655/145069	88.0	105184/120926	87.0	22471/24143	93.1	<0.001
Black/Black British	3963/145069	2.7	3615/120926	3.0	348/24143	1.4	
Asian/Asian British	8631/145069	6.0	7776/120926	6.4	855/24143	3.5	
Mixed	1769/145069	1.2	1553/120926	1.3	216/24143	0.9	
Other	3051/145069	2.1	2798/120926	2.3	253/24143	1.1	
Missing (as a proportion of total n)	*1238/146307*	*0.9*	*1144/122070*	*0.9*	*94/24237*	*0.4*	

Table 5.2. (continued) Social and demographic characteristics of the study population presented as a per pregnancy analysis by MLTC status

Social and demographic characteristics	Pregnancies to all women in the study population total n=146307		Pregnancies among non-MLTC women total n=122070		Pregnancies among MLTC women total n=24237		Chi-squared test for differences in proportion* p-value
	n/total n with data	%	n/total n with data	%	n/total n with data	%	
IMD Quintile							
1 (Most affluent)	29520/146218	20.2	25184/122000	20.6	4336/24218	17.9	<0.001
2	28391/146218	19.4	23948/122000	19.6	4443/24218	18.4	
3	28974/146218	19.8	24118/122000	19.8	4856/24218	20.1	
4	28474/146218	19.5	23582/122000	19.3	4892/24218	20.5	
5 (Most deprived)	30859/146218	21.1	25168/122000	20.6	5691/24218	23.5	
Missing (as a proportion of total n)	*89/146307*	*0.1*	*70/122070*	*0.1*	*19/24237*	*0.1*	

** Comparison of pregnancies among non-MLTC women and pregnancies among MLTC women*

5.3.2 Pregnancy and birth characteristics

The pregnancy and birth characteristics of the study population are shown in Table 5.3. Women with MLTC were more likely to have received antenatal care from a midwife by less than or equal to 10+0 weeks gestation compared to non-MLTC women. Pregnancies among MLTC women were also more likely to be to multiparous women, and to be complicated by any obstetric co-morbidity in pregnancy. Regarding birth characteristics, there were higher proportions of induction of labour and caesarean birth (elective and emergency), and anaesthetic interventions (regional and general anaesthetic) observed for pregnancies among MLTC women compared to pregnancies among non-MLTC women. Babies born to women with MLTC in pregnancy were more likely to be born prematurely and were more likely to be small for gestational age or extremely small for gestational age. There was a higher proportion of maternal admission to critical care for pregnancies among MLTC women.

There were no substantive differences in the observed patterns for pregnancy and birth characteristics of the study population based on a per woman analysis of the woman's first pregnancy episode in the dataset as shown in appendix D (Table D1).

Table 5.3. Pregnancy and birth characteristics of the study population presented as a per pregnancy analysis by MLTC status

Pregnancy and birth characteristics	**Pregnancies to all women in the study population** total n=146307		**Pregnancies among non-MLTC women** total n=122070		**Pregnancies among MLTC women** total n=24237		Chi-squared test for differences in proportion** p-value
	n/total n with data	%	n/total n with data	%	n/total n with data	%	
Parity							
Nulliparous	60374/146307	41.3	52318/122070	42.9	8056/24237	57.1	<0.001
Multiparous	85933/146307	58.7	69752/122070	57.1	16181/24237	66.8	
Previous caesarean birth for multiparous women							
No	69961/85933	81.4	56932/69752	81.6	13029/16181	80.5	0.001
Yes	15972/85933	18.6	12820/69752	18.4	3152/16181	19.5	
Booking gestation							
Booked at <10+0 weeks gestation	44782/114417	39.1	36487/95279	38.3	8304/19138	43.4	<0.001
Booked at ≥ 10+0 weeks gestation	69635/114417	60.9	58792/95279	61.7	10834/19138	56.6	
Missing (as a proportion of total n)	*31890/146307*	*21.8*	*26791/122070*	*22.0*	*5099/24237*	*21.0*	
Obstetric co-morbidity in pregnancy							
No	118205*/146307*	80.8	99200/122070	81.3	19005/24237	78.4	<0.001
Yes	28102*/146307*	19.2	22870/122070	18.7	5232/24237	21.6	
Onset of labour method for women with planned vaginal birth							
Spontaneous onset of labour	89986/121922	73.8	76986	75.0	13000/19240	25.0	<0.001
Induction of labour	31936/121922	26.2	25696	25.0	6240/19240	32.4	
*Missing (as a proportion of total n)**	*7944/129866*	*6.1*	*6433/109115*	*5.9*	*1511/20751*	*7.3*	
Mode of birth							
Vaginal birth	91131/142687	63.9	76538/119043	64.3	14593/23644	61.7	<0.001
Assisted vaginal birth (including breech)	17133/142687	12.0	14737/119043	12.4	2396/23644	10.1	
Elective caesarean birth	16441/142687	11.5	12955/119043	10.9	3486/23644	14.7	
Emergency caesarean birth	17982/142687	12.6	14813/119043	12.4	3169/23644	13.4	
Missing (as a proportion of total n)	*3620/146307*	*2.5*	*3027/122070*	*2.5*	*593/24237*	*2.5*	
Anaesthetic intervention at birth							
No anaesthetic/local anaesthetic	80928/139351	58.1	68334/116221	58.8	12594/23130	54.5	<0.001
Regional anaesthetic	48580/139351	34.9	39986/116221	34.4	8594/23130	37.2	
General anaesthetic	9843/139351	7.1	7901/116221	6.8	1942/23130	8.4	
Missing (as a proportion of total n)	*6956/146307*	*4.8*	*5849/122070*	*4.8*	*1107/24237*	*4.6*	

Table 5.3. (continued) Pregnancy and birth characteristics of the study population presented as a per pregnancy analysis by MLTC status

Pregnancy and birth characteristics	Pregnancies to all women in the study population total n=146307		Pregnancies among non-MLTC women total n=122070		Pregnancies among MLTC women total n=24237		Chi-squared test for differences in proportion** p-value
	n/total n with data	%	n/total n with data	%	n/total n with data	%	
Gestation at birth	n	%	n	%	n	%	
Birth at less than 37+0 weeks gestation	6656/*146307*	4.5	5139/*122070*	4.2	1517/*24237*	6.3	<0.001
Birth at 37+0 weeks gestation and above	139651/*146307*	95.5	116931/*122070*	95.8	22720/*24237*	93.7	
Birthweight less than the 10th centile for sex and gestation at birth							
No	130351/143391	90.9	108930/119559	91.1	21421/23832	89.9	<0.001
Yes	13040/143391	9.1	10629/119559	8.9	2411/23832	10.1	
Missing (as a proportion of total n)	*2916/146307*	*2.0*	*2511/122070*	*2.1*	*405/24237*	*1.7*	
Birthweight less than the 3rd centile for sex and gestation at birth							
No	138976/143391	96.9	116011/119559	97.0	22965/23832	96.4	<0.001
Yes	4415/143391	3.1	3548/119559	3.0	867/23832	3.6	
Missing (as a proportion of total n)	*2916/146307*	*2.0*	*2511/122070*	*2.1*	*405/24237*	*1.7*	
Maternal admission to critical care							
No	145699/146307	99.6	121606/122070	99.6	24093/24237	99.4	<0.001
Yes	608/146307	0.4	464/122070	0.4	144/24237	0.6	

** total n =128966, women coded as giving birth by elective caesarean section excluded from this group*

*** Comparison of pregnancies among non-MLTC women and pregnancies among MLTC women.*

5.3.3 Severe adverse maternal outcomes

The results for severe adverse maternal and perinatal outcomes by MLTC status and for type and complexity of MLTC are shown in Table 5.4 and 5.5.

Table 5.4. Proportions and rates of severe adverse maternal and perinatal outcomes by MLTC status and for type and complexity of MLTC

Outcome	All pregnancies in study population n outcome events/total n with data (%) Rate of outcome event (95% CI)	Pregnancies among women without MLTC n outcome events/total n with data (%) Rate of outcome event (95% CI)	Pregnancies among women with MLTC n outcome events/total n with data (%) Rate of outcome event (95% CI)	p-value[a]	Pregnancies among women with MLTC from 2 conditions n outcome events/total n with data (%) Rate of outcome event (95% CI)	Pregnancies among women with MLTC from 3+ conditions n outcome events/total n with data (%) Rate of outcome event (95% CI)	p-value[b]	Pregnancies among women with physical health MLTC n outcome events/total n with data (%) Rate of outcome event (95% CI)	Pregnancies among women with mental health MLTC n outcome events/total n with data (%) Rate of outcome event (95% CI)	Pregnancies among women with mixed MLTC n outcome events/total n with data (%) Rate of outcome event (95% CI)	p-value[c]
Early maternal death	6/146307 (0.004) 4.1 (1.5 to 8.9)	6/122070 (0.005) 4.9 (1.8 to 10.7)	**	0.275	**	**	-	**	**	**	-
Late maternal death	19/146301 (0.01) 13 (7.8 to 20.3)	13/122064 (0.01) 10.6 (5.7 to 18.2)	6/24237 (0.02) 24.8 (9.1 to 53.9)	0.078	**	**	-	**	**	**	-
Severe maternal morbidity	2223/146307 (1.52) 151.9 (145.7 to 158.3)	1698/122070 (1.39) 139.1 (132.6 to 145.8)	525/24237 (2.17) 216.6 (198.7 to 235.7)	<0.001	311/16846 (1.85) 184.6 (164.8 to 206.1)	214/7391 (2.9) 289.54 (252.5 to 330.3)	<0.001	89/3432 (2.59) 259.3 (208.8 to 318.2)	126/7816 (1.61) 161.2 (134.5 to 191.6)	310/12989 (2.39) 238.7 (213.1 to 266.4)	<0.001
Stillbirth	450/146255 (0.31) 3.08 (2.8 to 3.4)	367/122036 (0.3) 3.01 (2.7 to 3.3)	83/24229 (0.34) 3.43 (2.7 to 4.2)	0.283	55/16840 (0.33) 3.27 (2.5 to 4.2)	28/7389 (0.38) 3.79 (2.5 to 5.4)	0.447	13/3430 (0.38) 3.79 (2 to 3.4)	23/7815 (0.29) 2.94 (1.9 to 4.4)	47/12984 (0.36) 3.62 (2.7 to 4.8)	0.561
Neonatal death	122/145805 (0.08) 0.84 (0.7 to 1)	88/121659 (0.07) 0.72 (0.6 to 0.9)	34/24146 (0.14) 1.41 (1.1 to 2)	0.001	21/16785 (0.13) 1.25 (0.8 to 1.9)	13/7361 (0.18) 1.76 (0.9 to 3)	0.002	5/3417 (0.15) 1.46 (0.5 to 3.4)	8/7792 (0.1) 1.03 (0.4 to 2)	21/12937 (0.16) 1.62 (1 to 2.5)	0.004

Table 5.4. (continued) Proportions and rates of severe adverse maternal and perinatal outcomes by MLTC status and for type and complexity of MLTC

*** Cell suppression to prevent deductive disclosure*

a Chi-squared test for differences in proportions comparing pregnancies among non-MLTC women and pregnancies among MLTC women

b Chi-squared test for differences in proportions comparing pregnancies among non-MLTC women and pregnancies among MLTC women by MLTC complexity

c Chi-squared test for differences in proportions comparing pregnancies among non-MLTC women and pregnancies among MLTC women by MLTC type

Rate of maternal death calculated per 100,000 maternities

Rate of severe maternal morbidity calculated per 10,000 maternities

Rate of stillbirth calculated per 1000 births

Rate of neonatal death calculated per 1000 live births

Table 5.5. Multivariable regression models investigating the association between MLTC and severe adverse maternal and perinatal outcomes

Severe Maternal Morbidity	**Model A base model** Crude OR (95% CI) Total n=137593	p-value	**Model A adjusted model [1]** Adjusted OR (95% CI) Total n=137593	p-value	**Model B base model** Crude OR (95% CI) Total n=146307	p-value	**Model B adjusted model [2]** Adjusted OR (95% CI) Total n=146307	p-value
All MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
MLTC	1.57 (1.41-1.74)	<0.001	1.59 (1.43-1.76)	<0.001	1.57 (1.42-1.73)	<0.001	1.54 (1.39-1.7)	<0.001
Complexity of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
2 conditions MLTC	1.34 (1.18-1.51)	<0.001	1.36 (1.2-1.54)	<0.001	1.33 (1.18-1.51)	<0.001	1.32 (1.17-1.5)	<0.001
3+ conditions MLTC	2.09 (1.81 -2.43)	<0.001	2.11 (1.8-2.46)	<0.001	2.11 (1.83-2.44)	<0.001	2.04 (1.76-2.36)	<0.001
Type of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
Physical health MLTC	1.93 (1.55-2.4)	<0.001	1.88 (1.51-2.35)	<0.001	1.89 (1.52-2.34)	<0.001	1.76 (1.41-2.18)	<0.001
Mental health MLTC	1.17 (0.97-1.4)	0.107	1.19 (0.99-1.44)	0.067	1.16 (0.97-1.39)	0.108	1.18 (0.98-1.42)	0.216
Mixed MLTC	1.72 (1.51-1.94)	<0.001	1.73 (1.52-1.97)	<0.001	1.73 (1.53-1.96)	<0.001	1.69 (1.49-1.91)	<0.001
Stillbirth	**Model A base model** Crude OR (95% CI) Total n=137543	p-value	**Model A adjusted model [1]** Adjusted OR (95% CI) Total n=137543	p-value	**Model B base model** Crude OR (95% CI) Total n=146255	p-value	**Model B adjusted model [2]** Adjusted OR (95% CI) Total n=146255	p-value
All MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
MLTC	1.16 (0.91-1.48)	0.222	1.11 (0.87-1.43)	0.370	1.14 (0.9-1.45)	0.283	1.07 (0.84-1.36)	0.325
Complexity of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
2 conditions MLTC	1.13 (0.86-1.51)	0.376	1.1 (0.83-1.47)	0.510	1.09 (0.82-1.44)	0.568	1.03 (0.78-1.38)	0.553
3+ conditions MLTC	1.22 (0.82-1.82)	0.327	1.16 (0.78-1.73)	0.474	1.26 (0.86-1.85)	0.238	1.15 (0.5-1.69)	0.257
Type of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
Physical health MLTC	1.32 (0.76-2.31)	0.322	1.32 (0.76-2.29)	0.331	1.26 (0.72-2.2)	0.412	1.2 (0.69-2.09)	0.397
Mental health MLTC	1.03 (0.67-1.56)	0.903	0.98 (0.64-1.5)	0.923	0.98 (0.64-1.49)	0.920	0.93 (0.61-1.42)	0.932
Mixed MLTC	1.2 (0.88-1.64)	0.245	1.15 (0.84-1.58)	0.378	1.2 (0.89-1.63)	0.231	1.11 (0.82-1.52)	0.275

Table 5.5. (continued) Multivariable regression models investigating the association between MLTC and severe adverse maternal and perinatal outcomes

Neonatal death	**Model A base model** Crude OR (95% CI) Total n=137122	p-value	**Model A adjusted model [1]** Adjusted OR (95% CI) Total n=137122	p-value	**Model B base model** Crude OR (95% CI) Total n=145805	p-value	**Model B adjusted model [2]** Adjusted OR (95% CI) total n=145805	p-value
All MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
MLTC	1.97 (1.31-2.94)	0.001	1.94 (1.29-2.91)	0.001	1.95 (1.31-2.89)	0.001	1.84 (1.22-2.76)	<0.001
Complexity of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
2 conditions MLTC	1.8 (1.11-2.91)	0.016	1.79 (1.1-2.92)	0.018	1.73 (1.07-2.78)	0.024	1.66 (1.03-2.71)	0.04
3+ conditions MLTC	2.33 (1.28-4.29)	0.006	2.27 (1.24-4.14)	0.008	2.44 (1.36-4.38)	0.003	2.21 (1.21-4.01)	0.009
Type of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
Physical health MLTC	2.11 (0.86-5.2)	0.105	2.01 (0.82-4.9)	0.127	2.02 (0.82-4.98)	0.125	1.76 (0.71-4.36)	0.223
Mental health MLTC	1.48 (0.71-3.06)	0.289	1.48 (0.71-3.09)	0.293	1.41 (0.69-2.93)	0.343	1.43 (0.69-2.97)	0.341
Mixed MLTC	2.21 (1.36-3.61)	0.001	2.19 (1.35-3.55)	0.001	2.25 (1.39-3.61)	0.001	2.09 (1.28-3.41)	0.003

[1] Model A adjusted for maternal age, ethnicity, smoking status and socioeconomic status
[2] Model B adjusted for maternal age, ethnicity, smoking status, socioeconomic status and maternal BMI

The EHRs and linked datasets include evidence of 25 maternal deaths in this cohort during the study period with approximately one quarter (6 deaths) occurring in pregnancy or up to 42 days after birth, and the remaining three quarters (19 deaths) occurring in the extended postnatal period. Due to low outcome event numbers, it was not possible to explore the association between MLTC and maternal death in logistic regression models. There was some evidence of a trend towards an increased rate of late maternal death for pregnancies among women with MLTC, but this was not significant at the 95% confidence level (p=0.078).

A total of 2223 events consistent with SMM were observed across the study period, equating to 1.5% of pregnancies in total being complicated by this outcome. The rate of SMM was higher for pregnancies to women with MLTC (rate 216.6 per 10,000 maternities, 95% CI 198.7-235.7) than for pregnancies to women without MLTC (rate 139.1 per 10,000 maternities, 95% CI 132.6-145.8). MLTC in pregnancy was associated with a significantly increased odds of SMM (aOR 1.59, 95% CI 1.43-1.76) in both the base and fully adjusted multivariable logistic regression models. There was evidence that the risk of SMM was increased for women with complex MLTC (complex MLTC aOR 2.11, 95% CI 1.8-2.46; 2 condition MLTC aOR 1.36, 95% CI 1.2-1.54). There was also evidence of a differential distribution of risk of SMM based on type of MLTC. Pregnancies to women with physical health MLTC or mixed MLTC were more likely to be complicated by SMM (physical MLTC aOR 1.88, 95% CI 1.51-2.35; mixed MLTC aOR 1.73, 95% CI 1.52-1.97), whereas pregnancies with mental health MLTC did not appear to be at increased risk of this adverse outcome (mental health MLTC aOR 1.19, 95% CI 0.99-1.44) compared to the reference population (non-MLTC women).

5.3.4 Severe adverse perinatal outcomes

The results for severe adverse maternal and perinatal outcomes by MLTC status and for type and complexity of MLTC are shown in Table 5.4 and 5.5.

A total of 450 stillbirths occurred during the study period equating to a rate of 3.08 per 1000 births, (95% CI 2.8-3.4). There was no evidence of a difference in the rate of stillbirth for pregnancies to women with MLTC (rate 3.43 per 1000 births, 95% CI 2.7-4.2) and those without MLTC (rate 3.01 per 1000 births, 95% CI 2.7 to 3.3). MLTC in pregnancy was not associated with an increased odds of stillbirth (aOR 1.11, 95% CI 0.87-1.43). This association remained consistent even when MLTC was stratified by type and complexity. The proportion of births and ongoing pregnancies occurring within the study population across six gestational timeframes by MLTC status is shown in appendix D (Table D2). At each gestational timeframe examined apart from the timeframe from 22+0 to 27+6 weeks gestation, a higher proportion of births occurred among MLTC women with a corresponding higher proportion of ongoing pregnancies among non-MLTC women (p=<0.001).

A total of 122 neonatal deaths occurred during the study period equating to a rate of 0.84 per 1000 livebirths (95% CI 0.7-1.0). The rate of neonatal death was higher for pregnancies to women with MLTC (rate 1.41 per 1000 livebirths, 95% CI 1.1- 2.0) than pregnancies to women without MLTC (rate 0.72 per 1000 livebirths, 95% CI 0.6-0.9). MLTC in pregnancy was associated with a significantly increased odds of neonatal death (aOR1.94, 95% CI 1.29-2.91) in both the base and fully adjusted multivariable logistic regression models. There was no significant difference in the odds of neonatal death based on stratification for complexity of

MLTC (complex MLTC aOR 2.27, 95% CI 1.24-4.14; 2 condition MLTC aOR 1.79, 95% CI 1.1-2.29). Women with mixed MLTC remained the only group with an increased odds of neonatal death compared to the base population when MLTC was stratified based on type.

5.3.5 Sensitivity analyses and missing data

A second model (base model B and adjusted model B) was constructed with partially observed covariates imputed using multiple imputation for all outcomes under investigation. This model is presented in Table 5.5. The imputation of missing covariates did not substantively change the effect estimates across any of the outcomes examined compared to the main model (base model A and adjusted model A). A third model (base model C and adjusted model C) was constructed using a restricted cohort of pregnancies with compete data for all confounding covariates and was additionally adjusted to control for the effect of maternal BMI. This model is presented in appendix D (Table D3). Similar effect estimates were obtained as for the larger complete case analysis (base model A and adjusted model A) which was adjusted for maternal age, ethnicity, IMD and smoking status and for the model with imputed missing data (base model B and adjusted model B) for all maternal and perinatal outcomes except neonatal death. While the association between MLTC and neonatal death remained statistically significant overall, the measure of effect became statistically insignificant upon stratification by type of MLTC and for complex MLTC following adjustment. This is most likely due to low outcome event numbers and consequently reduced statistical power in the restricted complete case analysis. A fourth model (base model D and adjusted model D) was constructed as a per woman analysis using the woman's first pregnancy in the cohort for women with complete data for IMD, maternal age, ethnicity

and smoking status. This model is presented in appendix D (Table D3). The observed associations remained consistent in the per woman analysis (base model D and adjusted model D) when compared to the main model (base model A adjusted model A).

5.4 Discussion

5.4.1 Contribution to knowledge

To my knowledge, this work represents one of the largest and most comprehensive studies of the association between MLTC and severe adverse maternal and perinatal outcomes to date. It reveals MLTC to be an important driver of inequalities in maternal and perinatal health outcomes during pregnancy and in the immediate postpartum period. This study also presents robust analysis based on sub-groups of MLTC revealing important differences in differential risk based on type and complexity of MLTC.

5.4.2 Interpretation of findings and comparison to the literature

5.4.2.1 Pregnancy and birth characteristics

Differences in the pregnancy and birth characteristics for pregnancies to women with MLTC compared with pregnancies to women without MLTC are reported in this study. Some of these differences such as increased rates of obstetric and anaesthetic intervention, preterm birth or the difference in baby's birthweight among pregnancies to women with MLTC could plausibly contribute to the increased risk of adverse maternal and perinatal outcomes described in this study (298, 299).

This study also found that women with MLTC were more likely to have had their first antenatal appointment in accordance with NICE guidance which recommends that the 'booking' appointment should occur no later than 10+0 weeks gestation (46). The proportion of women who have a booking appointment within this time frame is commonly used as a broad marker of access to and adequacy of antenatal care. Late booking (after 10+0 weeks gestation) has been shown to be associated with a number of adverse pregnancy outcomes and is consistently identified as significant factor among women who die during pregnancy or after birth (27, 300). It would therefore be reasonable to expect that women with MLTC would be more likely to have a late booking gestation as a feature of their pregnancy, which does not appear to be the case.

There are however, arguably, good reasons to be cautious about over-interpreting the significance of this observation. The use of the booking gestation as a marker of access to and adequacy of antenatal care relies on the assumptions that there will be sufficient time for the woman to receive a minimum number of antenatal contacts, to participate in recommended screening and for any unknown or evolving risks to be identified and addressed (46, 301). All of these are important features of antenatal care, designed to improve maternal and perinatal outcomes. The booking gestation alone, however, does not equate to being a marker of whether existing pathways of care are fit-for purpose, tell us how much healthcare was actually provided and used, or measure patient experience. All of these factors may be pertinent to the relationship between MLTC and severe adverse maternal and perinatal outcomes, but are not measured within this data.

5.4.2.2 Maternal death

Maternal death was initially included within this study due to its undeniable importance as a measure of maternal health (302). It must be acknowledged, however, that the size of the final study population is not large enough to allow for robust investigation of maternal death. This is also compounded by the rate of maternal death reported in this study being lower than the rates estimated by the MBRRACE-UK confidential enquiry into maternal death (27). The rate of maternal death reported in this study was 4.1 per 100,000 maternities, while the rate reported by MBRRACE-UK for the triennium 2019 to 2021 was 10.1 per 100,000 maternities (excluding maternal deaths caused by Covid-19) (27). Confidential enquiry is universally agreed to be one of the most comprehensive and robust methodologies with which to study maternal death (303), therefore the rates presented in MBRRACE-UK are highly likely to be an accurate estimate of the maternal death rate of the UK.

A validation study of death recording in CPRD conducted by Gallagher et al. reported the vast majority of patient deaths were captured within CPRD, but that discrepancies in the accuracy of the date of death were observed (226). In particular, the date of death recorded in CPRD was later than the date of death according to ONS death registration data in up to 1/5th of patients. Delays to the registration of deaths for reasons such as referral to the Coroner and requirement for post-mortem in the context of unexpected or unnatural deaths, were thought to underlie this discrepancy. As most maternal deaths are unanticipated, they are arguably highly likely to be subject to delayed death registration for these reasons. Death date being recorded in CPRD as later than the actual date of death

would result in a misclassification of early maternal deaths as late maternal death, and the under-ascertainment of late maternal deaths.

The composition of the study population may also be contributing to the lower than expected rate of maternal death reported in this study. As previously discussed in chapter 3 (section 3.7.6), there appears to be an over-representation of women of white ethnicity and women in the highest socioeconomic quintile in the final study population. These represent maternal groups with the lowest overall rates of maternal death in the UK (27). Despite pre-existing maternal medical conditions being consistently identified as an important contributing factor to the risk of maternal death (41, 290, 304), due to the aforementioned issues with case ascertainment, it is not possible to draw firm conclusions about the association between MLTC and maternal death from this study. As previously discussed, however, the study of maternal death can be augmented through the study of SMM (305), and it would arguably be reasonable to interpret that the associations reported in this study for SMM may be equally applicable to the relationship between MLTC and maternal death.

5.4.2.3 Severe maternal morbidity

Based on measurement with a composite indicator adapted from the EMMOI (227), this study reports that 1.5% of pregnancies were affected by SMM. It is increasingly recognised that the study of SMM is limited by the lack of standardisation across studies for both outcome definitions and methodologies (306-308). This means that direct comparison of even basic information such as prevalence rates between studies is problematic. Regarding the accuracy of the estimate presented in this study, it is reassuring that the rate reported

here reliably fits within the range of estimates reported in previous studies from high-income settings using population-based data sources and covering a similar time period to this study (44, 309, 310). A higher rate of SMM was observed for pregnancies among MLTC women compared to pregnancies among non-MLTC women. This association also persisted in the fully adjusted multivariable logistic regression models. The existence of pre-existing health conditions have consistently been reported to be a risk factor for SMM (42, 311-313) therefore this finding of increased risk associated with MLTC is plausible in the context of these previous findings.

This study also found important differences regarding the risk of SMM based on MLTC type and complexity. Pregnancies to women with complex MLTC were observed to have a differentially increased risk of SMM compared to those with MLTC comprised of 2 conditions only. Only a very small number of studies have examined the relationship between pre-existing co-morbidity or multiple co-morbidity and SMM (310, 313-316). Of these studies, only Brown et al. and Stanhope et al. have stratified their analyses to specifically account for complex MLTC consisting of three or more pre-existing health conditions (310, 315). A differential increased risk of severe maternal morbidity was observed for complex MLTC in both these studies, and supports the results presented in this chapter. Adverse health outcomes associated with complex multimorbidity have been more comprehensively studied in the general population, predominately among older adults. Studies have reported that patients with complex MLTC were more likely to experience a range of poorer health outcomes including lower healthy life expectancy with increased frailty, increased mortality following acute illness or emergency surgery and higher rates of avoidable harm including adverse drug events (317-319). The findings reported by these studies of a differential risk of

adverse health outcomes associated with complex MLTC, provide support to the plausibility of the differential risk of adverse maternal outcome reported in this study.

When stratified by type of MLTC, pregnancies to women with mental health MLTC did not appear to be at increased risk of SMM compared to the base population (pregnancies to non-MLTC women). The composite indicator used to measure SMM in this study was purposefully constructed to include as many important causes of maternal morbidity and mortality as was possible. It is notable however, that the majority of SMM events included relate to complications of physical health conditions or physical health outcomes, and only one (acute psychosis) mental health SMM is included. Other types of SMM relevant to mental health outcomes are not comprehensively captured by the composite indicator in its current form (320, 321). If women with mental health MLTC are more likely to experience mental health SMM events rather than physical health SMM events, then currently SMM would be underestimated in this group. Furthermore, HES APC provides a record of admissions to secondary care, but does not include records of care given in Accident and Emergency departments or admission to secondary care mental health facilities. Arguably women presenting for care with symptoms consistent with psychosis would be more likely to be managed in a community setting with psychiatric support or admitted to secondary care mental health facilities rather than secondary care in an acute hospital ward. This would again have the effect of a potential underestimation of mental health SMM in this study.

5.4.2.4 Stillbirth

There was no evidence of a difference in the rate of stillbirth between pregnancies to women with MLTC and pregnancies to those without. There is evidence from a number of studies that show pre-existing medical conditions are a risk factor for stillbirth, so the plausibility of this finding requires careful consideration (322-325). These studies tend to only include a limited number of individual conditions, and there have been no previous studies specifically exploring the risk of stillbirth associated with maternal MLTC. Surveillance data from MBRRACE-UK estimated the stillbirth rate to be 3.33 per 1000 births in 2020, having decreased by 21% since 2013 (285). Similarly to the study of maternal death, perinatal mortality surveillance conducted through MBRRACE-UK is understood to be highly comprehensive with respect to case ascertainment, meaning the rates estimated from this source are likely to be reflective of the true rate at the population level. The overall rate of stillbirth observed in this study was 3.08 per 1000 births, which is marginally lower than the rate reported by MBRRACE-UK.

There are several reasons why this may be the case. First the proportion of birth recorded as preterm in this study is 4.6% which is lower that estimated by ONS analysis of birth characteristics in England and Wales which generally sits between 7-8% annually (244). As discussed in chapter 3 (section 3.8.5), the processes of validating matched pregnancy-delivery episode pairs may have resulted in a greater proportion of preterm births being ineligible to remain in the final study population. As over 70% of stillbirths are recorded in pregnancies less than 37 weeks gestation (244, 285) the relative under ascertainment of preterm births in this study could have contributed to the lower than expected rate of

stillbirth reported here. Second, studies have previously reported increased rates of stillbirth among women from minority ethnic groups and women who are living in socioeconomic deprivation (205). As previously highlighted, there appears to be an over-representation of women of white ethnicity, and a higher proportion of women who are in the highest socioeconomic quintile compared to the lowest socioeconomic quintile in the final study population. This could also contribute to the lower than expected rate of stillbirth reported here. As stillbirth is not a common outcome, having fewer outcome events than anticipated may contribute to a loss of statistical power and consequently result in a finding of no statistically significant difference between the two comparison groups. The observation of no statistically significant association between MLTC and the odds of stillbirth, may also be related to the timing of birth for pregnancies among women with MLTC. Apart from extremely preterm gestations (<28+0 weeks) it was seen that at all gestational timeframes up to 41+6 weeks gestation a greater proportion of women with MLTC had given birth compared to non-MLTC women. As the risk of stillbirth is void once birth has taken place, any increased baseline risk of stillbirth for pregnancies among MLTC women could plausibly be offset by women in this group giving birth at relatively earlier gestations comparted to non-MLTC women.

5.4.2.5 Neonatal death

In contrast to the results presented for stillbirth, there was evidence of a significant association between MLTC and an increased odds of neonatal death in this study. A number of well-established risk factors for neonatal death have been identified including congenital abnormality, complications of prematurity and complications from birth such as trauma and

hypoxic brain injury (285). Data from MBRRACE-UK identifies congenital abnormalities and the complications of prematurity as major contributing factors to neonatal death in the UK (285). In this study we reported an increased likelihood of preterm birth for pregnancies among MLTC women. There is also evidence that the risk of neonatal death is elevated even among early term births (37+0 -39 weeks gestation) compared to later term birth (326). Again, this study reports that the proportion of early-term births was increased among pregnancies to MLTC women compared to non-MLTC women. Both observations would support the plausibility of the observed association between MLTC in pregnancy and increased risk of neonatal death.

It was not possible to collect information within this dataset about fetal congenital abnormality, however, several studies have previously identified pre-existing maternal medical conditions as a risk factor for fetal congenital abnormality (327-329). It is possible therefore, that pregnancies among MLTC women may be at increased risk of fetal congenital abnormality and in turn neonatal death. A recent systematic review by Thunbo et al. highlighted the potential role of exposure to polypharmacy with an increased risk of fetal congenital abnormality (330). This review was, however, limited by the heterogeneity and quality of the included studies, and a pooled estimation of risk was not possible. Increased polypharmacy among adults with MLTC is consistently reported in the literature, and there is no obvious reason to believe this would not also be an issue affecting women of reproductive age with MLTC (331). Further investigation into the role of polypharmacy may be a valuable adjunct to developing our understanding of the association between MLTC and adverse perinatal outcomes.

Although this study supports the presence of a significant association between MLTC and neonatal death, it is important to note that the rate of neonatal death is lower than expected. The most recent MBRRACE-UK perinatal surveillance report estimated a rate of neonatal death of 1.53 deaths per 1000 live births in 2020 (285), and the rate reported from this study was 0.84 per 1000 live births. As for stillbirth and maternal death, the demography of the study population in conjunction with the lower proportion of preterm birth could in part account for this observation. The lower than expected rate of neonatal death may also be due to under-ascertainment of cases. As described in chapter 3 (section 3.4.1) one way of identification of cases of neonatal death was through the presence of a date of death in the baby's primary care records. Babies who died shortly following birth, and therefore were never registered at a primary care practice would be missed using this method. While attempts were made to improve case ascertainment by using additional information from the mother's primary care records, the consistency with which neonatal death read codes are recorded is unclear. There is however, no obvious reason to believe that there would be differential recording of neonatal death based on maternal MLTC status. This means that although the rate of neonatal death in this study was lower than expected, the within cohort comparison of pregnancies to women with MLTC and pregnancies to women without MLTC remains valid.

5.4.3 Strengths and limitations

The main strengths of this study are as follows:

1. This is a large study which arguably contains many more women and pregnancies than could reasonably be recruited and studied through traditional prospective cohort

methods. This made it feasible to include important but uncommon maternal and perinatal health outcomes, and led to the identification of novel findings about their relationship with MLTC. The size of this study also allowed for the robust sub-group analysis based on both type and complexity of MLTC, which revealed information about differential risk of poorer outcomes particularly for SMM.

2. This study utilises linkage between primary and secondary care datasets. As 98% of the population of the UK are registered with a general practitioner and 98% of births in the UK occur in a NHS hospital or midwifery setting, this arguably allows for the most comprehensive assessment of the relationship between the exposure and outcomes under investigation.

The main limitations of this study are as follows:

1. HES APC is an administrative dataset and recorded codes relate to remuneration of clinical activity rather than for the purposes of detailing aspects of clinical care provision. While this can give an 'overview' of clinical care or diagnoses, the codes used can be poorly defined, lack specific clinical detail or imperfectly represent the conditions they pertain to. One way to address this is through the use of composite outcome indicators, which allow for cases to be identified using as much information as possible from the data without over-reliance on non-specific or poorly performing codes. While this serves to improve case ascertainment, it is not possible to determine granular details of clinical events using composite outcome indicators. For example, we can infer that an event consistent with SMM has occurred if the woman has a code for 'cardiac arrest' in the clinical record, but it is not possible to further understand the aetiology of the event within the data. The ability to translate findings from studies using administrative

healthcare data into practicable and actionable recommendations is consequently limited by this. Composite indicators are also not invulnerable to issues with data quality. For example, the original EMMOI upon which the outcome indicator in this study was based does not include blood transfusion or postpartum haemorrhage due to the data for these events being found to be unreliable (227). Obstetric haemorrhage represents an important cause of maternal death and morbidity in the UK, so the inability to study this within the HES APC is an important limitation. The ability to comprehensively capture mental health SMM using HES APC alone is also a relevant consideration, and may have plausibly resulted in an under-estimation of mental health morbidity in this study.

2. The women who were eligible for inclusion in the final study population appeared to have different characteristics to the maternity population of the UK based on comparison with ONS and National Maternity and Perinatal Audit data (244, 246). The implications of this regarding selection bias and generalisability are discussed in chapter 3 (section 3.7.6), and these discussion points also apply to this study. In this study a lower than anticipated outcome event rate for three of the four outcomes under investigation was observed. In particular, features specific to maternal and neonatal deaths make it more likely that the true rates of these outcomes cannot be reliably captured in this type of linked routinely collected data. While the within cohort comparisons made in this study are likely valid, this observation exemplifies the fact that these datasets are not constructed for the purposes of population health surveillance or research. At present this means that the use of routine data sits as an adjunct to, rather than a replacement of more traditional research and surveillance methods for maternal and perinatal health.

3. The models constructed to investigate the association between MLTC and severe adverse maternal and perinatal outcomes were adjusted for a number of well-established confounding variables that were identified a priori. It is important to note, however, that there are a number of covariates such as educational attainment, migrant status or exposure to violence and abuse which are plausible confounders that are not measured in this dataset. It not possible to discount the presence of residual confounding as a source of bias due to unmeasured covariates in this analysis.

5.3.4. Conclusion

This study shows MLTC in pregnancy to be an important driver of inequality in maternal and perinatal health due to its association with increased odds of severe maternal morbidity and neonatal death. There was evidence of a gradient of differential risk based on complexity of MLTC for both severe maternal morbidity and neonatal death. Women with mixed MLTC and physical health MLTC were at greater risk of severe maternal morbidity compared to women with mental health MLTC. There are limitations to the use of a composite outcome indicator to capture severe maternal morbidity, and this may have underestimated the burden of severe maternal morbidity from causes related to mental health.

Chapter 6: Investigating the association between MLTC and severe and common maternal mental health outcomes in the extended postpartum period

6.1 Introduction and research objectives

The profound physiological, psychological, and social transitions that occur during pregnancy and around the time of birth act to create a period of unique risk for women with respect to mental health (332, 333). Indeed, perinatal mental health disorders are one of the commonest complications of pregnancy and contribute substantially to the overall burden of maternal morbidity and mortality (334). Their impact on early parenting experiences and potential contribution to poorer infant and child outcomes also reiterates their importance (335). There is evidence to suggest that perinatal mental health disorders are becoming increasingly prevalent, and that certain population groups appear to be more likely to experience these adverse outcomes (336-338). The risk of developing perinatal mental health disorders for women with MLTC has not previously been explored and represents an important adjunct to developing our understanding of the impact of MLTC on maternal health.

The study presented in chapter 5 found that MLTC was associated with an increased odds of SMM, however, the possibility of under ascertainment of mental health SMM was identified as a limitation of this study. The inclusion of additional types of mental health SMM and attempts to increase case ascertainment using supplementary data sources are required to address this limitation. The study presented in chapter 5 also used an empirical threshold of

42 days postpartum as the endpoint of follow-up time for SMM events, which is consistent with the majority of published research (308, 339). There is, however, a growing recognition that pregnancy-related factors remain an important contributor to an elevated risk of adverse health outcomes for mothers even up to one year after giving birth (27, 340-342). A clear example of this can be taken from the MBRRACE-UK report on maternal death covering the triennium 2018 to 2020 which showed that 86% of maternal deaths occurred in the postnatal period, with 54% occurring between 42 days and up to a year after birth (34). In the extended postpartum period, suicide remains the leading cause of direct maternal death (29). These observations provide a strong mandate to investigate the risk of adverse maternal mental health outcomes associated with MLTC over an extended period of follow-up time after birth.

This chapter addresses research objective 5 of this thesis:
To investigate the association between MLTC and common and severe perinatal mental health disorders up to one year after birth.

6.2 Methods

6.2.1 Data sources

The primary data sources used in this study are CPRD GOLD, CPRD pregnancy register and the HES APC dataset. Additional linkage between CPRD pregnancy register and the 2019 Index of Multiple Deprivation and Office of National Statistics Death Registration data was used to provide information about socioeconomic status and maternal death.

A detailed description of the data sources used in this study can be found in chapter 3 (section 3.2).

6.2.2 Study population

The study population consisted of women who:

a) Were aged between 15 and 49 years old at the time of pregnancy.
b) Had a pregnancy with an estimated start date between the 1st of January 2007 and the 31st of December 2017.
c) Had a pregnancy that was a minimum gestational length of 22+0 weeks and resulted in either a late fetal loss, stillbirth or livebirth.
d) Had pregnancy data that was research quality (woman is registered for at least one year and practice is up-to-standard for at least one year prior to the estimated start date of the pregnancy).
e) Remained actively registered with a CPRD contributing practice with a last collection date for data that is a minimum of 56 days following the estimated end date of the pregnancy.
f) Had a pregnancy in the CPRD pregnancy register that can be matched and validated with a delivery record in the HES APC dataset.

A detailed description of the derivation of the study population, including the application of inclusion and exclusion criteria and the matching and validation of pregnancy records to delivery records can be found in chapter 3 (sections 3.6, 3.7 and 3.8).

6.2.3 Exposure under investigation

The main exposure under investigation was MLTC which was defined as a woman having any combination of two or more long-term physical health, mental health or infectious conditions prior to the start of pregnancy. MLTC was also considered by type and complexity. Women with two or more physical health conditions were considered to have physical health MLTC, women with two or more mental health conditions were considered to have mental health MLTC, and women with at least one physical and one mental health condition were considered to have mixed MLTC. Women who had three or more health conditions prior to the start of pregnancy were considered to have complex MLTC.
A detailed description of the measurement of exposure status can be found in chapter 3 (section 3.3).

6.2.4 Social and demographic characteristics

Information about maternal age, ethnicity, smoking status, BMI and socioeconomic status was extracted from the EHRs for all women in the study population. Variables indicating maternal age, smoking status and BMI were derived on a per pregnancy basis using the estimated start date of the pregnancy, and socioeconomic status and ethnicity were derived on a per woman basis.

A detailed description of the derivation of the social and demographic variables can be found in chapter 3 (section 3.5.1).

6.2.5 Outcomes under investigation

The outcomes under investigation in this study were severe maternal mental health disorders (acute psychosis or self-harm including thoughts of self-harm, thoughts of suicide and non-fatal suicide attempt) and common maternal mental health disorders (postnatal depression and/or postnatal anxiety.

The outcome events of acute psychosis and self-harm were identified through the presence of the woman having either a relevant read code in CPRD GOLD or an ICD-10 code in HES APC between the end of pregnancy and up to one year after birth. Evidence of the woman having an active postnatal common mental health disorder (CMHD) was based the triangulation approach described by Tianyi et al. (233) and is summarised is Figure 6.1.

Figure 6.1. Algorithm used in ascertaining evidence of active postpartum anxiety or depression in the extended postnatal period

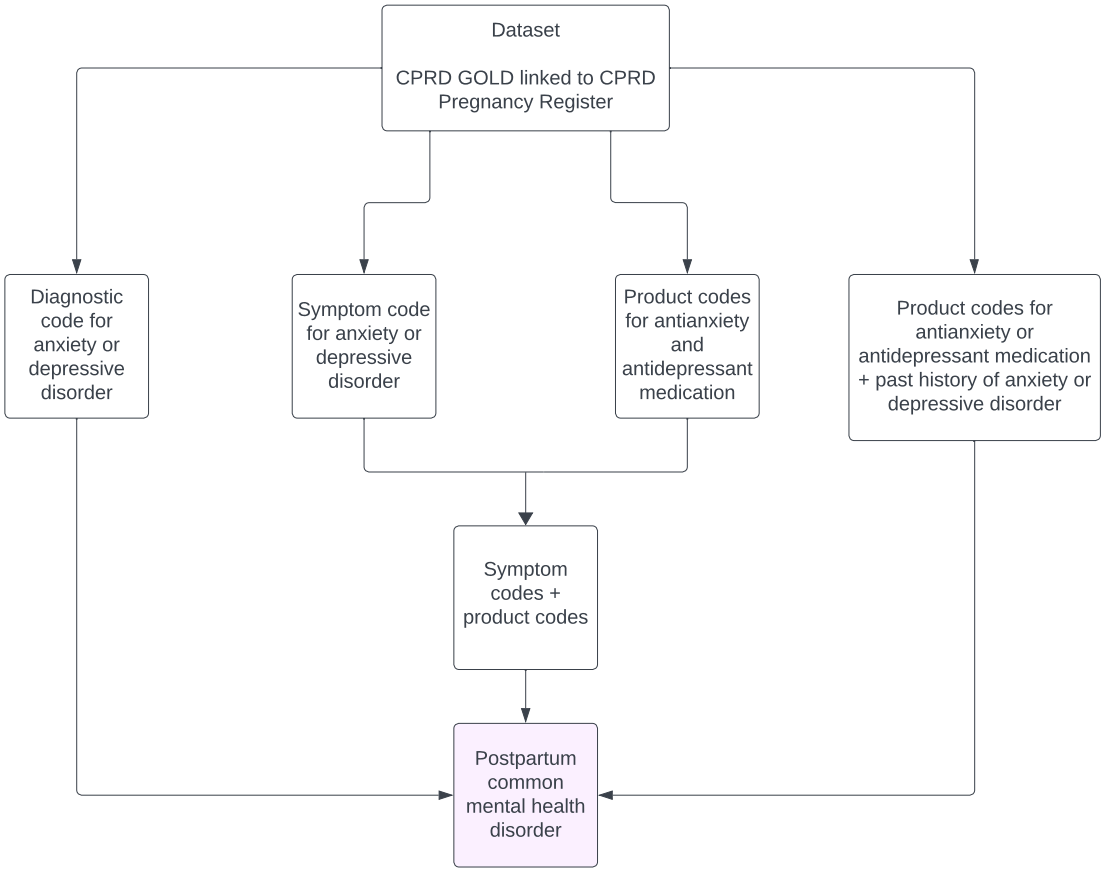


Figure 6.1. adapted from Tianyi et al. (233)

A detailed description of the outcome variables and their derivation can be found in chapter 3 (section 3.4.2).

6.2.6 Sample size

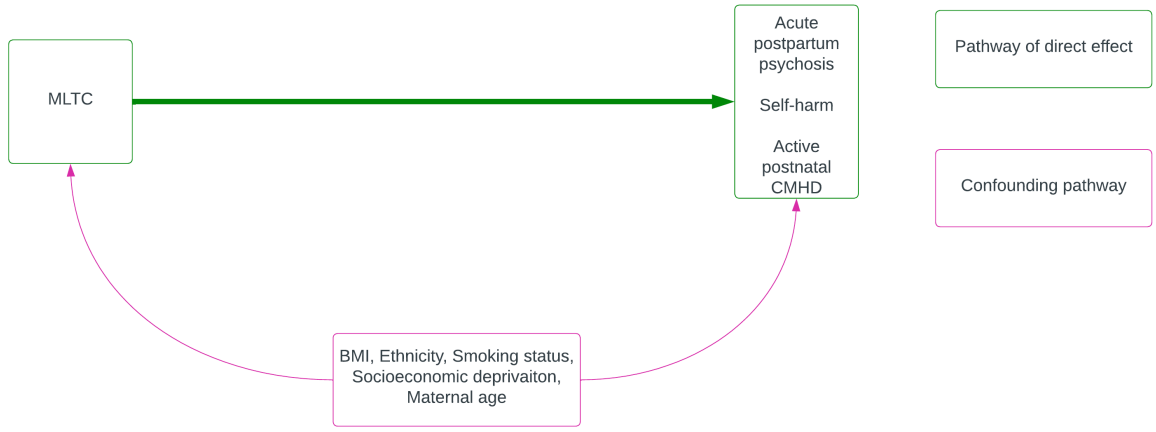
The sample size of this study was fixed by the number of pregnancy episodes that met the data quality criteria and had could be matched to a validated delivery episode in HES APC. It was not feasible to set a minimum required sample size prior to the data cleaning and

curation. All women who met the inclusion criteria were included in this study, and we attempted to maximise case ascertainment for all outcomes under investigation.

6.2.7 Proposed causal relationship between MLTC and severe and common maternal mental health outcomes

Directed acyclic graphs (DAGs) were constructed to explicitly outline the proposed causal relationship between the exposure and the outcome variables (291). A simplified schematic diagram of the final version of the DAG used to guide the analysis undertaken in this shown in Figure 6.2.

Figure 6.2. Directed acyclic graph describing the proposed causal relationship between MLTC and the maternal mental health outcomes.



The covariates included in this DAG were selected based on a combination of structured literature review, expert clinical knowledge and the conceptual models presented in chapter 1 (section 1.2, Figure 1.1 and Figure 1.2). The minimum adjustment set to account for confounding identified by the DAG was maternal BMI, socioeconomic status, maternal age, smoking status and ethnicity. All DAGs were constructed using the online software DAGitty.

6.2.8 Statistical analysis

Descriptive statistics (numbers and proportions) were used to describe the social and demographic characteristics and MLTC status for the study population and by outcome. Differences in the characteristics of pregnancies where the outcome event occurred and those where it did not were assessed using a chi-squared test for differences in proportions. The rates for all outcome events were estimated per 1000 person years of follow-up time based on MLTC status and by type and complexity of MLTC.

To investigate the association between MLTC and each of the outcomes, Cox regression was used to estimate hazard ratios and 95% confidence intervals. This type of regression model was chosen to account for varying lengths of follow-up time across the extended postpartum period. Within the models each pregnancy was treated as a discrete unit of analysis, and robust standard errors were used account for clustering for women who had more than one pregnancy within the study period. Follow-up time began at the end of the pregnancy, and stopped at the earliest time point when either the outcome event occurred, the woman died, the women transferred out of the GP practice, the GP practice stopped contributing data to CPRD, or the end of the extended postpartum period was reached. A minimum set of adjustment covariates (BMI, Ethnicity, Maternal age, Socioeconomic status (IMD quintile) and Smoking status) were identified using the DAG shown in figure 6.2, and Cox models were constructed to examine the relative influence of these covariates on the observed associations. The proportional hazards assumption which assumes that the hazards ratio is constant over time was assessed using cumulative hazard plots and Schoenfeld residuals.

The amount of missing data in this study was the same as that described for the study of the association between MLTC and severe adverse maternal and perinatal outcome in chapter 5 (section 5.2.9). For this reason, the same approach was taken to account for missing data in this study. Overall, 137,593 pregnancies (94.0%) have complete data for socioeconomic status, maternal age, ethnicity, and smoking status, and 105,819 pregnancies (72.3%) had complete data for the previously listed covariates in addition to maternal BMI. All pregnancies were assigned an exposure and an outcome status based on information recorded within the woman's EHR. The main model presented (model A base model and model A adjusted model) is a complete case analysis where data were available for maternal

age, ethnicity, smoking status and socioeconomic status. This model was adjusted for all potential confounding covariates apart from BMI. The second model presented (model B base model and model B adjusted model) is constructed with partially observed covariates imputed through multiple imputation using the chained equations method, and was adjusted for all confounding variables. The number of imputations included within the model (30 imputations) was determined by the proportion of incomplete cases within the cohort, based on the commonly used rule that the number of imputations should be at least equal to the percentage of incomplete cases (297). Finally, to further explore the impact of missing data, a third model (model C base model and model C adjusted model) was constructed which is a complete case analysis where data were available for maternal age, ethnicity, smoking status, socioeconomic status and maternal BMI. This model was adjusted for all potential confounding covariates, as per the DAG.

In this cohort the exposure status of MLTC was inclusive of a diagnoses of pre-existing mental health condition, with depression and anxiety constituting the vast burden of morbidity from mental health causes prior to pregnancy. A previous diagnosis of depression or anxiety is also considered to be a risk factor for the development of postpartum depression or anxiety. For these reasons, a supplementary analysis was undertaken in which the rates of active postnatal CMHD and self-harm by total number of pre-existing health conditions and whether those conditions were physical or mental health conditions were estimated. The purpose of this was to better understand the contribution of pre-existing mental health conditions to the observed associations. This supplementary analysis is not reported for acute psychosis as the number of outcome events within each strata is too small to robustly interpret and compare outcome event rates across the cohort. Pre-existing

depression and anxiety have not been shown to be risk factor for acute psychosis, so it is also unnecessary to conduct these additional analyses for this outcome.

All results were considered to be statistically significant at the 5% confidence level, and all analyses were conducted in StataMP version 17 (Statacorp, College station, USA). In accordance with CPRD governance requirements, table cells with numbers smaller than five were suppressed to prevent deductive disclosure.

6.3 Results

6.3.1 Population characteristics:

A total of 146,307 pregnancies to 121,211 women were included in this study. Of these 24,237 (16.6%) were pregnancies to women with MLTC and 120,070 (83.4%) were pregnancies to women without MLTC. The social and demographic characteristics of the study population with respect to MLTC status are the same as those presented in chapter 5 (Table 5.2). The social and demographic characteristics of the study population with respect to the outcome event status are shown in Table 6.1.

Table 6.1. Social and demographic characteristics of the study population for all pregnancies by outcome event status

Social and demographic characteristics	Pregnancies among all women in the study population Total n=146307		Acute psychosis					Self-harm					Active postnatal CMHD				
			Event did not occur		Event did occur			Event did not occur		Event did occur			Event did not occur		Event did occur		
	n	%	n	%	n	%	p-value*	n	%	n	%	p-value*	n	%	n	%	p-value*
Maternal Age (Total n with data=146307)																	
Less than 20 years	6078	4.2	6076	4.2	**	**	0.905	5998	4.1	80	19.5	<0.001	4963	3.9	1115	5.8	<0.001
20- 34 years	106209	72.6	106159	72.6	50	71.4		105916	72.6	293	71.5		91966	72.5	14243	73.5	
35-39 years	27488	18.8	27473	17.8	15	21.4		27461	18.8	27	6.6		24287	19.1	3201	16.5	
More than 40 years	6532	4.5	6529	4.5	**	**		6522	4.5	10	2.4		5718	4.5	814	4.2	
Smoking status (Total n with data=138795)																	
Current smoker	33768	24.3	33755	24.3	13	20.3	0.71	33560	24.3	208	52.9	<0.001	26792	22.3	6976	37.2	<0.001
Ex-Smoker	24793	17.9	24782	17.9	11	18		24739	17.9	54	13.7		21112	17.6	3681	19.6	
Non-smoker	80234	57.8	80194	57.8	40	62.5		80103	57.9	131	33.3		72141	60.1	8093	43.2	
Missing (as a proportion of total n)	7512	5.1	7506	5.1	6	8.57		7495	5.1	17	4.2		6889	5.4	623	3.2	
BMI category (Total n with data=108931)																	
Underweight	4094	54.8	4091	3.8	**	**	0.129	4082	3.8	12	4.5	0.201	3494	3.7	600	4.0	<0.001
Healthy Weight	55673	17.0	55653	51.1	20	38.5		55547	51.1	126	46.8		49062	52.2	6611	44.1	
Overweight	28037	23.1	28024	25.7	13	25		27971	25.7	66	24.5		24182	25.8	3855	25.7	
Obese	21127	19.4	21111	19.4	16	30.8		21062	19.4	65	24.2		17184	18.3	3943	26.3	
Missing (as a proportion of total n)	37376	25.6	37358	25.55	18	25.7		37235	25.5	141	34.4		33012	26.0	4364	22.5	
Ethnicity (Total n with data=145069)																	
White	122655	88.0	127601	88	54	77.1	0.018	127245	88	380	92.7	<0.001	109268	86.9	18387	95.3	<0.001
Black/Black British	3963	2.7	3960	2.7	**	**		3957	2.7	6	1.5		3778	3	185	1.0	
Asian/Asian British	8631	6.0	8642	6.0	7	10.0		8620	6	11	2.7		8200	6.5	431	2.2	
Mixed	1769	1.2	1768	1.2	**	**		1764	1.2	5	1.2		1613	1.3	156	0.8	
Other	3051	2.1	3046	2.1	5	7.1		3043	2.1	8	2		2907	2.3	144	0.8	
Missing (as a proportion of total n)	1238	0.9	1238	0.85	**	**		1238	0.85	**	**		1168	0.92	70	0.4	

Table 6.1. (continued) Social and demographic characteristics of the study population for all pregnancies by outcome event status

Social and demographic characteristics	Pregnancies among all women in the study population Total n=146307		Acute psychosis				p-value*	Self-harm				p-value*	Active postnatal CMHD				p-value*
			Event did not occur		Event did occur			Event did not occur		Event did occur			Event did not occur		Event did occur		
	n	%	n	%	n	%		n	%	n	%		n	%	n	%	
IMD Quintile (Total n with data=146218)																	
1 (Most affluent)	29520	20.2	29500	20.2	20	28.6	0.271	29488	20.2	32	7.8	<0.001	26628	21	2892	14.9	<0.001
2	28391	19.4	28381	19.4	10	14.3		28355	19.4	56	13.7		25024	19.7	3367	17.4	
3	28974	19.8	28959	19.8	15	21.4		28910	19.8	64	15.7		25190	19.9	3784	19.6	
4	28474	19.5	28459	19.5	15	21.4		28384	19.5	90	22.0		24330	19.2	4144	21.4	
5 (Most deprived)	30859	21.1	30849	21.1	10	14.3		30692	21.1	167	40.8		25686	20.3	5173	26.7	
Missing (as a proportion of total n)	89	0.1	89	0.1	**	**		88	0.1	**	**		76	0.1	13	0.1	

**Chi-squared test for differences in proportion comparing pregnancies where the outcome event occurred to those where the outcome event did not occur for those with available data*
*** Cell suppression to prevent deductive disclosure due to low event numbers*

Comparison of the social and demographic characteristics for pregnancies with and without the outcome event of acute psychosis show that women with this outcome were more likely to be of from a minority ethnic group. There was also a trend observed towards women being more likely to have a raised BMI ≥30kg/m^2 and being socioeconomically advantaged, however this was not statistically significant at the 95% confidence level. For the outcome event of self-harm, women with this outcome were more likely to be socioeconomically disadvantaged, aged less than 20 years old, be current smokers and be of white ethnicity. For the outcome event of active postnatal CMHD, similar patterns were observed as for women who had the outcome event of self-harm for ethnicity, smoking status and socioeconomic disadvantage. Those with an active postnatal CMHD were also more likely to be less than 35 years old and to have a raised BMI >30kg/m^2.

6.3.2 Maternal mental health outcomes in the extended postnatal period

The results for maternal mental health outcome in the extended postnatal period by MLTC status and for type and complexity of MLTC are shown in Tables 6.2 and 6.3.

Table 6.2. Proportions and rates of maternal mental health outcomes by MLTC status and by type and complexity of MLTC

Outcome	All pregnancies in study population	Pregnancies among women without MLTC	Pregnancies among women with MLTC		Pregnancies among women with MLTC from 2 conditions	Pregnancies among women with MLTC from 3+ conditions		Pregnancies among women with physical health MLTC	Pregnancies among women with mental health MLTC	Pregnancies among women with mixed MLTC	
	n outcome events/total n with data (%) Rate of outcome event (95% CI)	n outcome events/total n with data (%) Rate of outcome event (95% CI)	n outcome events/total n with data (%) Rate of outcome event (95% CI)	p-value[a]	n outcome events/total n with data (%) Rate of outcome event (95% CI)	n outcome events/total n with data (%) Rate of outcome event (95% CI)	p-value[b]	n outcome events/total n with data (%) Rate of outcome event (95% CI)	n outcome events/total n with data (%) Rate of outcome event (95% CI)	n outcome events/total n with data (%) Rate of outcome event (95% CI)	p-value[c]
Acute psychosis	70/146307 (0.05) 0.38 (0.3 to 0.49)	37/122070 (0.03) 0.25 (0.18 to 0.34)	33/24237 (0.14) 1.04 (0.74 to1.46)	<0.001	24/16846 (0.14) 1.09 (0.73 to 1.63)	9/7391 (0.12) 0.92 (0.48 to 1.77)	<0.001	**	17/7816 (0.22) 1.66 (1.03 to 2.67)	15/12989 (0.12) 0.87 (0.52 to 1.44)	<0.001
Self-harm	410/146307 (0.28) 2.25 (2.04 to 2.48)	246/122070 (0.2) 1.63 (1.44 to 1.85)	164/24237 (0.68) 5.16 (4.4 to 6.02)	<0.001	90/16846 (0.53) 4.09 (3.33 to 5.03)	74/7391 (1.0) 7.58 (6.03 to 9.51)	<0.001	8/3432 (0.23) 1.86 (0.93 to 3.72)	60/7816 (0.77) 5.86 (4.55 to 7.55)	96/12989 (0.74) 5.57 (4.56 to 6.8)	<0.001
Active postnatal CMHD	19373/146307 (13.2) 113.9 (112.3 to 115.5)	11065/112070 (9.1) 77.4 (76 to 78.9)	8308/24237 (34.3) 306.9 (300.4 to 313.6)	<0.001	5091/16846 (30.2) 266.1 (258.9 to 273.5)	3217/7391 (43.5) 405.6 (391.8 to 419.8)	<0.001	330/3432 (9.6) 82.5 (74.1 to 91.9)	3062/7816 (39.2) 358.5 (346 to 371.4)	4916/12989 (37.9) 338.4 (329 to 348.2)	<0.001

All rates of outcome events are expressed as per 1000 person-years of follow-up time
a Chi-squared test for differences in proportions comparing pregnancies of non-MLTC women with MLTC women
b Chi-squared test for differences in proportions comparing pregnancies of non-MLTC women with pregnancies for women with 2 condition MLTC and pregnancies for women with 3+ conditions MLTC
c Chi-squared test for differences in proportions comparing pregnancies of non-MLTC women with pregnancies to women with physical health, mental health and mixed MLTC
*** Cell suppression to prevent deductive disclosure*

Table 6.3. Multivariable regression models investigating the association between MLTC and maternal mental health outcomes

Acute psychosis	**Model A base model** Crude HR (95% CI) Total n=137593	p-value	**Model A adjusted model [1]** Adjusted HR (95% CI) Total n=137593	p-value	**Model B base model** Crude HR (95% CI) Total n=146307	p-value	**Model B adjusted model [2]** Adjusted HR (95% CI) Total n=146307	p-value
All MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
MLTC	4.87 (2.98-7.95)	<0.001	5.81 (3.51-9.61)	<0.001	4.48 (2.8-7.16)	<0.001	4.95 (3.05-8.06)	<0.001
Complexity of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
2 conditions MLTC	5.27 (3.10-8.95)	<0.001	6.21 (3.62-10.69)	<0.001	4.7 (2.8-7.9)	<0.001	5.19 (3.07-8.78)	<0.001
3+ conditions MLTC	3.97 (1.83-8.61)	<0.001	4.85 (2.21-10.66)	<0.001	4.01 (1.93-8.29)	<0.001	4.4 (2.08-9.29)	<0.001
Type of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
Physical health MLTC	1.08 (0.15-7.91)	0.94	1.04 (0.14-7.65)	0.967	0.96 (0.13-7.02)	0.970	0.88 (0.12-6.35)	0.967
Mental health MLTC	8.06 (4.47-14.5)	<0.001	10.5 (5.71-19.3)	<0.001	7.17 (4.03-12.74)	<0.001	8.72 (4.82-15.79)	<0.001
Mixed MLTC	3.96 (2.11-7.42)	<0.001	4.99 (2.62-9.49)	<0.001	3.8 (2.08-6.93)	<0.001	4.32 (2.32-8.01)	<0.001
Self-harm	**Model A base model** Crude HR (95% CI) Total n=137593	p-value	**Model A adjusted model [1]** Adjusted HR (95% CI) Total n=137593	p-value	**Model B base model** Crude HR (95% CI) Total n=146307	p-value	**Model B adjusted model [2]** Adjusted HR (95% CI) Total n=146307	p-value
All MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
MLTC	3.44 (2.81-4.2)	<0.001	3.52 (2.86-4.33)	<0.001	3.29 (2.7-4.01)	<0.001	3.5 (2.84-4.3)	<0.001
Complexity of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
2 conditions MLTC	2.72 (2.13-3.48)	<0.001	2.79 (2.18-3.58)	<0.001	2.61 (2.05-3.22)	<0.001	2.77 (2.16-3.55)	<0.001
3+ conditions MLTC	5.05 (3.88-6.56)	<0.001	5.23 (3.99-6.85)	<0.001	4.85 (3.74-6.29)	<0.001	5.25 (4.01-6.88)	<0.001
Type of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
Physical health MLTC	1.21 (0.60-2.45)	0.597	1.46 (0.72-2.95)	0.296	1.17 (0.60-2.39)	0.381	1.49 (0.7-2.87)	0.331
Mental health MLTC	3.91 (2.94-5.2)	<0.001	3.86 (2.88-5.17)	<0.001	3.83 (2.77-5.18)	<0.001	3.82 (2.86-5.12)	<0.001
Mixed MLTC	3.72 (2.94-4.73)	<0.001	3.82 (2.99-4.88)	<0.001	3.62 (2.89-4.8)	<0.001	3.81 (2.98-4.87)	<0.001

Table 6.3. (continued) Multivariable regression models investigating the association between MLTC and maternal mental health outcomes

Active postnatal CMHD	**Model A base model** Crude HR (95% CI) Total n=137593	p-value	**Model A adjusted model [1]** Adjusted HR (95% CI) Total n=137593	p-value	**Model B base model** Crude HR (95% CI) Total n=146307	p-value	**Model B adjusted model [2]** Adjusted HR (95% CI) Total n=146307	p-value
All MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
MLTC	4.14 (4.02-4.26)	<0.001	3.86 (3.75-3.98)	<0.001	4.18 (4.07-4.311)	<0.001	3.85 (3.74-3.97)	<0.001
Complexity of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
2 conditions MLTC	3.57 (3.45-3.69)	<0.001	3.35 (3.24-3.47)	<0.001	3.62 (3.5-3.74)	<0.001	3.36 (3.25-3.48)	<0.001
3+ conditions MLTC	5.53 (5.32-5.76)	<0.001	5.13 (4.93-5.34)	<0.001	5.59 (5.37-5.81)	<0.001	5.06 (4.86-5.27)	<0.001
Type of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
Physical health MLTC	1.08 (0.97-1.21)	0.173	1.16 (1.04-1.29)	0.009	1.08 (0.97-1.2)	0.18	1.13 (1.01-1.26)	0.033
Mental health MLTC	4.82 (4.62-5.02)	<0.001	4.35 (4.17-4.53)	<0.001	4.9 (4.71-5.11)	<0.001	4.41 (4.23-4.59)	<0.001
Mixed MLTC	4.63 (4.47-4.79)	<0.001	4.3 (4.15-4.45)	<0.001	4.68 (4.53-4.84)	<0.001	4.25 (4.11-4.4)	<0.001

[1] Model A adjusted for maternal age, ethnicity, smoking status and socioeconomic status

[2] Model B adjusted for maternal age, ethnicity, smoking status, socioeconomic status and maternal BMI

6.3.2.1 Acute psychosis

A total of 70 events of acute psychosis occurred in the study period, representing a rate of 0.38 (95% CI 0.3-0.49) per 1000 person-years of follow-up time. The rate of acute psychosis was higher among pregnancies to women with MLTC (rate 1.04 (95% CI 0.74-1.46) per 1000 person-years of follow-up time) compared to pregnancies without MLTC (rate 0.25 (95% CI 0.18-0.34) per 1000 person-years follow-up time). MLTC in pregnancy was associated with a significantly increased risk of acute psychosis (aHR 5.81, 95%CI 2.98-7.95) in both the base and fully adjusted Cox regression models. There was no evidence of a differential risk of acute psychosis based on complexity of MLTC. The risk of acute psychosis was elevated for pregnancies with mental health MLTC (aHR 10.5, 95% CI 5.71-19.3) and mixed MLTC (aHR 4.99, 95% CI 2.62-9.49), but not for pregnancies with physical health MLTC (aHR 1.04, 95% CI 0.14-7.65) compared to the reference population.

6.3.2.2 Self-harm events

A total of 410 events consistent with self-harm, thoughts of self-harm, suicidal thoughts or non-fatal suicide attempt occurred in the study period, representing a rate of 2.25 (95%CI 2.04-2.48) per 1000 person-years follow-up time. The rate of self-harm events was higher among pregnancies to women with MLTC (rate 5.16 (95%CI 4.4-6.02) per 1000 person-years follow-up time) compared to pregnancies to women without MLTC (rate 1.63 (95%CI 1.44-1.85) per 1000 person-years follow-up time. MLTC in pregnancy was associated with a significantly increased risk of a self-harm event (aHR 3.52, 95% CI 2.81-4.2) in both the base and fully adjusted Cox regression models. There was evidence of differential risk based on

complexity of MLTC, with pregnancies to women with complex MLTC having a higher risk of a self-harm event (aHR 5.23, 95% CI 3.99-6.85) compared to pregnancies with MLTC from 2 conditions only (aHR 2.79, 95% CI 2.18-3.58). Regarding type of MLTC, the risk of a self-harm was increased among pregnancies with mental health MLTC (aHR 3.86, 95%CI 2.88-5.17) and mixed MLTC (aHR 3.82, 95% CI 2.99-4.88), but not significantly raised for pregnancies with physical health MLTC (aHR 1.46, 95%CI 0.72-2.95) compared to the reference group.

6.3.2.3 Active postnatal common mental health disorders

The prevalence of active postnatal CMHD in the extended postnatal period was 13.2% overall, equating to a rate of 113.9 (95%CI 112.3-115.5) per 1000 person-years follow-up time. The rate of active postnatal CMHD was higher among pregnancies to women with MLTC (rate 306.9 (95%CI 300.4-313.6) per 1000 person-years follow-up time) compared to pregnancies without MLTC (rate 77.4 (95%CI 76-78.9) per 1000 person-years follow-up time). The risk of active postnatal CMHD was significantly raised among pregnancies to women with MLTC (aHR 3.86, 95%CI 3.75-3.98), compared to the reference group in both the base and fully adjusted Cox regression models. Similarly to the patterns observed for self-harm, there was evidence of differential risk based on both type and complexity of MLTC. Pregnancies to women with complex MLTC had a higher risk of active postnatal CMHD (aHR 5.13, 95%CI 4.93-5.34), compared to pregnancies with MLTC from 2 conditions only (aHR 2.79, 95% CI 2.18-3.68). The risk of active postnatal CMHD was increased among pregnancies with mental health MLTC (aHR 4.35, 95% CI 4.17-4.53), and pregnancies with mixed mental health MLTC (aHR 4.3, 95% CI 4.15-4.45), pregnancies with physical health MLTC (aHR 1.16, 95%CI 1.04-1.26) compared to the reference group.

6.3.3 Sensitivity analyses and missing data

In the second model presented (model B base model and model B adjusted model) partially observed covariates were imputed using multiple imputation for all outcomes under investigation. The imputation of missing covariates did not substantively change the effect estimates across any of the outcomes examined compared to the main models (model A base model and model A adjusted model). In addition, a restricted complete case analysis was undertaken for all pregnancies with complete data for BMI, maternal age, ethnicity, IMD and smoking status. The model for the restricted complete case analysis (model C base model and model C adjusted model) is presented in appendix E (Table E1). All statistically significant associations of effect observed in the main model remained present in the restricted complete case analysis. For the outcomes of self-harm and active postnatal CMHD, adjustment of the crude model for all covariates including BMI resulted in a slight reduction in the effect size. For the outcome of acute psychosis, adjustment of the crude model for all covariates including BMI appeared to increase the effect size, although the wide confidence intervals indicating the lower levels of precision around these estimates are noted. These results suggest that while maternal BMI does to some extent act a confounder, it does not explain the presence of an association between MLTC and maternal mental health disorders in the extended postnatal period.

The rates of active postnatal CMHD and self-harm by total number of pre-existing health conditions and whether those conditions included mental health conditions is shown in appendix E (Table E2 and E3). Overall, rates of active postnatal CMHD and self-harm were higher among women who had any history of a mental health condition, compared to

women with no pre-existing health conditions or women with one or more physical health conditions. Women with MLTC from 2 or 3+ conditions that was inclusive of a pre-existing mental health condition, however, were observed to have a higher rate of active postnatal CMHD compared to non-MLTC women with one pre-existing mental health condition. There was no significant difference in the rate of self-harm for women with MLTC from 2 conditions inclusive of a pre-existing mental health condition, and non-MLTC women with one pre-existing mental health condition. Women with MLTC from 3+ conditions inclusive of a pre-existing mental health condition were seen to have a significantly elevated rate of self-harm compared to non-MLTC women with one pre-existing mental health condition.

6.4 Discussion

6.4.1 Contribution to knowledge

To my knowledge, this work represents the first exploration of the association between MLTC in pregnancy and common and severe perinatal mental health disorders. It reveals that women with MLTC remain at increased risk of adverse maternal mental health outcomes compared to women without MLTC for up to one year after birth. The inclusion of a broader conceptualisation of mental health SMM, and the use of an extended time-frame for event follow-up are novel features of this study, and provide new insights into inequalities into maternal health outcomes.

6.4.2 Interpretation of findings and relation to literature

6.4.2.1 Acute postpartum psychosis

The prevalence of acute postpartum psychosis in this study was estimated to be 0.05% (95% CI 0.037-0.059) across the study period. This is lower that the commonly cited prevalence estimate of 1 per 1000 births, which is based on findings from six population-based studies included in a systematic review presented by VanderKruik et al. (343). Acute postpartum psychosis is known to have a rapid onset and is regarded as a psychiatric emergency, making it a condition that is more likely to require specialised management through secondary care mental health services (344). This study was able to identify cases through primary care records and admissions to acute secondary care, however, it was not possible to use datasets detailing attendance to Accident and Emergency not resulting in admission to secondary care, or care provided within secondary care mental health services. These limitations around case ascertainment within this study may account for the slightly lower estimate of prevalence than might have been anticipated from review of the wider literature.

This study found that women with MLTC had a higher risk of acute postpartum psychosis compared to women without, and that women with mixed MLTC and mental health MLTC appeared to be at differentially increased risk compared to women without MLTC or those with physical health MLTC (who were observed to have no increased risk compared to the reference group). Although acute postpartum psychosis can occur in the absence of identifiable risk factors, women who have a pre-existing diagnosis of bipolar or

schizoaffective disorder, those who have previously experienced postpartum psychosis, and those with a family history of postpartum psychosis are known to have an elevated risk (344). Although not investigated as part of the remit of this work, it is possible that women with mixed or mental health MLTC are more likely to have these identifiable pre-existing risk factors for acute postpartum psychosis compared to women with physical health MLTC or non-MLTC women.

Assessment of the distribution of the social and demographic characteristics among women with a diagnosis of acute postpartum psychosis requires caution due to the overall rarity of the outcome event and consequent small numbers within each of the component strata. The risk of acute postpartum psychosis based on ethnicity has not been comprehensively described in the literature. Previous studies examining severe mental illness with psychotic features in non-pregnant populations, however, suggest that women from minority ethnic groups experience these conditions at a higher rate than women of white ethnicity (345, 346). The observation of a higher proportion of acute postpartum psychosis among women from minority ethnic groups may therefore be plausible in the context of the relationship between ethnicity and severe mental illness described in the wider literature.

6.4.2.2 Self-harm

Acts of self-harm, self-harm or suicidal ideation and non-fatal suicide attempts are all representations of acute psychological distress in the individual. They can also be related to exacerbations of concurrent mental health disorders and are a strong risk factor for completed suicide (347, 348). The overall prevalence of self-harm reported in this study was

0.28% across the entire study period. A recent systematic review by Ayre et al. investigated the prevalence and correlates of self-harm in the perinatal period (349). The pooled prevalence rate from eight studies using administrative data of hospital admissions to secondary care was estimated to be 32 per 100,000 births, which is lower than equivalent prevalence rate from this study which is 280 per 100,000 births. The studies included in the review were noted to be markedly heterogenous, which limits the robustness of the estimate. The outcomes measured within the studies included in the systematic review were also much narrower than the outcomes included in this study. For example, three studies measured intentional poisoning only, two studies measured self-inflicted injuries only and three studies measured admissions for attempted suicide. The study presented in this chapter included acts of self-harm, self-harm or suicidal ideation and non-fatal suicide attempt as outcome events. The broader conceptualisation of relevant outcome events in this study, combined with the potential for additional case ascertainment through primary care data in addition to secondary care data, may account for the observed discrepancy in the estimated prevalence rate.

A recent study by Hope et al. used a population of women identified through the CPRD pregnancy register to investigate perinatal self-harm (350). This study reported a baseline rate of self-harm of 3.92 per 1000 person-years of follow-up time, with a rate of 3.88 in the first three months after the end of pregnancy, and a rate of 4.16 between 6 to 12 months after the end of pregnancy. The rate of self-harm estimated in this study was 2.8 per 1000 person-years of follow-up time, which is lower that the estimate presented by Hope et al. Although the source populations used in both studies is the same, the inclusion criteria for the study populations differed, which may explain the discrepancy in the observed outcome

event rates. The study presented in this chapter only included pregnancies with a gestation above 22+0 weeks resulting in a livebirth or stillbirth outcome, whereas the study presented by Hope et al. included any pregnancy within the pregnancy register irrespective of gestation or outcome. There is some evidence to suggest that pregnancy resulting in a livebirth is protective against self-harm and suicide (351, 352), therefore we might plausibly expect to find a marginally lower rate of self-harm among a cohort of women with predominately livebirth outcomes compared to a population inclusive of all pregnancy outcomes .

This study found that women with MLTC have a significantly elevated risk of self-harm, self-harm and suicidal ideation or non-fatal suicide attempt up to one year after giving birth compared to women without MLTC. A systematic review and meta-analysis conducted by Xiong et al. reported an increased odds of suicidal ideation among adults with MLTC (353), and an increased risk of self-harm and suicidal ideation has also been reported in previous co-morbidity studies (354-357). The finding of an increased risk of self-harm, self-harm and suicidal ideation or non-fatal suicide attempt among women with MLTC is therefore plausible in the context of this previous work. Increased risk of self-harm and suicide has also been consistently shown to be associated with chronic pain and conditions causing fatigue (358-361). In the cohort of women included in this study, a large burden of morbidity among those with MLTC was from combinations of physical or mental health conditions with conditions causing pain or fatigue. This again supports the plausibility of the finding of an increased risk of self-harm, self-harm and suicidal ideation or non-fatal suicide attempt among women with MLTC.

This study also found a differentially increased risk of self-harm among pregnancies to women with complex MLTC. Two studies exploring the association between physical MLTC, suicidal ideation and attempted suicide reported an incremental increase in risk associated with increasing numbers of health conditions (354, 356). A number of studies have also reported that individuals with co-morbid physical and mental health conditions have the highest risk of experiencing psychological distress and self-harm ideation (353, 355, 362). Within our study population, the majority of complex MLTC (86.7%) is comprised of individuals who have co-morbid physical and mental health disorders. The finding reported in this study of increased risk associated with complex MLTC is therefore plausible in the context of previous published work around risk associated with co-morbid physical and mental health conditions. The risk of self-harm was also seen to be differentially elevated based on type of MLTC, with pregnancies to women with mixed MLTC and mental health MLTC having higher risk than pregnancies to women with physical health MLTC. In the systematic review presented by Ayre et al. there was evidence that perinatal self-harm was more common among women with a history of serious mental illness which was defined as mental illness requiring contact with secondary mental healthcare services (349). Although we were not able to specifically examine severity of mental health disorders within the remit of this work, it may be that a higher distribution of severe mental health disorders among women with mental health MLTC is a factor underlying the differentially elevated risk of self-harm.

This study reported that women who had a self-harm event were more likely to be younger mothers, current smokers and living in socioeconomic deprivation. Previous studies have shown that self-harm is more likely to occur in younger women compared to older

individuals, and is strongly associated with socioeconomic deprivation which is consistent with the patterns observed in this study (231, 363, 364). This study also found that women of white ethnicity were more likely to have a self-harm event compared to women of minority ethnic backgrounds. Overall, there is a lack of consensus and in-depth exploration in the published literature regarding the relationship between risk of self-harm and ethnicity.

A systematic review presented by Al-Sharifi et al. concluded that there was evidence to suggest higher rates of self-harm among some minority ethnic groups, with a higher risk among Black women in particular (365). Meta-analysis was not possible within this review, however, due to the marked heterogeneity in ethnic group categorisation across the included studies. Two more recent studies from the UK, however, found higher rates of self-harm among individuals of White British ethnicity (366, 367). It is interesting to note that similarly to this work, these studies used admission to secondary health care and coding of self-harm events within electronic patient records to assess rates of self-harm. A study by Polling et al. reported wide variations in admission practices across four different hospitals in South London following assessment of individuals presenting with self-harm (368). In particular, hospitals with more deprived and ethnically diverse populations were less likely to admit individuals to hospital following a self-harm event, raising the possibility that service-use data may under-ascertain self-harm in minority ethnic groups. Additionally, a study by Crawford et al. found that individuals of Black and South Asian ethnicity were less likely to receive medical assessment following attempted suicide compared to individuals of white ethnicity (369). This again raises important considerations regarding the use of hospital admissions data to understand patterns of ethnicity and self-harm, and suggests that caution

is required when interpreting the observed patterns regarding ethnicity and self-harm events within this study.

6.4.2.3 Active postnatal common mental health disorders

This study found that active postnatal CMHDs were common in the study population overall, with an estimated prevalence of 13.2%. This rate is similar to that estimated by a study conducted by Tianyi et al. (233), but slightly lower than other population-based estimates of prevalence which range from between 10 to 20% (370). The lower prevalence rate reported in this study is likely related to differences in study design, with population-based survey designs consistently more likely to report higher prevalence rates due to their ability to identify cases from self-reported symptoms and somatic presentations, which are not reliably ascertained in routinely collected datasets.

This study reported a higher rate of active postnatal CMHD among women with MLTC compared to those without. There are no published studies exploring the risk of postnatal mental health disorders associated with MLTC. Studies conducted in the general adult population, however, consistently show that chronic health conditions and MLTC are associated with increased rates of affective mental health disorders and overall lower levels of psychological wellbeing (371-374). These observations support the findings reported in this study. Work exploring psychological wellbeing in pregnancy and the postpartum period conducted by Kelly et al. showed that women with long-term conditions reported lower psychological wellbeing scores compared to those without (375). Kelly et al. also found that psychological wellbeing scores were progressively worse among women with higher order

counts of long-term conditions (375, 376). Although distinct concepts, psychological wellbeing and mental health are closely related with psychological wellbeing representing a core component of good mental health. The relationship between long-term health conditions and lower subjective wellbeing reported in the general adult population, alongside the finding of lower levels of psychological wellbeing among pregnant and postpartum women living with long-terms conditions supports the plausibility of the association between MLTC and a higher risk of active CMHD in the postpartum period reported in this study.

It is well-established that adults with MLTC have a higher use of healthcare, including a higher frequency of appointments in primary care compared to those without MLTC (12). NICE guidance recommends that all women are assessed during pregnancy and the postnatal period for anxiety and depressive disorder using tools such as the Generalised Anxiety Disorder 2-item (GAD2) and Whooley questionnaires (377). The National Maternity Survey of women who gave birth in 2020 reported that 78.3% of women reported being asked about their mental health postnatally, which is consistent with participant responses from previous iterations of the survey (378). It is possible that women with MLTC may be more likely to receive these assessments and have a mental health disorder detected and recorded in their clinical records, by virtue of having a higher number of contacts with primary care. This may in part account for the observed differences in prevalence of active postnatal CMHD between women with MLTC and non-MLTC women. It is important to note, however, that the last point of scheduled contact between women and primary care services relating to postpartum care occurs at 6-8 weeks after birth (377). Further assessment of mental health status at additional timepoints in the extended postnatal period, or the use of

assessment tools for opportunistic screening is not currently a recommendation for postnatal care. It is therefore unlikely that the reported difference in prevalence and risk is entirely due to differences in opportunistic assessment between the two groups alone.

In this study women with mixed MLTC and women with mental health MLTC were observed to have a substantially higher risk of active postnatal CMHD compared to women with physical health MLTC. Pre-existing mental health disorders are consistently shown to be an important risk factor for the development or exacerbation of perinatal mental health disorders (370). This raises an important point of consideration around the extent to which the elevated risk of active postnatal CMHD among women with mixed or mental health MLTC is due to a history of having any mental health disorder rather than MLTC per se. A supplementary analysis was undertaken to explore this. Non-MLTC women with one pre-existing mental health condition had a higher rate of active postnatal CMHD than non-MLTC women with one pre-exiting physical health condition or no health conditions. Women with MLTC from 2 and 3+ conditions inclusive of a pre-existing mental health condition, however, were observed to have a higher rate of active postnatal CMHD than non-MLTC women with one pre-existing mental health condition. This suggests that while having a pre-existing mental health conditions is an important component of the elevated risk for having active postnatal CMHD, it does not fully account for the patterns of risk reported for women with MLTC in this study.

Women with complex MLTC were also found to have a differentially increased risk of active postnatal CMHD. Studies exploring the impact of long-term conditions on mental health and psychological wellbeing in the general adult population have shown that increased levels of

psychological distress and lower health-related quality of life may be mediated by factors such as pain, functional limitation to physical activity and social isolation (371, 372, 374, 379). As highlighted above within the discussion of the association between complex MLTC and self-harm, psychological distress has previously been shown to be higher among individuals with complex MLTC (362, 380), and a large retrospective cohort study conducted using UK Biobank data found individuals with complex MLTC had an increased relative risk of experiencing chronic pain that was either widespread or affecting multiple sites of the body (381). While a recent systematic review presented by Hajek et al. highlighted a paucity of studies specifically exploring the association between MLTC and social isolation, there appeared a well-established relationship between MLTC and increased likelihood of loneliness (382). It is also interesting to note in the context of the majority of complex MLTC being comprised of co-morbid physical and mental health conditions (86%), that physical and mental health co-morbidity has previously been shown to have a synergistic interaction with worsening functional disability (383, 384). While it was not possible to explore the role of perceptions of pain, loneliness and functional limitations on the likelihood of having an active postnatal CMHD, it is plausible that these may also be important factors for women with complex MLTC in pregnancy.

Women with active postnatal CMHD were more likely to be younger, overweight or obese, current smokers and living in socioeconomic deprivation. These characteristics have previously been reported in the wider literature to be associated with an increased likelihood of perinatal mental health disorders (385-389). In this study, it was additionally observed that women of white ethnicity were more likely to have active postnatal CMHD compared to those from all other ethnic backgrounds. This finding requires additional

scrutiny in the context that previous work showing that women form minority ethnic groups may be more likely to experience CMHD both outside and within the perinatal period (390, 391).

There is emerging evidence of ethnic disparities in both the diagnosis and treatment of mental health disorders within primary care. A study by Catalao et al. used linked data from primary care and secondary care mental health services to explore inequalities in risk factors among non-pregnant women of reproductive age who has contact with secondary care mental health services (392). Women from ethnic minority backgrounds were less likely to have a diagnosis of depression recorded in primary care despite having received treatment for depression from secondary mental healthcare services. Another study by Prady et al. showed that women from minority ethnic backgrounds are less likely to be screened for perinatal CMHD and less likely to receive a diagnosis despite having symptoms consistent with the condition (393). Ethnic inequalities in access to community mental health services and treatment and support for perinatal mental health conditions has additionally been reported by other studies as well (394-397). If women from minority ethnic backgrounds are less likely to be diagnosed and treated for CMHD in primary care, this could explain the unanticipated patterns observed with regard to ethnicity and active postnatal CMHD in this study. Additionally, the importance of understanding cultural differences in idioms of distress and expression of symptoms associated with mental health disorders is becoming increasingly recognised (368, 397, 398). The adequacy with which current coding practices within routinely collected data account for this is not clear at present, but may plausibly contribute to an under-estimation of the burden of morbidity from CMHD among women from minority ethnic groups.

6.4.3 Strengths and limitations

The strengths of the study presented in chapter 5 regarding the size of the study population and consequent power to study rare events consistent with SMM are also applicable to this study.

The additional main strengths of this study are as follows:

1. This study utilises the longitudinal nature of the CPRD dataset. This has allowed for the exposure of MLTC to be measured prior to each pregnancy and for study participants to be followed-up for up to one year after birth for relevant outcome events. In particular, the extended period of follow-up facilitated by the use of this dataset would not be easily achievable using traditional prospective cohort methods for the number of pregnancies included in this study. This study has demonstrated the benefit of using a longer period of follow-up beyond the traditionally used timeframe of 42 days postpartum in the study of SMM. Morbidity relating to perinatal mental health is likely to be underestimated in studies that are unable to follow-up participants for up to one year after birth.
2. The inclusion of self-harm as a form SMM relevant to mental health in addition to the more commonly studied outcome of acute postnatal psychosis, has allowed for a more comprehensive appraisal of the burden of SMM due to mental health causes. Perinatal self-harm is a relatively under-researched phenomenon but one of great importance, particularly in the context of prevention of maternal suicide. The results presented in this study contribute to expanding the evidence base around perinatal self-harm and SMM.

3. The use of primary care data has facilitated the inclusion of common perinatal mental health disorders in this study as well as events consistent with SMM. This acts as an exemplar of how disparity in health outcomes is elevated for women with MLTC across the entire spectrum of morbidity with respect to perinatal mental health, not just confined to rare but severe outcomes. This lends credence to the conceptual model presented in chapter 1 which proposes that if women with MLTC experience a disproportionate burden of morbidity with regard to maternal death and SMM, they are also potentially more likely to experience a greater burden of morbidity from non-life-threatening adverse health outcomes.
4. This study chose to investigate the events representing SMM as two separate outcomes (acute psychosis and self-harm) rather than as a combined outcome. This was primarily because the patterns observed within the social and demographic covariates were markedly different between women who experienced acute psychosis and women who experienced self-harm. While combining different outcome events is often justified by the increase in statistical power gained, an unintended consequence of this would have been a loss of valuable information about socio-demographic patterning for these outcomes. This information is not only valuable to the interpretation of analyses undertaken, but also informs the discussion about how wider determinants of health might drive inequality in outcomes, and how practice, policy and future research might address this. This example again highlights another aspect of the potential fallibility of the use of composite outcome indicators in maternal and perinatal health research.

The limitations of the study presented in chapter 5 regarding the social and demographic characteristics of the study population and consequent implications for generalisability the wider maternity population, and the possibility of residual cofounding are also applicable to this study.

The additional main limitations of this study are as follows:

1. The identification of cases of SMM and active postnatal CMHD was dependent on the presence of medical codes and product codes in the clinical records. This method of case ascertainment is unable to capture those who have symptoms consistent with the outcome, but do not have a relevant diagnostic code recorded in the clinical record. It was also not possible to identify or triangulate cases from evidence of the use of psychological therapies or support from third-sector organisations, as these are not reliably identified within the primary care records. While the use of both primary and secondary care data sources facilitates improved case ascertainment, this study was not able to use data about admission to secondary care mental health services or attendance to accident and emergency departments to identify additional cases. These caveats around case ascertainment represent a potential source of misclassification bias, and would likely underestimate the prevalence of perinatal mental health disorders overall.
2. There are several variables that have been identified in the wider literature as being associated with increased risk of perinatal mental health disorders. Examples include sleep deprivation, exposure to domestic violence, adequacy of social networks, exposure to pain or trauma, and experience of perceived difficulty associated with early parenthood. These factors may represent mediators or effect modifiers of the association between MLTC and adverse maternal mental health outcomes. It is not

possible to robustly identify information about these variables from with the CPRD or HES APC datasets. While these datasets have allowed for the identification of an association between MLTC and the adverse perinatal mental health outcomes under investigation, in their current iteration their ability to generate further information to augment our understanding of this association is limited.

6.4.4 Conclusion

This study shows that women with MLTC in pregnancy are at increased risk of experiencing both severe and common perinatal mental health disorders up to one year after giving birth. Evidence of differential risk based on type and complexity of MLTC was found. The inclusion of an additional type of mental health severe morbidity within the outcome measures and the use of an extended follow-up period revealed a previously undocumented risk of SMM for women with mental health MLTC.

Chapter 7: Conclusion and future directions

7.1 Summary of research

7.1.1 Epidemiology of MLTC in pregnancy

Research in context: MLTC has been shown to be an increasingly prevalent health concern in the general population, however, there remains a paucity of evidence about the epidemiology of MLTC in pregnant populations. Robust epidemiological evidence is a necessity for both effective planning of health care services and the prioritisation of MLTC within policy as a health concern in pregnant populations. A detailed investigation of the epidemiology of MLTC in pregnancy would also afford new insights into why pregnant women with MLTC appear to experience a disproportionate burden of severe adverse outcomes associated with pregnancy.

The systematic review presented in chapter 2 showed that despite there being a considerable volume of literature exploring the population-based prevalence of MLTC, no study had constructed a definition and operationalisation of MLTC in pregnancy that was felt to be wholly suitable for use in this work. A consensus-based approach guided by expert-opinion was used to identify a suitable definition and operationalisation of MLTC for use in these studies.

In the first component study of this thesis the epidemiology of MLTC in pregnancy in the UK was investigated. A total of 422,091 pregnancies among 331,517 women across a ten-year

period were included in the study population. The prevalence of MLTC was 16.3% overall and increased over the time-period of the study. This increase in prevalence across time is consistent with what is reported in other studies (9, 135, 185), and shows that management of MLTC in pregnancy is likely to become an increasingly common feature of maternity care. Women with MLTC were observed to have different social and demographic characteristics compared to non-MLTC women. Overall MLTC women were more likely to be older, have a BMI ≥30mg/kg^2, be current smokers and be living in socioeconomic deprivation. This study also found that women with MLTC were more likely to be white. This finding was unanticipated and may be due to women from minority ethnic groups facing barriers to accessing primary care or delays to diagnosis of chronic health conditions (256, 258, 259, 261, 263). Additionally, the extent to which current coding frameworks and practices adequately capture differences in cultural or ethnic presentations and perceptions of illness is not clear at present from the published literature and warrants further investigation (368, 398).

MLTC was further conceptualised by type and complexity. The predominant group type of MLTC observed in this study was mixed MLTC (54%) consisting of women who had at least one physical health and one mental health condition. Physical health only MLTC accounted for 14.8% of MLTC, and mental health only MLTC accounted for 31.2% of MLTC. Among pregnancies with MLTC in this study, 30.8% were classified as having complex MLTC consisting of three or more conditions, and the vast majority of complex MLTC (86.7%) was comprised of co-morbid physical and mental health disorders. For pregnancies among women with complex MLTC, a gradient was observed across all social and demographic characteristics described apart from ethnicity. The estimates of the prevalence of MLTC

overall, and of complex MLTC were slightly higher than anticipated based on what has previously been reported in the literature. A high burden of morbidity among MLTC women in this work was from gynaecological conditions, endocrine conditions and conditions causing pain and fatigue. The systemic review presented in chapter 2 showed that some of these conditions are less consistently included in previous population-based research of MLTC. As these conditions are likely to be important causes of morbidity among women of reproductive age, this may account for the higher prevalence reported in this study and suggests that previous studies have potentially underestimated the burden of MLTC and complex MLTC among younger women.

7.1.2 Associations between MLTC and maternal and perinatal outcomes

Research in context: MBRRACE-UK has consistently shown that women with pre-existing medical conditions are more likely to die during pregnancy or in the postpartum period. This suggests that MLTC may be an important driver of inequalities in maternal health. The inextricable relationship between maternal and perinatal health, means adverse perinatal outcomes may also be more common among women with MLTC. Despite the important signal provided by MBRRACE-UK, the exact magnitude and direction of this association has not previously been delineated.

In the second component study of this thesis, the association between MLTC and severe adverse maternal and perinatal outcomes in pregnancy and the immediate postnatal period was explored. A total 146,307 pregnancies to 121,211 women were included in the study population. Overall 1.5% of pregnancies in the study period were affected by SMM with a

higher rate of SMM observed among pregnancies to MLTC women compared to pregnancies to non-MLTC women. MLTC was associated with an increased odds of SMM (aOR 1.59, 95% CI 1.43-1.76) and there was evidence that pregnancies among women with complex MLTC were at differentially increased risk of SMM (complex MLTC aOR 2.11, 95% CI 1.8-2.46; 2 condition MLTC aOR 1.36, 95% CI 1.2-1.54). Previous studies using a more limited number of co-morbidities than investigated in this work report an association between increased odds of SMM and increasing condition count, supporting the plausibility of this observation (310, 315). There was also evidence of a differential distribution of risk of SMM based on type of MLTC. Pregnancies to women with physical health MLTC or mixed MLTC were more likely to be complicated by SMM (physical MLTC aOR 1.88, 95% CI 1.51-2.35; mixed MLTC aOR 1.73, 95% CI 1.52-1.97), whereas pregnancies among women with mental health MLTC did not appear to be at increased risk of this adverse outcome (mental health MLTC aOR 1.19, 95% CI 0.99- 1.44) compared to the reference population. Although the composite indicator used to measure SMM was purposefully constructed to include as many important causes of maternal morbidity and mortality as was feasible, proportionally more procedures and conditions related to physical health compared to mental health are represented. This may have led to an underestimation of SMM from mental health conditions overall, and subsequent underestimation of the burden of SMM among women with mental health MLTC. The rate of maternal death ascertained in this study did not allow for investigation of the association between MLTC and maternal death to be undertaken.

There was evidence of a significant association between MLTC and an increased odds of neonatal death in this study (aOR 1.94, 95% CI 1.29-2.91). An increased rate of prematurity and early-term delivery among MLTC women was identified as a possible factor contributing

to the increased risk of neonatal death in this group. When MLTC was stratified by complexity, there was no evidence of an increase in the odds of neonatal death among women with complex MLTC, however, this should be interpreted cautiously due to low outcome event numbers and the subsequent reduction in statistical power for sub-group analysis. There was no difference in the rate of stillbirth between pregnancies among women with MLTC and those to non-MLTC women, which was unanticipated due to some pre-existing medical conditions being shown to be a risk factor for stillbirth in the wider literature. Subsequent analysis exploring the proportions of births and ongoing pregnancies among MLTC women and non-MLTC women across six gestational timepoints showed that at each timepoint up to 41+6 weeks of pregnancy MLTC women were more likely to have given birth compared to non-MLTC women. Earlier gestation at birth could underlie the finding of no difference in the rate of stillbirth between the two groups despite the plausible assumption of increased risk among MLTC women for this outcome. It cannot, however, be discounted that the lower than expected rate of stillbirth in the study population overall may have reduced the statistical power needed to investigate this rare outcome leading to a finding of no difference between the two comparator groups.

The association between MLTC and severe and common maternal mental health disorders up to one year after birth was investigated in the third component study of this thesis. A total 146,307 pregnancies to 121, 211 women were included in the study population. The risk of acute psychosis following pregnancy was higher for MLTC women compared to non-MLTC women (aHR 4.87, 95% CI 2.98-7.95). There was no evidence of differential risk based on complexity of MLTC, however women with mental health MLTC and mixed MLTC had an elevated risk (mental health MLTC aHR 10.5, 95% CI 5.71-19.3; mixed MLTC aHR 4.99, 95% CI

2.62-9.49), whereas women with physical health MLTC did not appear to be at increased risk of this adverse outcome (physical health MLTC aHR 1.04, 95% CI 0.14-7.65). The differential risk based on type of MLTC may be due to differences in underlying risk factors for postpartum psychosis within the three cohorts of MLTC women, although this was not formally investigated as part of this work.

MLTC was associated with an increased risk of self-harm following pregnancy (aHR 3.52, 95% CI 2.86-4.33), and there was evidence that women with complex MLTC had a differentially elevated risk (complex MLTC aHR 5.23, 95% CI 3.99-6.85; 2 condition MLTC aHR 2.79, 95% CI 2.18-3.58). Previous studies have shown elevated risk of self-harm and psychological distress among adults with co-morbid physical and mental health disorder. The predominance of co-morbid physical and mental health disorders among women with complex MLTC may therefore contribute to this elevated risk. The risk of self-harm following pregnancy was also observed to be differentially elevated based on type of MLTC. Women with mental health and mixed MLTC had an increased risk (mental health MLTC aHR 3.86, 95% CI 2.88-5.17; mixed MLTC aHR 3.82, 95% CI 2.99-4.88), whereas women with physical health MLTC were not found to be at significantly increased risk compared to the reference group (physical health MLTC aHR 1.46, 95% CI 0.72-2.95).

As for severe mental health disorders, women with MLTC were found to have an increased risk of having an active postnatal CMHD up to one year after birth (aHR 3.86, 95% CI 3.75-3.98). Studies have previously shown lower levels of psychological wellbeing among adults with long-term conditions including during pregnancy and the postpartum period. This is consistent with the elevated risk of active postnatal CMHD among MLTC women reported

here. Women with complex MLTC were observed to have a differentially elevated risk of having an active postnatal CMHD (complex MLTC aHR 5.13, 95% CI 4.93-5.34); 2 condition MLTC aHR 3.35, 95% CI 3.24-3.47). This is consistent with the increased risk of CMHDs reported in the literature among adults with complex MLTC in the general population. Women with mental health MLTC and mixed MLTC were observed to a substantially higher risk of active postnatal CMDH (mental health MLTC aHR 4.35, 95% CI 4.17-4.53; mixed MLTC aHR 4.3, 95% CI 4.15-4.45) than women with physical health MLTC (aHR 1.16, 95% CI 1.04-1.29). Pre-existing mental health conditions are a known and important risk factor for the development or exacerbation of mental health conditions in the perinatal period (370). By definition, women with physical health MLTC do not have any pre-existing mental health conditions, and the absence of this risk factor may account for the overall lower risk of having an active postnatal CMHD.

7.1.3 Utility and methodological considerations of using routinely collected data in pregnancy research

Research in context: This thesis uses routinely collected data to investigate the epidemiology of MLTC in pregnancy and its association with several key maternal and perinatal outcomes. Although CPRD GOLD and the associated linked datasets have been used extensively in healthcare research generally, their use in pregnancy research is relatively new. Prudent reflection on the role and utility of these datasets to pregnancy research has been made throughout this thesis, alongside an explicit evaluation of the methodological approach and decisions involved in the identification of a pregnancy cohort with data of suitable quality for undertaking research.

The work presented in this thesis demonstrates the potential for routine data to be used to conduct robust and comprehensive epidemiological pregnancy research. A longitudinal cohort of pregnant women was identified from within the CPRD pregnancy register allowing for an investigation of the epidemiology of MLTC in pregnancy to be undertaken, and a subset of this cohort was used to allow for an investigation of the association between MLTC and severe adverse maternal and perinatal outcomes. The pregnancy cohort identified from within the CPRD pregnancy register is considerably larger than could plausibly be constructed using more traditional prospective cohort research methods. This has allowed for the study of rare outcome events and made it feasible to undertake sub-group analysis generating a more detailed picture of the implications of MLTC to maternal and perinatal health. The preliminary signals as to the importance of MLTC in inequitable maternal and perinatal outcomes were provided by MBRRACE-UK which consistently reports that women with multiple pre-existing health conditions are disproportionately represented among women who died during pregnancy or after giving birth. The use of the CPRD pregnancy register and associated linked datasets then allowed for the salience of these preliminary signals to be investigated at scale in a time and cost-effective manner, generating pertinent information about epidemiology and quantification of risk. This is arguably currently one of the great strengths of the use of routinely collected data in pregnancy research. A critical reflexivity around the limitations of routine data in pregnancy research has allowed for the identification of several topic areas that warrant further research in the future. This is discussed further in the following sections (sections 7.2.4 and 7.2.5).

The provenance of routinely collected datasets, however, make it an inarguable practicality that extensive data cleaning and curation is often required to generate data that is usable for

research. In this work, the identification of a cohort of authentic contemporaneous pregnancies required extensive data cleaning and management, while the application of data quality restrictions was deemed necessary to reduce misclassification bias in the measurement of MLTC status. The application of data quality restrictions, however, was observed to have important implications for the composition of the study population overall. Women with research quality pregnancy data were more likely to be of white ethnicity, to be older, and to be overweight or obese compared to women without research quality pregnancy data. Although the application of data quality restrictions did not appear to have an appreciable impact on the distribution of IMD or smoking status, comparison to nationally available maternity data suggests that the final study population had an over-representation of women in the least deprived socioeconomic group compared to the wider maternity population. Validation of the matching of pregnancy-delivery episode pairs between CPRD and HES APC was also undertaken. This was deemed necessary to ensure confidence that the correct pregnancy in CPRD was matched to the correct delivery-episode in HES APC, and that the associated time-frames for measuring the outcome events were accurate. This validation, however, appeared to result in the disproportionate loss of preterm births from the final cohort, potentially driven by preterm births being less likely to have accurate data around the start and end dates of the pregnancy.

Sampling bias is increasingly recognised as an important bias in studies using routinely collected data, and this work highlights that although CPRD data is derived from the general population, it is not a perfect reflection of that population even when accounting for large cohort sizes. This has implications for the generalisability of the findings of this work to the wider maternity population, and raises the important possibility that the burden of MLTC

has not been fully described for women living in socioeconomic deprivation and women from minority ethnic groups. The exclusion of individuals from vulnerable or marginalised populations has the potential to perpetuate or widen health inequalities for these groups, and is an important consideration for any future study using these datasets. Further to this, ethnicity and socioeconomic deprivation are known to be two extremely important drivers of inequalities in maternal and perinatal health, while prematurity is strongly associated with stillbirth and increased risk of neonatal death. The under-representation of women from minority ethnic groups and those from more deprived socioeconomic backgrounds alongside the disproportionate loss of preterm births from the study population may plausibly have contributed to the lower than anticipated rates of adverse outcomes for maternal death, stillbirth and neonatal death described.

7.2 Future directions: implications for clinical practice, policy-making and research

7.2.1 Adequate identification of MLTC as a risk factor for adverse pregnancy outcomes

This work provides compelling evidence for the role of MLTC as a driver of inequitable maternal and perinatal outcomes in the UK. It is unclear whether current approaches to the stratification of clinical risk in pregnancy would adequately identify women with MLTC as being at elevated risk of adverse outcomes (46). Evaluation of current guidance and clinical risk stratification practices against the characteristics of MLTC identified in this work would be a pragmatic and important next step. In the context of the increased risk of adverse maternal and perinatal outcomes shown by this work, it is also reasonable to consider if wider inclusion in established surveillance and screening in pregnancy would benefit women

with MLTC. This could include screening for preterm birth, enhanced monitoring of fetal growth and additional opportunities to monitor maternal parameters in the antenatal and postpartum period. The preconception period has previously been highlighted as a critical time-period during which health of women with pre-existing medical conditions could be optimised including a comprehensive review of symptom control and suitability of medications for pregnancy (27, 399, 400). The feasibility of offering this type of review to women identified in primary care as having MLTC should be explored.

This work also demonstrated that women with MLTC were at increased risk of active postnatal CMHD for up to one year after birth. Common complications and conditions related to pregnancy, such as postnatal CMHD, represent a considerable burden of morbidity overall and have a substantial impact on wellbeing and quality of life (334). The inclusion of this outcome has arguably provided a more comprehensive understanding of the implications of MLTC in pregnancy. A recent scoping review by Vogel et al. highlights the vast breadth of potential health problems in the extended postnatal period experienced by women as a result of pregnancy, alongside the paucity of high-quality evidence and clinical guidance pertaining to the extended postnatal period (401). In addition to focussing on severe adverse outcomes, future research should also seek to better understand inequalities in more common conditions and complications of pregnancy. There is also an urgent need for discussion among healthcare professionals and policy makers regarding the appropriateness of the last recommended healthcare contact resulting from pregnancy occurring at 6-8 weeks after birth (377). Extension of the time-frame for the provision of postnatal care alongside the inclusion of repeated assessments of maternal mental health and wellbeing in the extended postnatal period should be considered.

7.2.2 Ensuring current services are structured to meet the needs of women with MLTC

It is a well-established observation in wider healthcare that guidelines, clinical practice and the structure of health services predominately focus on the management of single health conditions (16). This often fails to account for the specific needs of individuals with MLTC, while also perpetuating deficits in training and knowledge among healthcare professionals (15, 16, 19). The detrimental impact of this on the health and wellbeing of those with MLTC is widely discussed in the literature. There are no well-founded reasons to believe that these observations made at the level of wider healthcare, are not equally applicable to maternity care and pregnant women with MLTC. Indeed, there currently exists no specific guidance about the optimal management of MLTC with regard to pre-conceptual, antenatal, intrapartum or postnatal care. A study by Taylor et al. evaluated guidelines for the multidisciplinary team management (MDT) of women with pre-existing diabetes or cardiac disease in pregnancy (402). This study reported a wide variation in the organisation of clinical services nationally, while a systematic review by Bick et al. highlighted the lack of a robust evidence base to inform optimal MDT models of care for women with long-term conditions in pregnancy (403). The ongoing development of this evidence base alongside the publication of specific guidance on provision of maternity care for women with MLTC should be prioritised.

This work demonstrated that a considerable burden of disease among women with MLTC is comprised of co-morbid mental and physical health conditions. The structure of healthcare services traditionally demarcates mental and physical health conditions, contributing to the creation of silos of care (404). The establishment of maternal medicine networks in the UK is

a laudable endeavour aiming to improve care for women with medical problems during pregnancy. The extent to which these networks, which according to service specifications will almost exclusively focus on physical health conditions, will be able to comprehensively meet the needs of those with mixed and complex MLTC is a valid concern (48). Similarly, while perinatal mental health networks are vital to the care of women with mental health conditions, they may not contain the necessary expertise to fully manage co-morbid physical and mental health conditions. This lack of integration of physical and mental healthcare is not specific to maternity services and has rightly become a focus of policy attention due to the potential for inequality and vulnerability created by disjointed and segregated care systems (404). An assessment of the structural organisation of maternity care in the UK, with a specific focus on how existing networks can facilitate the integration of care for women with physical and mental health co-morbidity should be undertaken.

7.2.3 Enabling a life-course approach to maternal health

The work presented in this thesis shows that women with MLTC have different social and demographic characteristics to non-MLTC women, including being more likely to smoke, more likely to have a raised BMI, and more likely to be living in socioeconomic deprivation. These factors are key social and behavioural determinants not only of maternal health, but also contribute to increased risk of poor health in older age, disability and premature mortality (209). It is clearly concerning that such marked disparities in these factors are present at such an early part of the life-course for women with MLTC. Public health practice shows that strategies to target social and behavioural determinants of health is often less effective when enacted at the level of individual healthcare alone, instead requiring action

across multiple systems and levels (405). The strengthening of collaborative partnerships between maternity, public health and primary care should be prioritised as a necessary part of ongoing work to improve maternal and perinatal health.

7.2.4 Improving the utility of routinely collected data for pregnancy research

It is notable that in this work, the expected event rate for neonatal death, maternal death and stillbirth was much lower that studies conducted using non-routine data sources would suggest (27, 285). This may in part be driven by the demography of the women who were eligible for inclusion in the final study population, but is also due to factors such as maternal and neonatal death being less likely to fulfil eligibility for criteria for linkage to mortality data (226), and babies who are never registered with a primary care practice not being identifiable through the CPRD mother-baby link. The original EMMOI was unable to include some important causes of SMM due to concerns about data quality within HES APC (227). Similarly in this work, it was found that ICD-10 and OPCS-4 coding frameworks were often insufficiently detailed or poor descriptors of clinical conditions and procedures common to obstetric practice. This places limitations on the depth of understanding that can be gained about SMM from this data source.

The inclusion of outcomes such as maternal death, SMM, neonatal death and stillbirth are integral to the study of maternal and perinatal health, in addition to being key metrics through which population health is monitored. Improved recording of birth outcomes in both primary and secondary care, and investigation of how cases of maternal and neonatal death can be more robustly ascertained in routine data would increase the quality of

available data for both research and population health surveillance. Expanding the codes available within ICD-10 and OPCS-4 coding frameworks to allow the explicit identification of obstetric procedures, intervention and diagnoses would arguably improve the utility of these datasets for undertaking pregnancy research. External validation of codes for a limited number of pregnancy conditions and complications has previously been undertaken in Norwegian and Danish birth registries (406-408). Similar external validation of pregnancy-specific diagnostic and procedure codes within CPRD GOLD and HES APC would additionally improve confidence in research outputs generated from the use of these datasets.

The work presented in this thesis used several available linked datasets. This both augmented the amount of information available for analysis, and allowed for the component studies to encompass the preconception, pregnancy and postpartum periods. Linkage to other datasets which are currently available through CPRD, such as HES Accident and Emergency, Outpatients and Mental Health Services Datasets would likely improve case ascertainment for exposure and outcome events and enhance our overall understanding of MLTC in pregnancy, but was not possible within the remit of this thesis. Patient perspectives and measures of patient experience are increasingly recognised as a vital component of the evaluation of healthcare including in the assessment of safety and efficacy (409). The development of linkages between CPRD and datasets containing Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs) would provide a valuable new dimension to our understanding of maternal health from routine data. Additionally, the development of linkages to datasets containing information about social care, health visiting and child health and education would allow for the potential to assess a

wider range of relevant health outcomes improving the utility of this type of data for pregnancy research.

7.2.5 The benefit of standardised outcome measures and extended surveillance

The complementary value of studying severe maternal morbidity to enhancing our understanding of the themes emerging from surveillance data of maternal death is demonstrated through this work. There is growing recognition that the study of maternal morbidity has been limited by a lack of consensus among researchers regarding the definition of severe maternal morbidity and which conditions should be included (410). Recent work conducted by the International Network of Obstetric Surveillance Systems (INOSS) has begun the process of trying to achieve this consensus, and will only serve to improve the strength of the evidence-base around severe maternal morbidity (411). A necessary next step with regard to the use of routine data will be to evaluate the validity of using these emerging consensus definitions across different data sources.

This work has also showed the value of having a broad conceptualisation of severe maternal morbidity. The use of self-harm, self-harm and suicidal ideation and near-miss suicide as markers of severe maternal morbidity is novel, and expanded the definition of SMM which has traditionally focussed more on complications related to physical health conditions and physical health outcomes. The inclusion of these outcome events facilitated a more comprehensive evaluation of severe maternal morbidity, and allowed for the description of patterns of risk for women with pre-existing mental health conditions that would otherwise not have been apparent using only pre-existing measures of SMM. To support the concept of parity of esteem between physical and mental health, future research on SMM must

address the disproportionate focus on physical health complications and outcomes. The use of an extended time period postnatally to investigate severe and common maternal mental health outcomes in this work additionally demonstrated the importance of expanding the time-frames for capturing SMM events, particularly those related to mental health. The investigation of severe adverse maternal health events in the extended postnatal period has previously been described as a "neglected responsibility" in terms of both adequate investment in data collection and effective health care planning (412). Future studies that choose not to use extended time-frames in the study of SMM should be required to carefully justify this, as it arguably provides a more comprehensive assessment of maternal health than the current status quo.

7.2.6 Developing a better understanding of the components of elevated risk for women with MLTC

It is not possible to comprehensively elucidate all the mechanisms through which MLTC increases the risk of adverse maternal and perinatal outcomes from these studies alone. Further research is needed to identify possible targets for interventions aimed at reducing inequitable outcomes for this group of women. Particular attention is warranted for women with complex MLTC, who were observed to have differentially elevated risk across almost all outcomes investigated. The role of factors such as condition severity and polypharmacy in mediating the proportionally worse outcomes experienced by women with complex MLTC could be comprehensively investigated from the data sources used in this thesis (413-415). Consideration should also be given to the use of longitudinal cohorts to facilitate the study of the development of MLTC across the life-course, including how individuals transition from non-MLTC states to 2 condition MLTC or complex MLTC. This type of methodological

approach may assist in the identification of higher risk combinations of health conditions and other factors contributing to the development of complex MLTC. A review by Cezard et al. synthesised the published literature that had used longitudinal approaches to studying MLTC (416). Overall, these approaches were found to be relatively uncommon compared to cross-sectional study designs, with marked heterogeneity between studies with regard to measurement of MLTC and outcomes studied. It was also notable within the review that only 11 out of 35 studies (31%) were inclusive of women of reproductive age, which again highlights the need for further research concentrating on MLTC in younger women.

This work also found a gradient of socioeconomic deprivation, obesity and smoking with complexity of MLTC, all of which are related to wider social determinants of health. The role of factors relating to social risk in adverse pregnancy outcomes is increasingly well recognised (24, 417). Indeed the most recent MBRRACE-UK report showed that women who were the most socioeconomically deprived were twice as likely to die in pregnancy compared to those least deprived, and that women with features of severe and multiple disadvantage were disproportionately over-represented among those who died (27). The use of routine data to assess social risk and social complexity is under-researched at present (418), and it is unclear whether factors most relevant to pregnancy outcome such as experience of domestic violence, insecure housing or refugee status are comprehensively captured in existing datasets. Future work should focus on the investigation and validation of social risk factors relevant to pregnancy within CPRD, as this has the potential to greatly augment our understanding of adverse pregnancy outcomes as a whole, as well as the contribution of these factors to poorer outcomes among women with complex MLTC.

It is a well-established principle that comprehensive antenatal care is integral to women having safe and healthy pregnancies (27, 46). The importance of optimising the structure of maternity care for women with MLTC is in part discussed above, however, the extent to which individuals can access and benefit from the provision of healthcare is dependent on many factors above and beyond service structure and availability (419, 420). One framework that has been widely used to assess barriers and facilitators to accessing healthcare, including recently in the evaluation of remote antenatal care and access to mental health services during the Covid-19 pandemic, is the construct of candidacy (421). This framework evaluates access to healthcare using seven features of candidacy, and explicitly accounts for factors operating the level of the individual, the organisation and the wider sociocultural, economic and political context (421). Qualitative enquiry and service-evaluation work using an established framework such as this could provide additional valuable information about barriers and facilitators to accessing and benefitting from the provision of antenatal care for women with MLTC.

Additionally to this, qualitative enquiry aimed at understanding the lived experiences of women with MLTC in pregnancy is needed. Concepts such as treatment burden (the effort required for patients to look after their own health and the impact this has on function and wellbeing) (422), symptom burden (the severity of symptoms and how difficult they are to control) (422) and treatment fatigue (when the workload to look after their health exceeds the personal capacity of the patient) (423) are becoming increasingly well recognised factors influencing patient wellbeing and health outcomes in adults with MLTC. Understanding how organisation and delivery of healthcare influences these concepts is becoming an evolving focus of MLTC research in the wider population (424). There are no studies at present which

explore the extent to which pregnant women with MLTC are likely to experience treatment burden, symptom burden or treatment fatigue, and future work in this area could provide a valuable adjunct to our understanding of the impact of MLTC on pregnancy outcome.

7.3 Conclusion

To my knowledge this thesis represents one of the largest and most comprehensive investigations of MLTC in pregnancy to date. MLTC was found to be a common health concern among pregnant women, and one that is likely to become increasingly prevalent in the future. Detailed description of the epidemiology will inform the development of healthcare services that can optimally meet the needs of MLTC women. The implications of MLTC to maternal and perinatal outcomes are also presented, including quantification of the magnitude of the associated risk. MLTC was found to be an important driver of inequitable maternal and perinatal outcomes associated with pregnancy. Strategies to improve maternal and perinatal health are unlikely to have a substantive impact unless MLTC in pregnancy is accounted for. The use of routine data in healthcare research is a rapidly evolving field, and there are clear advantages to its use to augment more well-established pregnancy research methods. Increased data linkages and better data quality will improve the utility of routine data to pregnancy research, while candid reflection within the research community is required regarding representation of vulnerable and complex populations groups in this type of research.

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Appendix A

Table A1. Search strategy for Ovid Medline database

1	(Multimorbid or Multi-morbid or Multimorbidity or Multi-morbidity or Multimorbidities or Comorbid or Co-morbid or Comorbidity or Co-morbidity or Polypathology or Poly-pathology or Multipathology or Multi-Pathology or Multi-condition or Multiple conditions or Multiple morbidities or Multiple chronic conditions or Multiple diseases or Multiple diagnoses or Multiple illness or Co-existing disease or Co-existing illness or Co-existing condition or Co-existing diagnoses or Coexisting disease or Coexisting illness or Coexisting condition or Coexisting diagnoses or Concurrent disease or Concurrent illness or Concurrent condition or Concurrent morbidities).mp
2	(Prevalence or Epidemiology or Epidemiologic or Pattern or Patterns or Proportion or Cluster or Number or Epidemioological or Epidemiological study or Population distribution or Measure or Incidence or Distribution or Rate or Trend or Trends or Measuring or Population based).mp
3	(Multimorbid or Multi-morbid or Multimorbidity or Multi-morbidity or Multimorbidities or Comorbid or Co-morbid or Comorbidity or Co-morbidity or Polypathology or Poly-pathology or Multipathology or Multi-Pathology or Multi-condition or Multiple conditions or Multiple morbidities or Multiple chronic conditions or Multiple diseases or Multiple diagnoses or Multiple illness or Co-existing disease or Co-existing illness or Co-existing condition or Co-existing diagnoses or Coexisting disease or Coexisting illness or Coexisting condition or Coexisting diagnoses or Concurrent disease or Concurrent illness or Concurrent condition or Concurrent morbidities) adj2 (Prevalence or Epidemiology or Epidemiologic or Pattern or Patterns or Proportion or Cluster or Number or Epidemioological or Epidemiological study or Population distribution or Measure or Incidence or Distribution or Rate or Trend or Trends or Measuring or Population based).mp
4	Exp animals/ not humans/
5	3 not 4
6	Limit 5 to English language

Table A2. Search strategy for Ovid Embase database

1	(Multimorbid or Multi-morbid or Multimorbidity or Multi-morbidity or Multimorbidities or Comorbid or Co-morbid or Comorbidity or Co-morbidity or Polypathology or Poly-pathology or Multipathology or Multi-Pathology or Multi-condition or Multiple conditions or Multiple morbidities or Multiple chronic conditions or Multiple diseases or Multiple diagnoses or Multiple illness or Co-existing disease or Co-existing illness or Co-existing condition or Co-existing diagnoses or Coexisting disease or Coexisting illness or Coexisting condition or Coexisting diagnoses or Concurrent disease or Concurrent illness or Concurrent condition or Concurrent morbidities).mp
2	(Prevalence or Epidemiology or Epidemiologic or Pattern or Patterns or Proportion or Cluster or Number or Epidemioological or Epidemiological study or Population distribution or Measure or Incidence or Distribution or Rate or Trend or Trends or Measuring or Population based).mp
3	(Multimorbid or Multi-morbid or Multimorbidity or Multi-morbidity or Multimorbidities or Comorbid or Co-morbid or Comorbidity or Co-morbidity or Polypathology or Poly-pathology or Multipathology or Multi-Pathology or Multi-condition or Multiple conditions or Multiple morbidities or Multiple chronic conditions or Multiple diseases or Multiple diagnoses or Multiple illness or Co-existing disease or Co-existing illness or Co-existing condition or Co-existing diagnoses or Coexisting disease or Coexisting illness or Coexisting condition or Coexisting diagnoses or Concurrent disease or Concurrent illness or Concurrent condition or Concurrent morbidities) adj2 (Prevalence or Epidemiology or Epidemiologic or Pattern or Patterns or Proportion or Cluster or Number or Epidemioological or Epidemiological study or Population distribution or Measure or Incidence or Distribution or Rate or Trend or Trends or Measuring or Population based).mp
4	Exp animals/ or nonhuman/ or not human/
5	3 not 4
6	Conference*.pt.
7	5 not 6
8	Limit 7 to English language

Table A3. Search strategy for Web of Science database

1	TI = ((multimorbid or multi-morbid or multimorbidity or multi-morbidity or multimorbidities or comorbid or co-morbid or comorbidity or co-morbidity or polypathology or poly-pathology or multipathology or multi-pathology or multi-condition or "multiple conditions" or "multiple morbidities" or "multiple chronic conditions" or "multiple diseases" or "multiple diagnoses" or "multiple illness" or "co-existing disease" or "co-existing illness" or "co-existing condition" or "co-existing diagnoses" or "coexisting disease" or "coexisting illness" or "coexisting condition" or "coexisting diagnoses" or "concurrent disease" or "concurrent illness" or "concurrent condition" or "concurrent morbidities") AND (prevalence or epidemiology or epidemiologic or pattern or patterns or proportion or cluster or number or epidemiological or "epidemiological study" or "population distribution" or measure or incidence or distribution or rate or trend or trends or measuring or "population based"))
2	TS = (animals or animal or mice or mus or mouse or murine or woodmouse or rats or rat or murinae or muridae or cottonrat or cottonrats or hamster or hamsters or cricetinae or rodentia or rodent or rodents or pigs or pig or swine or swines or piglets or piglet or boar or boars or sus scrofa or ferrets or ferret or polecat or polecats or mustela putorius or guinea pigs or guinea pig or cavia or callithrix or marmoset or marmosets or cebuella or hapale or octodon or chinchilla or chinchillas or gerbillinae or gerbil or gerbils or jird or jirds or merione or meriones or rabbits or rabbit or hares or hare or diptera or flies or fly or dipteral or drosphila or drosophilidae or cats or cat or carus or felis or nematoda or nematode or nematoda or nematode or nematodes or sipunculida or dogs or dog or canine or canines or canis or sheep or sheeps or mouflon or mouflons or ovis or goats or goat or capra or capras or rupicapra or chamois or haplorhini or monkey or monkeys or anthropoidea or anthropoids or saguinus or tamarin or tamarins or leontopithecus or hominidae or ape or apes or pan or paniscus or pan paniscus or bonobo or bonobos or troglodytes or pan troglodytes or gibbon or gibbons or siamang or siamangs or nomascus or symphalangus or chimpanzee or chimpanzees or prosimians or bush baby or prosimian or bush babies or galagos or galago or pongidae or gorilla or gorillas or pongo or pygmaeus or pongo pygmaeus or orangutans or pygmaeus or lemur or lemurs or lemuridae or horse or horses or pongo or equus or cow or calf or bull or chicken or chickens or gallus or quail or bird or birds or quails or poultry or poultries or fowl or fowls or reptile or reptilia or reptiles or snakes or snake or lizard or lizards or alligator or alligators or crocodile or crocodiles or turtle or turtles or amphibian or amphibians or amphibia or frog or frogs or bombina or salientia or toad or toads or epidalea calamita or salamander or salamanders or eel or eels or fish or fishes or pisces or catfish or catfishes or siluriformes or arius or heteropneustes or sheatfish or perch or perches or percidae or perca or trout or trouts or char or chars or salvelinus or fathead minnow or minnow or cyprinidae or carps or carp or zebrafish or zebrafishes or goldfish or goldfishes or guppy or guppies or chub or chubs or tinca or barbels or barbus or pimephales or promelas or poecilia reticulata or mullet or mullets or seahorse or seahorses or mugil curema or atlantic cod or shark or sharks or catshark or anguilla or salmonid or salmonids or whitefish or whitefishes or salmon or salmons or sole or solea or sea lamprey or lamprey or lampreys or pumpkinseed or sunfish or sunfishes or tilapia or tilapias or turbot or turbots or flatfish or flatfishes or sciuridae or squirrel or squirrels or chipmunk or chipmunks or suslik or susliks or vole or voles or lemming or lemmings or muskrat or muskrats or lemmus or otter or otters or marten or martens or martes or weasel or badger or badgers or ermine or mink or minks or sable or sables or gulo or gulos or wolverine or wolverines or minks or mustela or llama or llamas or alpaca or alpacas or camelid or camelids or guanaco or guanacos or chiroptera or chiropteras or bat or bats or fox or foxes or iguana or iguanas or xenopus laevis or parakeet or parakeets or parrot or parrots or donkey or donkeys or mule or mules or zebra or zebras or shrew or shrews or bison or bisons or buffalo or buffaloes or deer or deers or bear or bears or panda or pandas or wild hog or wild boar or fitchew or fitch or beaver or beavers or jerboa or jerboas or capybara or capybaras)
3	#1 NOT #2

Table A4. Search strategy for CINAHL database

1	TI = (Multimorbid or Multi-morbid or Multimorbidity or Multi-morbidity or Multimorbidities or Comorbid or Co-morbid or Comorbidity or Co-morbidity or Polypathology or Poly-pathology or Multipathology or Multi-pathology or Multi-condition or Multiple conditions or Multiple Morbidities or Multiple chronic conditions or Multiple diseases or Multiple diagnoses or Multiple illness or Co-existing disease or Co-existing illness or Co-existing condition or Co-existing diagnoses or Coexisting disease or Coexisting illness or Coexisting condition or Coexisting diagnoses or Concurrent disease or Concurrent illness or Concurrent condition or Concurrent morbidities) N5 (Prevalence or Epidemiology or Epidemiologic or Pattern or Patterns or Proportion or Cluster or Number or Epidemiological or Epidemiological study or Population distribution or Measure or Incidence or Distribution or Rate or Trend or Trends or Measuring or Population based)

Limiters - Publication Type: Journal Article; Language: English
Expanders - Apply equivalent subjects
Search modes - Boolean/Phrase

Table A5. Summary of critical appraisal ratings for studies included in review

Primary author and year of publication	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Adams (82)							
Agrawal (86)							
Afshar (83)							
Agur (2)							
Alaba (88)							
Araujo (90)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Ba (91)							
Barnett (10)							
Basham (93)							
Booth (95)							
Carvalho (97)							
Cassel (3)							
Chung (101)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Diaz (105)							
Frolich (108)							
Fu (109)							
Garcia-Olmos (111)							
Hayek (118)							
Hu (123)							
Hosseinpoor (122)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Lund Jensen (149)							
Kilairi (132)							
Khan (131)							
King (134)							
Lee (142)							
Kuwornu (137)							
Lai (138)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	**Assessment of relevancy**	**Assessment of reliability**		**Assessment of validity**			**Assessment of applicability**
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Newman (162)							
Meems (153)							
Lowe (147)							
Newman (163)							
Lenzi (143)							
Pefoyo (156)							
Ramond-Roquin (171)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Orueta (167)							
Nunes (165)							
Rocca (173)							
Ryan (175)							
Rzewuska (176)							
Salisbury (106)							
Singh (179)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Van den akker (184)							
Van Oostrom (185)							
Verest (186)							
Vinjerui (187)							
Wang (190)							
Ward (192)							
Willadsen (193)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Violan (188)							
Roberts (172)							
Ruel (174)							
Agborsangaya (84)							
Fortin (68)							
Jovic (128)							
Cimarras-otal (103)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Cabassa (96)							
Aoki (89)							
Ioakeim-Skoufa (124)							
Ge (113)							
Gimeno-Feliu (115)							
Han (117)							
Gupta (116)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Shi (178)							
Jankovic (396)							
Jawed (126)							
Jovic (127)							
Katikireddi (129)							
Keats (130)							
Laires (139)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Lebenbaum (141)							
Larsen (140)							
Li (146)							
Makinco (151)							
Loza (148)							
Marques (152)							
Mokraoui (71)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Navickas (161)							
Mondor (155)							
Pati (169)							
Pache (168)							
Puth (170)							
Ornstein (166)							
Nicholson (164)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Schiotz (177)							
Taleshan (182)							
Wang (191)							
Wang (189)							
Geda (114)							
Ahmadi (87)							
Craig (104)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Hone (119)							
Steffler (180)							
Kim (133)							
Forslund (107)							
Boersma (94)							
Kone (135)							
Chen (99)							

Table A5. (continued) Summary of critical appraisal ratings for studies included in review

Primary author	Assessment of relevancy	Assessment of reliability		Assessment of validity			Assessment of applicability
	Is the study relevant to the topic under investigation?	Is the study presented clearly?	Is the research methodology presented in sufficient detail the study could be replicated?	Is the study methodology appropriate for the scope of research?	Is the methodology free from bias?	Are the conclusions explicit and transparent?	Is this study applicable to research in pregnant populations?
Subramaniam(181)							
Kumar (136)							
Agborsangaya (85)							
Fuchs (110)							

Appendix B

Table B1. Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Cardiovascular					
Ischaemic heart disease	Definition: Symptomatic myocardial ischaemia caused by coronary artery disease. Conditions included in code list: Acute coronary syndrome (STEMI, NSTEMI, unstable angina) and stable angina.	Read code	X		Cassell et al. (3) Warren-Gash et al. (425)
Hypertension	Suggested definition: A condition causing persistently raised systolic and/or diastolic blood pressure Conditions included in code list: Primary hypertension, Secondary hypertension, Accelerated (malignant) hypertension	Read code		X	Cassell et al. (3)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Valvular heart disease	Suggested definition: Disease or damage to any heart valve resulting in impaired function. Conditions included in code list: Any regurgitant or stenotic lesions of the heart valves (aortic, tricuspid, mitral, pulmonary) or replacement of valve with prosthesis.	Read code	X		Matthews et al. (426)
Congenital structural heart disease	Suggested definition: A birth defect resulting in a structural abnormality of the heart Conditions included in code list: Atrial and ventral septal defects, coarctation of aorta, tetralogy of Fallot, transposition of the great arteries.	Read code	X		Hammad et al. (427)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Aortopathy	Suggested definition: A group of disorders characterised by dilation of the aorta, aortic aneurysm and aortic dissection. Conditions included in list: Confirmed aortopathy of any aetiology and heritable conditions causing aortopathy e.g. Marfan's syndrome.	Read code	X		Own code list
Cardiac failure	Suggested definition: A progressive and irreversible state of end-organ damage resulting in functional impairment of the myocardium	Read code	X		Cassel et al. (3) with exclusion of codes for neonatal heart failure and with additional code for cardiac asthma.

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Endocrine					
Hyperthyroidism	Suggested definition: A state of pathologically increased production and secretion of thyroid hormone from the thyroid gland Conditions included in code list: Grave's disease, Thyrotoxicosis secondary to toxic multinodular goitre, ectopic thyroid tissue, exogenous thyroid tissue.	Read code		X (Read code in preconception period)	Richardson et al. (428)
Hypothyroidism	Suggested definition: A state of pathologically decreased production and secretion of thyroid hormone from the thyroid gland. Conditions included in code list: Primary autoimmune hypothyroidism and hypothyroidism secondary to iodine deficiency, thyroidectomy and radioiodine treatment.	Read code	X		Richardson et al. (428)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Diabetes	Suggested definition: A condition characterised by hyperglycaemia secondary to lack of or reduced sensitivity to endogenous insulin Conditions included in code list: Type 1 diabetes, Type 2 diabetes	Read code	X		Cassell et al. (3) Bhaskaran et al. (429)
Polycystic Ovarian Syndrome	Suggested definition: A disorder characterised by a combination of hyperandrogenism, polycystic ovaries and anovulation/oligo-ovulation	Read code	X		Cherskov et al. (430)
Adrenocortical insufficiency	Suggested definition: A condition characterised by glucocorticoid and mineralocorticoid deficiency Conditions included in code list: Primary adrenocortical insufficiency (Addison's disease), secondary adrenocortical insufficiency of any aetiology	Read code	X		Own code list

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Respiratory					
Cystic fibrosis	Suggested definition: A progressive autosomal recessive condition characterised by chronic pulmonary infection and bronchiectasis.	Read code	X		Own code list
Pulmonary fibrosis	Suggested definition: A disease primarily affecting the lung parenchyma resulting to scarring and thickening of lung tissue. Conditions included in code list: Idiopathic pulmonary fibrosis, non-specific interstitial pneumonitis, occupational interstitial lung disease, pneumoconiosis, extrinsic allergic alveolitis.	Read code	X		Cassell et al. (3)
Sarcoidosis	Suggested definition: A multisystem granulomatous disorder that is predominately a pulmonary condition, but can be associated with extra-pulmonary manifestations.	Read code	X		Own code list

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Asthma	Suggested definition: A condition characterised by dyspnoea, cough and wheeze caused by reversible airways obstruction.	Read code + Prodcode		X (Read code ever recorded and any prescription for medication to treat asthma in the preconception period)	Cassell et al. (3) Silverwood et al. (431)
Rheumatology					
Rheumatoid arthritis	Suggested definition: A systemic inflammatory disease characterised by symmetrical deforming peripheral polyarthritis.	Read code	X		Cassell et al. (3) Lee et al. (211) Muller et al. (432)
Ankylosing spondylitis	Suggested definition: A chronic inflammatory disease of the spine and sacroiliac joints.	Read code	X		Lee et al. (211)
Systemic Lupus Erythematosus	Suggested definition: An autoimmune connective tissue disease characterised by inflammation and tissue damage affecting multiple organs.	Read code	X		Rees et al. (254) Strongman et al. (429)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Gastroenterology					
Inflammatory bowel disease	Suggested definition: A chronic inflammatory disease that can affect any part of the gut from mouth to anus (Crohn's disease) or remain limited to the colonic mucosa. Conditions included in code list: Crohn's disease and ulcerative colitis.	Read code	X		Cassell et al. (3)
Coeliac disease	Suggested definition: An autoimmune mediated disorder primarily affecting the small intestine resulting in pain and malabsorption.	Read code	X		Lee et al. (211) Strongman et al. (429)
Alcohol-related liver disease	Suggested definition: Damage to the liver caused by excessive alcohol consumption.	Read code		X (Read code in preconception period)	Lee et al. (211)
Non-alcoholic steatohepatitis	Suggested definition: An advanced form of non-alcoholic fatty liver disease caused by the accumulation of fat deposits in the liver	Read code	X		Lee et al. (211)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Infective hepatitis	Suggested definition: Inflammation of the liver secondary to viral infection Conditions included in code list: Hepatitis B, Hepatitis C	Read code		X (Read code in preconception period)	Cassell et al. (3)
Chronic hepatitis, cirrhosis and liver failure	Suggested definition: A progressive and irreversible state of end-organ damage resulting in functional impairment of the liver	Read code	X		Cassell et al. (3)
Neurology					
Cerebrovascular disease	Suggested definition: Symptomatic cerebral ischaemia secondary to arterial insufficiency Conditions included in code list: Ischaemic stroke, haemorrhagic stroke, transient ischaemic attack.	Read code	X		Cassell at al. (3) Matthews et al. (433)
Migraine	Suggested definition: A chronic headache condition often associated with sensory disturbance and gastrointestinal symptoms.	Prodcode		X (Prescription for 4 or more prescription only medications to treat acute migraine in the preconception period)	Cassell et al. (3)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Epilepsy	Suggested definition: A neurological disorder characterised by sudden recurrent episodes of sensory disturbance, loss of consciousness or convulsions associated with abnormal electrical activity in the brain.	Read code + Prodcode		X (Read code ever recorded and any prescription for antiepileptic medication in the preconception period)	Cassell et al. (3) Iwagami et al. (434)
Renal					
Chronic renal failure	Suggested definition: A state of progressive loss of renal function eventually resulting in the need for renal replacement therapy. Conditions included in code list: CKD stages 3, 4 or 5	Read code or eGRF measurement	X		Ramagopalan et al. (435)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Dermatology					
Psoriasis	Suggested definition: An immune mediated disease characterised by scaly red skin patches caused by systemic inflammation. Conditions included in code list: Psoriasis and psoriatic arthropathy	Read code + Prodcode		X (Read code ever recorded + any prescription for DMARDs in preconception period in the absence of a read code for any other autoimmune condition)	Cassell et al. (3) Forbes et al. (436)
Eczema	Suggested definition: An inflammatory skin condition characterised by dry skin, itchiness, rashes, scaly patches, blisters and skin infections.	Read code + Prodcode		X (Read code ever recorded + any prescription for DMARDs in preconception period in the absence of a read code for any other autoimmune condition)	Cassell et al. (3) Forbes et al. (436)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Infection					
HIV	Suggested definition: A viral infection of CD4+ T-cells leading to progressive immune system dysfunction, opportunistic infection and malignancy Conditions included in code list: Primary HIV infection and associated complications of HIV infection including those constituting AIDS	Read code	X		Evans et al. (437)
Transplant					
Solid organ transplant	Suggested definition: The receipt of a donor organ to replace a damaged or missing organ usually as a definitive treatment for end-organ failure. Conditions included in code list: Transplant of kidneys, liver, heart, lungs, pancreas.	Read code	X		Dos Santos et al. (438)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Cancer					
Cancer	Suggested definition: A large group of diseases that can originate in any organ or tissue of the body when abnormal cells grow uncontrollably and go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs.	Read code		X (Read code in preconception period)	Cassell et al. (3)
Gynaecology					
Pelvic floor dysfunction	Suggested definition: A condition in which the pelvic floor muscles around the bladder, anal canal and vagina do not work properly. Conditions included in code list: Pelvic organ prolapse, urinary incontinence and faecal incontinence.	Read code	X		Own code list
Leiomyoma	Suggested definition: A benign tumour of the smooth muscle of the myometrium	Read code		X (Read code in preconception period)	Own code list

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Dysfunctional uterine bleeding	Suggested definition: A disorder characterised by uterine bleeding that may be irregular, unscheduled or heavy.	Read code		X (Read code in preconception period)	Own code list
Pain and fatigue					
Pelvic pain	Suggested definition: Intermittent or constant pain in the lower abdomen or pelvis, not occurring exclusively with menstruation or intercourse and not associated with pregnancy. Conditions included in code list: Endometriosis, Adenomyosis, Painful bladder syndrome, Chronic pelvic inflammatory disease	Read code	X		Own code list
Fibromyalgia	Suggested definition: A rheumatic condition characterised by musculoskeletal pain with stiffness and localised tenderness at specific points on the body	Read code	X		Collin et al. (439)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Myalgia encephalomyelitis	Suggested definition: A complex condition causing a wide range of symptoms predominately characterised by a persistent and overwhelming fatigue affecting physical and mental function.	Read code		X (Read code in preconception period)	Collin et al. (439)
Irritable bowel syndrome	Suggested definition: A disorder of the gastrointestinal tract associated with chronic pain and altered bowel habit.	Read code or Prodcode		X (Read code in preconception period or prescription for 4 or more antispasmodics in the preconception period)	Cassell et al. (3)
Painful condition requiring prescription only medication	Suggested definition: Pain that lasts for three months or longer which can be secondary to an underlying condition or primary in nature.	Prodcode		X (Prescription for 4 or more prescription-only analgesics in the preconception period or prescription for 4 or more specified anti-epileptics in the last 12 months in the absence of an epilepsy read code ever recorded)	Cassell et al. (3)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Mental health					
Depression	Suggested definition: A common mental disorder characterised by persistent low mood in the presence of additional core symptoms and not secondary to other causes such as grief, medication or alcohol and drug misuse.	Read code	X		Cassell et al. (3)
Anxiety	Suggested definition: A collection of disorders characterised by feelings of excessive fear or anxiety Conditions included in code list: Generalised anxiety disorder, Specific anxiety disorder, Phobias, Obsessive compulsive disorder, PTSD	Read code	X		Cassell et al. (3)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Eating disorder	Suggested definition: A range of disorders characterised by abnormal or deranged eating habits and distortions of body image. Conditions included in code list: Anorexia, Bulimia, Binge eating disorder	Read code	X		Cassell et al. (3) Windfurh et al. (440)
Schizophrenia	Suggested definition: An illness characterised by the presence of psychotic symptoms occurring in the absence of a primary organic disorder or structural abnormality of the brain.	Read code	X		Cassell et al. (3)
Bipolar illness	Suggested definition: A illness characterised by periods of profound depression alternating with periods of excessively elated or irritable mood.	Read code	X		Cassell et al. (3) Hardoon et al. (441)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Non-organic psychosis	Suggested definition: A disorder characterised by the presence of hallucinations and delusions occurring in the absence of functional or structural pathology.	Read code	X		Cassell et al. (3) Hardoon et al. (441) Oiler et al. (229)
Learning disability	Suggested definition: a significant reduced ability to understand new or complex information, to learn new skills (impaired intelligence) with a reduced ability to cope independently (impaired social functioning) which started before adulthood.	Read code	X		Cassell et al. (3) to exclude codes for learning difficulty and include codes for special educational needs
Autism	Suggested definition: A non-progressive developmental disability resulting in persistent difficulties with communication, social interaction, and restrictive and repetitive behaviours or interests.	Read code	X		Hagberg et al. (442)

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Personality disorder	Suggested definition: A range of disorders occurring when the innate and enduring characteristics of an individual cause distress or difficulty for the individual or in their relationships with others	Read code	X		Cassell et al. (3) Abel et al. (388)
Haematology					
Thromboembolic disease	Suggested definition: An inherited or acquired coagulopathy that predisposes to thrombosis. Conditions included in code list: Deep vein thrombosis, Pulmonary embolus, Cerebral venous sinus thrombosis	Read code	X		Lee et al. (211) Matthews et al. (433)
Sickle cell anaemia	Suggested definition: An auto-recessive disorder in which the production of abnormal haemoglobin results in Vaso-occlusive crises.	Read code	X		Own list

Table B1. (continued) Provenance of final code lists and determination of exposure status

Condition	Description of condition	Identification of individuals with condition in CPRD	Exposure status		Provenance of code list
			Evidence of diagnosis of condition at any point in the clinical record prior to the estimated start date of the pregnancy	Evidence of active disease status in the preconception period (12 months prior to the estimated start date of the pregnancy)	
Thalassemia	Suggested definition: A group of genetic diseases caused by unbalanced haemoglobin synthesis with underproduction or no production of one globin chain.	Read code	X		Own list

For conditions where the exposure is based on read code ever recorded:

- **The condition is life-long and progressive or life-long without the expectation of remission.**
  - Chronic hepatitis, cirrhosis and liver failure
  - Cardiac failure
  - Hypothyroidism
  - Diabetes
  - Adrenocortical insufficiency
  - Cystic fibrosis
  - Pulmonary fibrosis
  - Non-alcoholic steatohepatitis
  - Chronic renal failure
  - HIV
- **The condition is life-long with the possibility of periods of remission or symptom improvement. Remission is clinically defined as low disease activity rather than the complete absence of disease activity, and maintenance of remission is likely to require ongoing active clinical management.**
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Ankylosing spondylitis

    - Inflammatory bowel disease
    - Coeliac disease
    - Sickle cell anaemia
    - Polycystic ovarian syndrome
    - Pelvic floor dysfunction
    - Pelvic pain
    - Sarcoidosis
    - Fibromyalgia
- **The condition may be episodic in nature, but a past-history of diagnosis elevates the risk of relapse in the antenatal or postnatal period or may impact maternal or perinatal outcomes.**
    - Depression
    - Anxiety
    - Eating disorder
    - Bipolar illness
    - Non-organic psychosis
    - Schizophrenia
- **The condition may occur only once and be treated, but a past-history of diagnosis elevates the risk of the condition recurring in the antenatal or postnatal period or may affect maternal and perinatal outcomes.**
    - Thromboembolic disease
    - Ischaemic heart disease
    - Cerebrovascular disease
- **The condition may not require active clinical management outside of pregnancy, but the presence of the condition may limit the necessary physiological adaptations required for pregnancy affecting maternal and perinatal outcomes.**
    - Congenital structural heart disease
    - Valvular heart disease
    - Thalassemia
    - Aortopathy
- **The condition is expected to cause persistent challenges for the individual throughout their lifetime.**
    - Learning disability
    - Autism
    - Personality disorder
- **The status of the individual will not change once the health event has occurred**
    - Solid organ transplant

For conditions where the exposure based on evidence of active disease status in the preconception period:

- **The condition is chronic, but potential curative treatments exist, or the condition may be reversed with lifestyle modifications.**
  - Infective hepatitis
  - Hyperthyroidism
  - Alcohol-related liver disease
  - Cancer
  - Hypertension
- **The condition is associated with a wide spectrum of severity, and mild forms of the disease would not reasonably be expected to impact maternal or perinatal outcomes.**
  - Asthma
  - Psoriasis
  - Eczema
  - Leiomyoma
- **The condition may be episodic in nature with the possibility of periods in time where the disease is quiescent. Inactive disease is not expected to impact maternal or perinatal outcome.**
  - Epilepsy
  - Irritable bowel syndrome
  - Myalgic encephalomyelitis
  - Painful condition requiring prescription-only analgesics
  - Migraine
  - Dysfunctional uterine bleeding

Table B2. Constituent medical codes, read codes and read terms used to identify health conditions for which the code list was created de novo for use in the component studies in this thesis

Abnormal uterine bleeding		
Medcode	Read code	Read term
10531	1573.00	H/O: menorrhagia
128	K592000	Menorrhagia
812	K592011	Heavy periods
2384	K59yx11	Dysfunctional uterine bleeding
6238	1573.11	H/O: heavy periods
15022	K5A0.00	Premenopausal menorrhagia
47026	K59A.00	Premenopausal postcoital bleeding
20795	K5A0.11	Climacteric menorrhagia
93526	K5A6.00	Perimenopausal menorrhagia
8544	K593.11	Pubertal bleeding and menorrhagia
1941	K597.00	Postcoital bleeding
4050	7E0D600	Endometrial ablation
3617	7E06711	Endometrial laser ablation
9892	7E0F700	Endometrial laser ablation
89576	7E0G400	Radiofrequency endometrial ablation
84148	7E0DB00	Endoscopic balloon ablation of endometrium
3105	7E0D.11	Therapeutic hysteroscopy
18078	7E0G100	Endometrial balloon ablation
346	7E0E.11	Diagnostic hysteroscopy
908	7E0Ez11	Hysteroscopy NEC
4618	7E0E200	Dilatation and curettage NEC with hysteroscopy NEC
105304	8HS1.00	Referral for hysteroscopy
5598	7E0E100	Diagnostic hysteroscopy and endometrial biopsy
4694	7E0F111	Endometrial biopsy
29737	7E0D311	Endoscopic endometrial polypectomy
100129	3B4..00	Failed endometrial biopsy
7789	7E0D700	Endoscopic endometrial polypectomy
12748	7E0F800	Endometrial biopsy
99747	7E0F900	Endometrial sampling using pipelle
21215	K543200	Glandular endometrial hyperplasia

1269	K540.11	Endometrial polyp
46084	K543000	Adenomatous endometrial hyperplasia
37561	K543100	Cystic endometrial hyperplasia
Leiomyoma		
Medcode	Read code	Read term
759	B78..00	Uterine leiomyoma - fibroids
432	B78..11	Fibroids
8655	BBK0011	Fibroid uterus
28324	BBK0000	Leiomyoma NOS
3402	B78z.00	Uterine leiomyoma NOS
41134	B782.00	Subserous uterine leiomyoma
32719	B780.00	Submucous uterine leiomyoma
12512	B781.00	Intramural uterine leiomyoma
55349	B781.11	Mural fibroids
4117	7E06111	Excision fibroid
5021	7E06y11	Vaginal myomectomy
93437	7E0DC00	Transcervical resection of fibroid
21255	7E0D012	Endoscopic myomectomy
20349	7E0D013	Myomectomy
24300	7E0D015	Hysteroscopic myomectomy
2517	7E06100	Open myomectomy
20655	7E06112	Myomectomy
5562	15A9.12	H/O: myomectomy
98291	7A54A00	Perc embolisation of uterine fibroid using fluoroscopic guid
47130	15A9.00	H/O: myomectomy/hysterotomy
Pelvic floor dysfunction		
Medcode	Read code	Read term
3283	R083.00	Incontinence of urine
5196	16F..00	Double incontinence
31220	R083100	Urethral sphincter incontinence
52763	Kyu5A00	Other specified urinary incontinence
5844	1A24.11	Stress incontinence - symptom
13428	393..11	Bowels - continence
15400	R083z00	Incontinence of urine NOS
15918	1593.00	H/O: stress incontinence
1437	R076.00	Incontinence of faeces

3887	1A26.00	Urge incontinence of urine
1929	1A24.00	Stress incontinence
15555	R076z00	Incontinence of faeces NOS
3182	K198.00	Stress incontinence
17620	K586.00	Stress incontinence - female
27623	R076100	Sphincter ani incontinence
6161	1A23.00	Incontinence of urine
17320	R083200	Urge incontinence
24719	19EF.00	Urgent desire for stool
49417	39H0.00	Continence reassessment
94673	9Nl8.00	Seen by continence nurse
22095	ZLA2400	Seen by continence nurse
31256	393..12	Bowels-incontinence assessment
45492	ZL22400	Under care of continence nurse
13424	394..11	Bladder-incontinence assessmnt
13423	394..12	Bladder- continence assessment
25901	ZL62400	Referral to continence nurse
2739	8C14.00	Incontinence care
40789	39H..00	Continence assessment
25899	8HTX.00	Referral to incontinence clinic
12138	8C14.11	Continence care
43222	ZQ3C.00	Bowels incontinence assessment
29192	8H7w.00	Referral to continence nurse
20728	317A.00	Pad test for incontinence
94021	7B33C00	Insertion retropubic dev fem stress urinary incontinence NEC
17637	8D7..12	Incontinence control
98767	7B33800	Insertion retropubic device stress urinary incontinence NEC
46614	Z1J..00	Procedures to aid continence
45495	Z9EA.00	Provision of incontinence appliance
106548	9NgY.00	Continence care equipment available at home
48601	8D71.00	Incontinence control
63436	Z6Q8.00	Biofeedback technique
45901	Z6K1.00	Biofeedback therapy
97037	7B38900	Introduction of transobturator sling
57283	7B32500	Introduction of transobturator tape
85494	7B32400	Partial removal of tension-free vaginal tape

93869	7B32600	Removal of transobturator tape
92169	7B32300	Total removal of tension-free vaginal tape
100822	773Dy00	OS other operations on the anal sphincter control continence
17040	7733000	Posterior repair of anal sphincter
68374	773D.00	Other operations on the anal sphincter to control continence
104801	773Dz00	OS other operations on anal sphincter control continence NOS
17771	7B31211	Burch colposuspension
4202	7B31200	Colposuspension of bladder neck
17099	7733100	Anterior repair of anal sphincter
1903	K510.00	Vaginal wall prolapse without uterine prolapse
6819	K51..00	Genital prolapse
96896	K518.00	Female rectocele
211	K510000	Cystocele without uterine prolapse
105178	K519.00	Cystocele
2285	K510200	Rectocele without uterine prolapse
9803	1594.00	H/O: genital prolapse
7870	K512.00	Uterovaginal prolapse, incomplete
12845	K514000	Cystocele with unspecified uterine prolapse
7756	1594.11	H/O: procidentia
1057	K514.00	Uterovaginal prolapse, unspecified
3986	K513.11	Procidentia - uterine
1345	K511.00	Uterine prolapse without vaginal wall prolapse
17481	K510z00	Vaginal prolapse without uterine prolapse NOS
30419	K512000	Cystocele with first degree uterine prolapse
4575	K510300	Urethrocele without uterine prolapse
37185	K511z00	Uterine prolapse without vaginal wall prolapse NOS
12359	K512100	Cystocele with second degree uterine prolapse
9356	K513.00	Uterovaginal prolapse, complete
33440	K51z.00	Genital prolapse NOS
25974	K513000	Cystocele with third degree uterine prolapse
97649	Kyu9100	Other female genital prolapse
23941	K51y.00	Other genital prolapse
41895	K51yz00	Other genital prolapse NOS
6882	K511100	Second degree uterine prolapse
22757	K511000	First degree uterine prolapse
37790	K511200	Third degree uterine prolapse

20907	L244011	Cystocele affecting obstetric care
22659	K510400	Vaginal prolapse unspecified without uterine prolapse
37918	K510211	Proctocele without uterine prolapse
25278	K510100	Cystourethrocele without uterine prolapse
31821	J571.11	Procidentia - anus and/or rectum
35683	L244z00	Other uterine/pelvic floor abn in preg/childb/puerp NOS
39550	L244z11	Cystocele in pregnancy, childbirth or the puerperium NOS
64147	L244z12	Rectocele in pregnancy, childbirth or the puerperium NOS
32287	L244112	Rectocele - baby delivered
32286	L244111	Cystocele - baby delivered
20850	L244.11	Cystocele in pregnancy, childbirth and the puerperium
39492	L244.13	Rectocele in pregnancy, childbirth and the puerperium
51111	L244412	Rectocele complicating postpartum care - baby delivered prev
30378	L244312	Rectocele complicating antenatal care - baby not delivered
38439	L244411	Cystocele complicating postpartum care - baby delivered prev
66127	L244211	Cystocele - delivered with postpartum complication
57581	L244212	Rectocele - delivered with postpartum complication
101354	L244311	Cystocele complicating antenatal care - baby not delivered
58517	L244012	Rectocele affecting obstetric care
12255	7D1B400	Removal of ring pessary from vagina
7175	SP07900	Problem with vaginal pessary
83479	7D1B600	Insertion of ring pessary into vagina
631	7D18111	Anterior repair
28040	7D18z00	Other repair of vaginal prolapse NOS
3271	7D18.13	Pelvic floor repair
16175	7D19300	Sacrocolpopexy
2287	7D18211	Posterior repair
11151	7D18.12	Pelvic floor repair operation
5669	7D17z11	Manchester repair
28602	7D17.00	Repair of vaginal prolapse and amputation of cervix uteri
69708	7D17y00	Repair of vaginal prolapse & amputation of cervix uteri OS
9071	7D1B300	Change of vaginal pessary
15703	7D17z00	Repair of vaginal prolapse & amputation of cervix uteri NOS
11863	7D18.00	Other repair of vaginal prolapse
18931	7D19500	Sacrospinous fixation of vaginal vault
18606	7D18y00	Other specified other repair of vaginal prolapse

4233	7D17111	Fothergill anterior colporrhaphy and amputation of cervix
2060	7D18011	Anterior and posterior repair
Adrenocortical insufficiency		
Medcode	Read code	Read term
35760	A176.00	Tuberculosis of adrenal glands - Addison's disease
69198	F395000	Myopathy due to Addison's disease
4481	C154100	Addison's disease
12227	C154600	Addisonian crisis
4042	C154011	Addisonian crisis
42873	C154012	Adrenal crisis
2813	D010.11	Addison's anaemia
43631	M210.11	Addison's keloid
Cystic fibrosis		
Medcode	Read code	Read term
6220	C370.00	Cystic fibrosis
49770	C370z00	Cystic fibrosis NOS
100610	C370400	Arthropathy in cystic fibrosis
36622	C370111	Meconium ileus in cystic fibrosis
110454	C370700	Liver disease due to cystic fibrosis
69017	C370100	Cystic fibrosis with meconium ileus
18905	C370300	Cystic fibrosis with intestinal manifestations
93380	C10N100	Cystic fibrosis related diabetes mellitus
65344	C370000	Cystic fibrosis with no meconium ileus
106432	C370900	Exacerbation of cystic fibrosis
73065	C370y00	Cystic fibrosis with other manifestations
102922	C370800	Cystic fibrosis related cirrhosis
101408	9No7.00	Seen in cystic fibrosis clinic
100430	66k..00	Cystic fibrosis monitoring
18914	C370200	Cystic fibrosis with pulmonary manifestations
103224	C370500	Cystic fibrosis with distal intestinal obstruction syndrome
100520	66k0.00	Cystic fibrosis annual review
104679	8BPL.00	Pseudomonas aeruginosa eradication therapy
108481	8BPM.00	Burkholderia cepacia complex eradication therapy
Sarcoid		
Medcode	Read code	Read term
3865	AD5..00	Sarcoidosis

73284	Cyu0600	Sarcoidosis of other and combined sites
40613	AD55.00	Sarcoid arthropathy
52519	F396500	Myopathy due to sarcoidosis
47037	G558300	Sarcoid heart disease
34437	G5y7.00	Sarcoid myocarditis
26405	J63A.00	Hepatic granulomas in sarcoidosis
49075	AD51.00	Sarcoidosis of lymph nodes
72595	AD54.00	Sarcoidosis of inferior turbinates
27769	AD53.00	Sarcoidosis of skin
49454	F013.00	Meningitis due to sarcoidosis
47718	N233200	Myositis in sarcoidosis
55612	F326300	Multiple cranial nerve palsies in sarcoidosis
58841	AD52.00	Sarcoidosis of lung with sarcoidosis of lymph nodes
33980	AD50.00	Sarcoidosis of lung
3859	H57y200	Pulmonary sarcoidosis
40751	F374900	Polyneuropathy in sarcoidosis
Chronic pelvic pain		
Medcode	Read code	Read term
499	K50..00	Endometriosis
9492	K50z.00	Endometriosis NOS
16143	K501.11	Chocolate cyst of ovary
19266	K500000	Internal endometriosis
63749	Kyu9000	Other endometriosis
49603	K50y.00	Other endometriosis
66361	K50yz00	Other endometriosis NOS
50464	K503100	Endometriosis of the pouch of Douglas
22662	K503.00	Endometriosis of the pelvic peritoneum
50518	K504000	Endometriosis of the rectovaginal septum
19682	K501.00	Endometriosis of ovary
60784	K505200	Endometriosis of the rectum
68037	K50y300	Endometriosis of the vulva
37392	K504100	Endometriosis of the vagina
30091	K502.00	Endometriosis of the fallopian tube
62982	K505100	Endometriosis of the colon
48222	K50y200	Endometriosis of the umbilicus
41735	K500.00	Endometriosis of uterus

94268	K504z00	Endometriosis of the rectovaginal septum and vagina NOS
20194	K505.00	Endometriosis of the intestine
71993	K505000	Endometriosis of the appendix
97045	K505z00	Endometriosis of the intestine NOS
42092	K500z00	Endometriosis of uterus NOS
67137	K503000	Endometriosis of the broad ligament
36930	K50y000	Endometriosis of the bladder
50544	K503300	Endometriosis of the round ligament
60097	K506.00	Endometriosis in scar of skin
70854	K504.00	Endometriosis of the rectovaginal septum and vagina
61192	K500100	Endometriosis of myometrium
63232	K503200	Endometriosis of the parametrium
42424	K503z00	Endometriosis of the pelvic peritoneum NOS
36805	K500200	Endometriosis of cervix
69931	K50y100	Endometriosis of the lung
56751	BBL1.11	Stromal endometriosis
22007	K500111	Adenomyosis of endometrium
3432	K50..11	Adenomyosis
11585	K151.00	Chronic interstitial cystitis
29460	K151z00	Chronic interstitial cystitis NOS
9519	K16y500	Trabeculation of bladder
12175	7E0D800	Laparoscopic laser destruction of endometriosis
40101	7062H11	LUNA - Laparoscopic uterosacral nerve ablation
53557	7062H00	Laparoscopic uterosacral nerve ablation
41678	K401200	Chronic salpingo-oophoritis
47944	K400700	Subacute salpingo-oophoritis
30446	K401.00	Chronic salpingitis and oophoritis
4662	K401300	Chronic salpingitis
51488	A983600	Chronic gonococcal endometritis
16101	A983700	Chronic gonococcal salpingitis
27919	K411000	Chronic endometritis
10787	K410500	Subacute endometritis
110874	K400900	Subacute perisalpingitis
47496	K400800	Subacute salpingitis
54285	K408.00	Other chronic female pelvic peritonitis
60825	K401z00	Chronic salpingitis and oophoritis NOS

52261	K401000	Chronic oophoritis
42277	K404z00	Chronic pelvic inflammatory diseases NOS
38794	K404500	Female chronic pelvic peritonitis
85172	K401100	Chronic perioophoritis
Thalassemia		
Medcode	Read code	Read term
12235	D104400	Alpha trait thalassaemia
8866	D104300	Alpha thalassaemia
37808	D104311	Homozygous alpha thalassaemia
46733	D104700	Beta major thalassaemia
45151	D104011	Thalassaemia major - Cooley's anaemia
57144	D104600	Beta intermedia thalassaemia
31405	D104000	Thalassaemia major NEC
1171	D104.00	Thalassaemia
4666	D104z00	Thalassaemia NOS
73946	Dyu1100	Other thalassaemias
32943	D104900	Delta-beta thalassaemia
96960	65QF.00	Ant scr shows signifi carrier of sickle cell or thalassaemia
97180	65QE.00	Ant scr shows non sig carrier of sickle cell or thalassaemia
96959	68b0.00	Ant scr show iron defic/poss non signific alpha thalassaemia
1174	D104100	Thalassaemia minor NEC
21643	D104811	Beta thalassaemia
9864	D104500	Beta trait thalassaemia
54429	D104200	Thalassaemia with haemoglobin S disease
27761	D104800	Beta minor thalassaemia
103238	9No9.00	Seen in sickle cell and thalassaemia clinic
108418	8T0G.00	Referral to sickle cell and thalassaemia service
Sickle cell anaemia		
Medcode	Read code	Read term
107027	K0G..00	Sickle cell nephropathy
100001	1458.00	History of sickle cell anaemia
14242	42D4.00	RBC's - sickle cells present
31075	D104211	Sickle-cell thalassaemia
11874	F422100	Proliferative retinopathy due to sickle cell disease
110077	8Hx1.00	Referral to sickle cell specialist nurse
2277	N334200	Avascular necrosis of the head of femur

Aortopathy		
Medcode	Read code	Read term
98277	G71A.00	Aortic root dilatation
33430	7A19400	Operation on aneurysm of aorta NEC
102725	Gyu7100	Aortic aneurysm of unspecified site, ruptured
19996	7A14400	Replace aneurysm abdominal aorta by anast aorta to aorta NEC
97217	7A1B800	Endovascul insert stent infrarenal abdominal aortic aneurysm
97030	7A1B100	Endovascular stenting of suprarenal aortic aneurysm
95360	791Cz00	Operations on aortic root NOS
98175	7A1BD00	Endovascular insertion of stent for aorto-uniiliac aneurysm
53984	PGy2500	Ehlers-Danlos syndrome type VI
56200	P72z100	Congenital aneurysm of aorta
63408	7A13411	Tube graft abdominal Aortic aneurysm (emergency)
16711	PKy7B00	Stickler syndrome
64961	7A14000	Replace aneurysm ascend aorta by anast of aorta/aorta NEC
17767	G713.00	Abdominal aortic aneurysm which has ruptured
91462	7A1C200	Endov insertion of stent graft for thoracic aortic aneurysm
102719	Gyu7200	Aortic aneurysm of unspecified site, nonruptured
1735	G71..00	Aortic aneurysm
97109	7A1B700	Endovascular stenting for aorto-uniiliac aneurysm
70446	7A1B000	Endovascular stenting infrarenal abdominal aortic aneurysm
70415	PGy2300	Ehlers-Danlos syndrome type IV
104467	585I000	Abdominal aortic aneurysm screen ultrasound scan abnormal
26232	7A14411	Tube graft of Abdominal aortic aneurysm
98542	7A1BA00	Endovascular insertion of stent for thoracic aortic aneurysm
92925	7A11211	Y graft of abdominal Aortic aneurysm (emergency)
16993	14AE.00	H/O: aortic aneurysm
54192	7A13400	Emerg replace aneurysm abdom aorta by anast aorta/aorta NEC
66232	7A13300	Emerg replace aneurysm infrarenal aorta by anast aorta/aorta
89714	7A1C300	Endov ins stent graft for aortic dissection in any position
101195	G714300	Aneurysm of suprarenal aorta
42444	7A14100	Replace aneurysm thoracic aorta by anast of aorta/aorta NEC
100195	7A1B600	Endovascular stenting for aortic aneurysm of bifurcation NEC
99787	7A1BB00	Endovascular ins stent for aortic dissection in any position
6872	G71z.00	Aortic aneurysm NOS
16800	G711.11	Ruptured thoracic aortic aneurysm

11430	G715000	Thoracoabdominal aortic aneurysm, ruptured
69922	7A11200	Emerg repl aneurysm bifurc aorta by anast aorta to iliac a
31613	7A13.00	Emergency replacement of aneurysmal segment of aorta
101379	G714200	Infrarenal abdominal aortic aneurysm
66761	7A11z00	Replacement of aneurysmal bifurcation of aorta NOS
93959	7A1B.00	Transluminal operations on aneurysmal segment of aorta
45477	7A13y00	Emergency replacement of aneurysmal segment of aorta OS
57531	PKy7A11	Beals syndrome
55445	7A14y00	Other replacement of aneurysmal segment of aorta OS
9759	G718.00	Leaking abdominal aortic aneurysm
51061	7A1B200	Endovascular stenting of thoracic aortic aneurysm
27563	G711.00	Thoracic aortic aneurysm which has ruptured
93699	791C000	Aortic root replac us pul val auto ri vent pulm art val cond
95976	7A1B500	Endovascular stenting of aorto-uniiliac aneurysm
36651	7A14z00	Other replacement of aneurysmal segment of aorta NOS
936	PKy2.00	Marfan's syndrome
13572	G713.11	Ruptured abdominal aortic aneurysm
43108	7A14.00	Other replacement of aneurysmal segment of aorta
52358	7A11.00	Replacement of aneurysmal bifurcation of aorta
94331	7A1C.00	Translum insert stent graft for aneurysmal segment of aorta
16521	G710.00	Dissecting aortic aneurysm
16034	G716.00	Aortic aneurysm without mention of rupture NOS
1867	G714.00	Abdominal aortic aneurysm without mention of rupture
63920	G713000	Ruptured suprarenal aortic aneurysm
17220	7A13.11	Emergency repair of aortic aneurysm
51166	7A11311	Y graft abdominal Aortic aneurysm
96654	7A11000	Emerg repl aneurysm bifurc aorta by anast aorta to fem art
70353	791C200	Aortic root replacement using homograft
45521	G714000	Juxtarenal aortic aneurysm
83527	7A1B300	Endovascular stenting of aortic dissection in any position
40787	G716000	Thoracoabdominal aortic aneurysm, without mention of rupture
99722	7A13000	Emerg replace aneurysm asc aorta by anastom aorta to aorta
83577	7A1C000	Endovas ins stent graft for infrarenal abdom aortic aneurysm
85252	791C.00	Operations on aortic root
62301	7A11y00	Replacement of aneurysmal bifurcation of aorta OS
1736	7A14.11	Aortic aneurysm repair

17345	G714.11	AAA - Abdominal aortic aneurysm without mention of rupture
105621	Gyu7800	Aneurysm of aorta in diseases classified elsewhere
71668	791C400	Aortic root replacement
106780	7A1B900	Endovascular insertion stent for suprarenal aortic aneurysm
56495	7A11100	Replace aneurysm bifurc aorta by anast aorta to femoral art
91004	791C300	Aortic root replacement using mechanical prosthesis
15304	G715.00	Ruptured aortic aneurysm NOS
94683	791Cy00	Other specified operations on aortic root
103427	7A1C500	Endovas insertion of stent graft for aorto-uniiliac aneurysm
93060	7A13100	Emerg replace aneurysm thor aorta by anastom aorta to aorta
23532	G712.00	Thoracic aortic aneurysm without mention of rupture
90861	7A1Bz00	Transluminal operations on aneurysmal segment of aorta NOS
101698	68B5100	Aortic aneurysm screening abnormal
45474	7A13z00	Emergency replacement of aneurysmal segment of aorta NOS
94682	7A1C100	Endovas insert of stent graft for suprarenal aortic aneurysm

Table B3. Management of potential overlap between code lists

Code lists	Potential conflict	Suggested resolution
Sarcoidosis and Pulmonary fibrosis	Sarcoidosis is a type of interstitial lung disease that can cause pulmonary fibrosis.	If a woman has a diagnosis of sarcoidosis and a diagnosis of pulmonary fibrosis, to treat as a single diagnosis of sarcoidosis.
Cardiac failure and Ischaemic heart disease Cardiac failure and Valvular heart disease Cardiac failure and Congenital structural heart disease Cardiac failure and Hypertension	Cardiac failure represents the stage of irreversible end-organ damage that can result from a wide number of different cardiovascular conditions.	If a woman has a diagnosis of cardiac failure and a diagnosis for another cardiovascular condition, to treat as a single diagnosis of cardiac failure.
Chronic hepatitis, cirrhosis and liver failure and Infective hepatitis Chronic hepatitis, cirrhosis and liver failure and Non-alcoholic steatohepatitis Chronic hepatitis, cirrhosis and liver failure and Alcohol-related liver disease	Chronic hepatitis, cirrhosis and liver failure represents the stage of irreversible end-organ damage that can result from a wide number of different hepatic conditions.	If a woman has a diagnosis of Chronic hepatitis, cirrhosis and liver failure and a diagnosis for another hepatic condition, to treat as a single diagnosis of Chronic hepatitis, Cirrhosis and liver failure.
Dysfunctional uterine bleeding and Leiomyoma Dysfunctional uterine bleeding and Polycystic ovarian syndrome	Symptoms consistent with dysfunctional uterine bleeding can be present as part of the clinical presentation of Leiomyoma and Polycystic Ovarian syndrome.	If a woman has a diagnosis of dysfunctional uterine bleeding and a diagnosis of Leiomyoma, to treat as a single diagnosis of Leiomyoma. If a woman has a diagnosis of dysfunctional uterine and a diagnosis of Polycystic ovarian syndrome, to treat as a single diagnosis of Polycystic ovarian syndrome.

Table B3. (continued) Management of potential overlap between code lists

Code lists	Potential conflict	Suggested resolution
Non-organic psychosis and Bipolar illness Non-organic psychosis and Schizophrenia	The early presenting features of bipolar disorder and schizophrenia can substantially overlap, so a patient may have a broad diagnosis of non-organic psychosis prior to a more specific diagnosis of bipolar illness or schizophrenia being made.	If a woman has a diagnosis of non-organic psychosis and a diagnosis of schizophrenia, to treat as a single diagnosis of schizophrenia. If a woman has a diagnosis of non-organic psychosis and a diagnosis of bipolar illness, to treat as a single diagnosis of bipolar illness.
Hyperthyroidism and Hypothyroidism	The underlying disease or treatment options for hyperthyroidism can potentially cause irreversible damage to the thyroid gland resulting in hypothyroidism.	If a woman has diagnosis of hypothyroidism and a diagnosis of hyperthyroidism, to treat as a single diagnosis of hypothyroidism.
Solid organ transplant and Chronic renal failure Solid organ transplant and Chronic hepatitis, cirrhosis and liver failure Solid organ transplant and Cardiac failure	Solid organ transplant is a treatment option for end-stage organ failure.	If a woman has a diagnosis of solid organ transplant and a diagnosis any other end-organ failure, to treat as a single diagnosis of solid organ transplant.
Painful condition requiring prescription only medication and Pelvic pain Painful condition requiring prescription only medication and Fibromyalgia	Prescription only analgesia may be used as part of the management of pain resulting from the conditions causing pelvic pain or fibromyalgia.	If a woman has a diagnosis of pelvic pain and requires prescription only analgesia, to treat as a single diagnosis of pelvic pain. If a woman has a diagnosis of fibromyalgia and requires prescription only analgesia, to treat as a single diagnosis of fibromyalgia.

Table B3. (continued) Management of potential overlap between code lists

Code lists	Potential conflict	Suggested resolution
Bipolar illness and depression	Depression is a feature of bipolar illness.	If a woman has a diagnosis of depression and bipolar illness, to treat as a single diagnosis of bipolar illness.

Table B4. Review of codes included in original EMMOI code list including suggested amendments to codes and descriptions of morbidity categories

Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Acute abdomen	N73.3 Female acute pelvic peritonitis N73.5 Female pelvic peritonitis, unspecified K65.0 Acute peritonitis K65.9 Peritonitis, unspecified K35 Acute appendicitis K35.2 Acute appendicitis with generalized peritonitis K35.3 Acute appendicitis with localized peritonitis K35.8 Acute appendicitis, other and unspecified K37 Unspecified appendicitis	None identified	None identified	None identified
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Acute renal failure	O90.4 Postpartum acute renal failure N17 Acute renal failure N17.0 Acute renal failure with tubular necrosis N17.1 Acute renal failure with acute cortical necrosis N17.2 Acute renal failure with medullary necrosis N17.8 Other acute renal failure N17.9 Acute renal failure, unspecified N19 Unspecified kidney failure N99.0 Postprocedural renal failure	None identified	I12.0 Hypertensive renal disease with renal failure I13.1 Hypertensive heart and renal disease with renal failure	None identified
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Acute psychosis	F23 Acute and transient psychotic disorders F23.0 Acute polymorphic psychotic disorder without symptoms of schizophrenia F23.1 Acute polymorphic psychotic disorder with symptoms of schizophrenia	None identified	None identified	None identified

	F23.2 Acute schizophrenia-like psychotic disorder F23.8 Other acute and transient psychotic disorders F23.9 Acute and transient psychotic disorder, unspecified F53.1 Severe mental and behavioural disorders associated with the puerperium, not elsewhere classified			
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Cardiac arrest/failure or infarction	O89.1 Cardiac complications of anaesthesia during the puerperium O74.2 Cardiac complications of anaesthesia during labour and delivery O90.3 Cardiomyopathy in the puerperium I21 Acute myocardial infarction I21.0 Acute transmural myocardial infarction of anterior wall I21.1 Acute transmural myocardial infarction of inferior wall I21.2 Acute transmural myocardial infarction of other sites I21.3 Acute transmural myocardial infarction of unspecified site I21.4 Acute subendocardial myocardial infarction I21.9 Acute myocardial infarction, unspecified I42 Cardiomyopathy I42.0 Dilated cardiomyopathy I42.1 Obstructive hypertrophic cardiomyopathy I42.2 Other hypertrophic cardiomyopathy I42.3 Endomyocardial (eosinophilic) disease I42.4 Endocardial fibroelastosis I42.5 Other restrictive cardiomyopathy I42.6 Alcoholic cardiomyopathy		I11.0 Hypertensive heart disease with (congestive) heart failure I11.9 Hypertensive heart disease without (congestive) heart failure I13.0 Hypertensive heart and renal disease with (congestive) heart failure I13.2 Hypertensive heart and renal disease with both (congestive) heart failure and renal failure J80 Adult respiratory distress syndrome	Acute cardiac event including cardiac infarction, cardiac failure, cardiomyopathy and cardiac arrest New category for pulmonary oedema and ARDS

	I42.7 Cardiomyopathy due to drugs and other external agents I42.8 Other cardiomyopathies I42.9 Cardiomyopathy, unspecified I43* Cardiomyopathy in diseases classified elsewhere I43.0* Cardiomyopathy in infectious and parasitic diseases classified elsewhere I43.1* Cardiomyopathy in metabolic diseases I43.2* Cardiomyopathy in nutritional diseases I43.8* Cardiomyopathy in other diseases classified elsewhere I46 Cardiac arrest I46.0 Cardiac arrest with successful resuscitation I46.1 Sudden cardiac death, so described I46.9 Cardiac arrest, unspecified I50 Heart failure I50.0 Congestive heart failure I50.1 Left ventricular failure I50.9 Heart failure, unspecified J.81 Pulmonary oedema			
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Cerebral oedema or coma	G93.6 Cerebral oedema R40.2 Coma, unspecified	None identified	None identified	None identified
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Disseminated intravascular coagulopathy	D65 Disseminated intravascular coagulation (defibrination syndrome)	None identified	O45.0 Premature separation of placenta with coagulation defect (including placental abruption with excessive haemorrhage associated with afibrinoginaemia, disseminated intravascular coagulation,	None identified

			hyperfibrinolysis, hyperfibrinogenaemia) O46.0 Antepartum haemorrhage with coagulation defect (antepartum haemorrhage (excessive) associated with afibrinoginaemia, disseminated intravascular coagulation, hyperfibrinolysis, hyperfibrinogenaemia) O67.0 Intrapartum haemorrhage with coagulation defect (intrapartum haemorrhage (excessive) associated with afibrinoginaemia, disseminated intravascular coagulation, hyperfibrinolysis, hyperfibrinogenaemia) O72.3 Postpartum coagulation defects	
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Cerebrovascular accident	I60 Subarachnoid haemorrhage I60.0 Subarachnoid haemorrhage from carotid siphon and bifurcation I60.1 Subarachnoid haemorrhage from middle cerebral artery I60.2 Subarachnoid haemorrhage from anterior communicating artery I60.3 Subarachnoid haemorrhage from posterior communicating artery I60.4 Subarachnoid haemorrhage from basilar artery	None identified	None identified	None identified

	I60.5 Subarachnoid haemorrhage from vertebral artery I60.6 Subarachnoid haemorrhage from other intracranial arteries I60.7 Subarachnoid haemorrhage from intracranial artery, unspecified I60.8 Other subarachnoid haemorrhage I60.9 Subarachnoid haemorrhage, unspecified I61 Intracerebral haemorrhage I61.0 Intracerebral haemorrhage in hemisphere, subcortical I61.1 Intracerebral haemorrhage in hemisphere, cortical I61.2 Intracerebral haemorrhage in hemisphere, unspecified I61.3 Intracerebral haemorrhage in brain stem I61.4 Intracerebral haemorrhage in cerebellum I61.5 Intracerebral haemorrhage, intraventricular I61.6 Intracerebral haemorrhage, multiple localized I61.8 Other intracerebral haemorrhage I61.9 Intracerebral haemorrhage, unspecified I62 Other nontraumatic intracranial haemorrhage I62.0 Subdural haemorrhage (acute)(nontraumatic) I62.1 Nontraumatic extradural haemorrhage I62.9 Intracranial haemorrhage (nontraumatic), unspecified I63 Cerebral infarction I63.0 Cerebral infarction due to thrombosis of precerebral arteries I63.1 Cerebral infarction due to embolism of precerebral arteries			

	I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries I63.3 Cerebral infarction due to thrombosis of cerebral arteries I63.4 Cerebral infarction due to embolism of cerebral arteries I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic I63.8 Other cerebral infarction I63.9 Cerebral infarction, unspecified I64 Stroke, not specified as haemorrhage or infarction			
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Major complications of anaesthesia	O74.0 Aspiration pneumonitis due to anaesthesia during labour and delivery O74.1 Other pulmonary complications of anaesthesia during labour and delivery O74.2 Cardiac complications of anaesthesia during labour and delivery O74.3 Central nervous system complications of anaesthesia during labour and delivery O74.9 Complication of anaesthesia during labour and delivery, unspecified O89.0 Pulmonary complications of anaesthesia during the puerperium O89.1 Cardiac complications of anaesthesia during the puerperium O89.2 Central nervous system complications of anaesthesia during the puerperium O29.0 Pulmonary complications of anaesthesia during pregnancy	None identified	O29.6 Failed or difficult intubation during pregnancy O29.3 Toxic reaction to local anaesthesia during pregnancy	None identified

	O29.1 Cardiac complications of anaesthesia during pregnancy O29.2 Central nervous system complications of anaesthesia during pregnancy			
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Obstetric embolism (including amniotic fluid embolism)	O88 Obstetric embolism O88.0 Obstetric air embolism O88.1 Amniotic fluid embolism O88.2 Obstetric blood-clot embolism O88.3 Obstetric pyaemic and septic embolism O88.8 Other obstetric embolism	None identified	I26 Pulmonary embolism I26.0 Pulmonary embolism with mention of acute cor pulmonale I26.9 Pulmonary embolism without mention of acute cor pulmonale	Embolic event including pulmonary embolism, amniotic fluid embolism, septic embolism and air embolism
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Shock	R57.0 Cardiogenic shock R57.1 Hypovolaemic shock R57.2 Septic shock R57.8 Other shock R57.9 Shock, unspecified O75.1 Shock during or following labour and delivery T80.5 Anaphylactic shock due to serum T88.6 Anaphylactic shock due to adverse effect of correct drug or medicament properly administered	None identified	T78.2 Anaphylactic shock, unspecified T78.0 Anaphylactic shock due to adverse food reaction Nb: there are other coded relating to severe reactions to blood products – these maybe do not go in the shock category, but ? should be included in the future validated EMMOI	None identified
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Sickle cell anaemia with crisis	D57.0 Sickle-cell anaemia with crisis	None identified	None identified	None identified

Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Status asthmaticus	J46 Status asthmaticus	None identified	None identified	None identified
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Status epilepticus	G41 Status epilepticus G41.0 Grand mal status epilepticus G41.1 Petit mal status epilepticus G41.2 Complex partial status epilepticus G41.8 Other status epilepticus G41.9 Status epilepticus, unspecified	None identified	None identified	None identified
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Uterine rupture	O71.0 Rupture of uterus before onset of labour O71.1 Rupture of uterus during labour	None identified	None identified	None identified
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Eclampsia	O15 Eclampsia O15.0 Eclampsia in pregnancy O15.1 Eclampsia in labour O15.2 Eclampsia in the puerperium O15.9 Eclampsia, unspecified as to time period	None identified	None identified	None identified
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Sepsis	O85 Puerperal sepsis	None identified	O75.3 Other infection during labour (including sepsis during labour) A40 Streptococcal sepsis A40.0 Sepsis due to streptococcus, group A A40.1 Sepsis due to streptococcus, group B A40.2 Sepsis due to streptococcus, group D	If only 085 code is used then this should be time bound to the postpartum period only

			A40.3 Sepsis due to Streptococcus pneumoniae A40.8 Other streptococcal sepsis A40.9 Streptococcal sepsis, unspecified A41 Other sepsis A41.0 Sepsis due to Staphylococcus aureus A41.1 Sepsis due to other specified staphylococcus A41.2 Sepsis due to unspecified staphylococcus A41.3 Sepsis due to Haemophilus influenzae A41.4 Sepsis due to anaerobes A41.5 Sepsis due to other Gram-negative organisms A41.8 Other specified sepsis A41.9 Sepsis, unspecified (including septicaemia)	
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Cerebral venous thrombosis	O87.3 Cerebral venous thrombosis in the puerperium	None identified	I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic I67.6 Nonpyogenic thrombosis of intracranial venous system (including non-pyogenic thrombosis of cerebral vein and intracranial venous sinus)	If the 087.3 code is the only code used then this should be time bound to the postpartum period only

Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Assisted ventilation including tracheostomy	E85.1 Invasive ventilation (Includes endotracheal intermittent positive pressure ventilation) E85.2 Non-invasive ventilation NEC (Includes continuous positive airway pressure, intermittent positive pressure ventilation NEC, Negative pressure ventilation, Bilevel positive airway pressure, High flow continuous positive airway pressure) E42.1 Permanent tracheostomy E42.2 Cricothyroidostomy E42.3 Temporary tracheostomy (includes tracheostomy NEC, Traccheostomy, Placement of tracheostomy tube) E42.8 Other specified (Exteriorisation of trachea) E42.9 Unspecified (Exteriorisation of trachea)		E85.6: Continuous positive airway pressure E85.8: Other specified ventilation support E85.9: Unspecified ventilation support E89.9: Unspecified other respiratory support E89.8: Other specified other respiratory support Y73.3: Ventilatory support Y73.1: Cardiopulmonary bypass Y73.2: Extracorporeal circulation NEC	
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Curettage in combination with general anaesthetic	R28.1 Curettage of delivered uterus	Y80 General anaesthetic The additional use of this code does not help identify cases/is surplus to requirement	R28.8 Other specified (Instrumental removal of products of conception from delivered uterus) R28.9 Unspecified (Instrumental removal of products of conception from delivered uterus) Q10 Curettage of uterus Q10.1 Dilation of cervix uteri and curettage of products of conception from uterus Note: Use a subsidiary code to identify gestational age (Y95) Q10.2 Curettage of products of	It is not standard practice in the UK to instrument the uterus at the time of delivery, so I interpret this morbid event category is attempting to capture patients who are having a primary or secondary PPH caused by retained tissue requiring surgical evacuation of the uterus. Consider renaming morbid event category “Surgical evacuation of uterus”

			conception from uterus NEC Note: Use a subsidiary code to identify gestational age (Y95) Q10.3 Dilation of cervix uteri and curettage of uterus NEC Q10.8 Other specified Q10.9 Unspecified Q11 Other evacuation of contents of uterus Note: Use a subsidiary code to identify gestational age (Y95) Q11.1 Vacuum aspiration of products of conception from uterus NEC Includes: Dilation of cervix uteri and vacuum aspiration of products of conception from uterus NEC Q11.5 Vacuum aspiration of products of conception from uterus using rigid cannula Q11.6 Vacuum aspiration of products of conception from uterus using flexible cannula Q11.3 Evacuation of products of conception from uterus NEC	
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Dialysis	X40 Compensation for renal failure X40.1 Renal dialysis X40.2 Peritoneal dialysis NEC X40.3 Haemodialysis NEC X40.4 Haemofiltration X40.5 Automated peritoneal dialysis X40.6 Continuous ambulatory peritoneal dialysis	None identified	None identified	None identified

	X40.7 Haemoperfusion X40.8 Other specified X40.9 Unspecified X41.1 Insertion of ambulatory peritoneal dialysis catheter X42.1 Insertion of temporary peritoneal dialysis catheter			
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Evacuation of haematoma	P09.3 Evacuation of haematoma from vulva P27.1 Evacuation of haematoma from vagina T34.1 Open drainage of subphrenic abscess T34.2 Open drainage of pelvic abscess T34.3 Open drainage of abdominal abscess NEC T45.1 Image controlled percutaneous drainage of subphrenic abscess T45.2 Image controlled percutaneous drainage of pelvic abscess T45.3 Image controlled percutaneous drainage of abdominal abscess NEC T45.4 Image controlled percutaneous drainage of lesion of abdominal cavity NEC Y22 Drainage of organ NOC Y22.1 Aspiration of haematoma of organ NOC		T34.8 Other specified (open drainage of peritoneum) T34.9 Unspecified (open drainage of peritoneum) T46.8: Other specified other drainage of peritoneal cavity T46.9: Unspecified other drainage of peritoneal cavity T96.3: Debridement of soft tissue NEC T96.4: Evacuation of seroma from soft tissue Y05.5: Debridement of organ NOC Y22.8: Other specified drainage of organ NOC Y22.9: Unspecified drainage of organ NOC Y25.1: Suture of laceration of organ NOC Y25.2: Resuture of organ NOC Y32.1: Re-exploration of organ and surgical arrest of postoperative bleeding NOC Y32.2: Re-exploration of organ and other repair of organ NOC	This morbid event category contains relevant codes for management of haematoma, but also contains codes for the management of other intra-abdominal collection e.g. abscess. These codes are important to retain as they likely capture patients who have significant complications/severe morbidity but they are not accurately represented as evacuation of haematoma. Consider renaming morbid event category as “Management of haematoma and intra-abdominal or pelvic collection”

			Y32.3: Re-exploration of organ and packing of organ NOC Y32.8: Other specified re-exploration of organ NOC Y32.9: Unspecified re-exploration of organ NOC	
Morbid event	Codes included in original EMMOI code list (ICD-10 or OPCS-4 codes)	Suggested codes for removal from code list	Suggested codes for addition to code list	Suggested amendment to definition or categorisation of morbid event
Hysterectomy	Q07.1 Abdominal hysterocolpectomy and excision of periuterine tissue Q07.2 Abdominal hysterectomy and excision of periuterine tissue NEC Q07.3 Abdominal hysterocolpectomy NEC Q07.4 Total abdominal hysterectomy NEC Q07.5 Subtotal abdominal hysterectomy Q08 Vaginal excision of uterus Q08.1 Vaginal hysterocolpectomy and excision of periuterine tissue Q08.2 Vaginal hysterectomy and excision of periuterine tissue NEC Q08.3 Vaginal hysterocolpectomy NEC Q08.8 Other specified Q08.9 Unspecified Includes: Vaginal hysterectomy NEC	Q07.1 Abdominal hysterocolpectomy and excision of periuterine tissue Q07.3 Abdominal hysterocolpectomy NEC Q08.1 Vaginal hysterocolpectomy and excision of periuterine tissue Q08.3 Vaginal hysterocolpectomy NEC Q08 Vaginal excision of uterus Q08.2 Vaginal hysterectomy and excision of periuterine tissue NEC Q08.8 Other specified Q08.9 Unspecified Includes: Vaginal hysterectomy NEC	R25.1 Caesarean hysterectomy	Hysterectomy codes used should be time bound to only include the postpartum period. A vaginal approach to hysterectomy in the peripartum period would usually not be done because of restricted access to pelvic vessels and the pelvic sidewall. Colpectomy refers to the permanent closure of the vagina to treat severe pelvic organ prolapse. It is an uncommon operation, usually only offered to elderly patients.

Table B5. Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (ICD-10 codes)	Codes	Time frame
Acute abdomen	N73.3 Female acute pelvic peritonitis N73.5 Female pelvic peritonitis, unspecified K65.0 Acute peritonitis K65.9 Peritonitis, unspecified K35 Acute appendicitis K35.2 Acute appendicitis with generalized peritonitis K35.3 Acute appendicitis with localized peritonitis K35.8 Acute appendicitis, other and unspecified K37 Unspecified appendicitis K56.2 Volvulus K56.5 Intestinal adhesions bands with obstruction K56.6 Other and unspecified intestinal obstruction K59.3 Megacolon, not elsewhere classified	Start of pregnancy up to 42 days after birth
Acute renal failure	O90.4 Postpartum acute renal failure N17 Acute renal failure N17.0 Acute renal failure with tubular necrosis N17.1 Acute renal failure with acute cortical necrosis N17.2 Acute renal failure with medullary necrosis N17.8 Other acute renal failure N17.9 Acute renal failure, unspecified N19 Unspecified kidney failure N99.0 Postprocedural renal failure I12.0 Hypertensive renal disease with renal failure I13.1 Hypertensive heart and renal disease with renal failure	Start of pregnancy up to 42 days after birth
Acute psychosis	F23 Acute and transient psychotic disorders F23.0 Acute polymorphic psychotic disorder without symptoms of schizophrenia F23.1 Acute polymorphic psychotic disorder with symptoms of schizophrenia F23.2 Acute schizophrenia-like psychotic disorder F23.8 Other acute and transient psychotic disorders F23.9 Acute and transient psychotic disorder, unspecified F53.1 Severe mental and behavioural disorders associated with the puerperium, not elsewhere classified	Start of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (ICD-10 codes)	Codes	Time frame
Acute cardiac event (cardiac infarction, cardiac failure, cardiomyopathy and cardiac arrest)	O90.3 Cardiomyopathy in the puerperium I21 Acute myocardial infarction I21.0 Acute transmural myocardial infarction of anterior wall I21.1 Acute transmural myocardial infarction of inferior wall I21.2 Acute transmural myocardial infarction of other sites I21.3 Acute transmural myocardial infarction of unspecified site I21.4 Acute subendocardial myocardial infarction I21.9 Acute myocardial infarction, unspecified I42 Cardiomyopathy I42.0 Dilated cardiomyopathy I42.1 Obstructive hypertrophic cardiomyopathy I42.2 Other hypertrophic cardiomyopathy I42.3 Endomyocardial (eosinophilic) disease I42.4 Endocardial fibroelastosis I42.5 Other restrictive cardiomyopathy I42.6 Alcoholic cardiomyopathy I42.7 Cardiomyopathy due to drugs and other external agents I42.8 Other cardiomyopathies I42.9 Cardiomyopathy, unspecified I43* Cardiomyopathy in diseases classified elsewhere I43.0* Cardiomyopathy in infectious and parasitic diseases classified elsewhere I43.1* Cardiomyopathy in metabolic diseases I43.2* Cardiomyopathy in nutritional diseases I43.8* Cardiomyopathy in other diseases classified elsewhere I46 Cardiac arrest I46.0 Cardiac arrest with successful resuscitation I46.1 Sudden cardiac death, so described I46.9 Cardiac arrest, unspecified I50 Heart failure I50.0 Congestive heart failure I50.1 Left ventricular failure I50.9 Heart failure, unspecified I11.0 Hypertensive heart disease with (congestive) heart failure I11.9 Hypertensive heart disease without (congestive) heart failure I13.0 Hypertensive heart and renal disease with (congestive) heart failure I13.2 Hypertensive heart and renal disease with both (congestive) heart failure and renal failure	Start of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (ICD-10 codes)	Codes	Time frame
Acute respiratory compromise	J81 Pulmonary oedema J80 Adult respiratory distress syndrome	Start of pregnancy up to 42 days after birth
Cerebral oedema or coma	G93.6 Cerebral oedema R40.2 Coma, unspecified	Start of pregnancy up to 42 days after birth
Disseminated intravascular coagulopathy	O45.0 Premature separation of placenta with coagulation defect (including placental abruption with excessive haemorrhage associated with afibrinoginaemia, disseminated intravascular coagulation, hyperfibrinolysis, hyperfibrinogenaemia) O46.0 Antepartum haemorrhage with coagulation defect (antepartum haemorrhage (excessive) associated with afibrinoginaemia, disseminated intravascular coagulation, hyperfibrinolysis, hyperfibrinogenaemia) O67.0 Intrapartum haemorrhage with coagulation defect (intrapartum haemorrhage (excessive) associated with afibrinoginaemia, disseminated intravascular coagulation, hyperfibrinolysis, hyperfibrinogenaemia) D65 Disseminated intravascular coagulation (defibrination syndrome)	Start of pregnancy up to 42 days after birth
Status asthmaticus	J46 Status asthmaticus	Start of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (ICD-10 codes)	Codes	Time frame
Cerebrovascular accident	I60 Subarachnoid haemorrhage I60.0 Subarachnoid haemorrhage from carotid siphon and bifurcation I60.1 Subarachnoid haemorrhage from middle cerebral artery I60.2 Subarachnoid haemorrhage from anterior communicating artery I60.3 Subarachnoid haemorrhage from posterior communicating artery I60.4 Subarachnoid haemorrhage from basilar artery I60.5 Subarachnoid haemorrhage from vertebral artery I60.6 Subarachnoid haemorrhage from other intracranial arteries I60.7 Subarachnoid haemorrhage from intracranial artery, unspecified I60.8 Other subarachnoid haemorrhage I60.9 Subarachnoid haemorrhage, unspecified I61 Intracerebral haemorrhage I61.0 Intracerebral haemorrhage in hemisphere, subcortical I61.1 Intracerebral haemorrhage in hemisphere, cortical I61.2 Intracerebral haemorrhage in hemisphere, unspecified I61.3 Intracerebral haemorrhage in brain stem I61.4 Intracerebral haemorrhage in cerebellum I61.5 Intracerebral haemorrhage, intraventricular I61.6 Intracerebral haemorrhage, multiple localized I61.8 Other intracerebral haemorrhage I61.9 Intracerebral haemorrhage, unspecified I62 Other nontraumatic intracranial haemorrhage I62.0 Subdural haemorrhage (acute)(nontraumatic) I62.1 Nontraumatic extradural haemorrhage I62.9 Intracranial haemorrhage (nontraumatic), unspecified I63 Cerebral infarction I63.0 Cerebral infarction due to thrombosis of precerebral arteries I63.1 Cerebral infarction due to embolism of precerebral arteries I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries I63.3 Cerebral infarction due to thrombosis of cerebral arteries I63.4 Cerebral infarction due to embolism of cerebral arteries I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries I63.8 Other cerebral infarction I63.9 Cerebral infarction, unspecified I64 Stroke, not specified as haemorrhage or infarction	Start of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (ICD-10 codes)	Codes	Time frame
Major complications of anaesthesia	O74.0 Aspiration pneumonitis due to anaesthesia during labour and delivery O74.1 Other pulmonary complications of anaesthesia during labour and delivery O74.2 Cardiac complications of anaesthesia during labour and delivery O74.3 Central nervous system complications of anaesthesia during labour and delivery O74.9 Complication of anaesthesia during labour and delivery, unspecified O89.0 Pulmonary complications of anaesthesia during the puerperium O89.1 Cardiac complications of anaesthesia during the puerperium O89.2 Central nervous system complications of anaesthesia during the puerperium O29.0 Pulmonary complications of anaesthesia during pregnancy O29.1 Cardiac complications of anaesthesia during pregnancy O29.2 Central nervous system complications of anaesthesia during pregnancy O29.6 Failed or difficult intubation during pregnancy O29.3 Toxic reaction to local anaesthesia during pregnancy	Start of pregnancy up to 42 days after birth
Embolic event (pulmonary embolism, amniotic fluid embolism, septic embolism and air embolism)	O88 Obstetric embolism O88.0 Obstetric air embolism O88.1 Amniotic fluid embolism O88.2 Obstetric blood-clot embolism O88.3 Obstetric pyaemic and septic embolism O88.8 Other obstetric embolism I26 Pulmonary embolism I26.0 Pulmonary embolism with mention of acute cor pulmonale I26.9 Pulmonary embolism without mention of acute cor pulmonale	Start of pregnancy up to 42 days after birth
Shock	R57.0 Cardiogenic shock R57.1 Hypovolaemic shock R57.2 Septic shock R57.8 Other shock R57.9 Shock, unspecified O75.1 Shock during or following labour and delivery T80.5 Anaphylactic shock due to serum T88.6 Anaphylactic shock due to adverse effect of correct drug or medicament properly administered T78.2 Anaphylactic shock, unspecified T78.0 Anaphylactic shock due to adverse food reaction A48.3 Toxic shock syndrome	Start of pregnancy up to 42 days after birth
Sickle cell anaemia with crisis	D57.0 Sickle-cell anaemia with crisis	Start of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (ICD-10 codes)	Codes	Time frame
Status epilepticus	G41 Status epilepticus G41.0 Grand mal status epilepticus G41.1 Petit mal status epilepticus G41.2 Complex partial status epilepticus G41.8 Other status epilepticus G41.9 Status epilepticus, unspecified	Start of pregnancy up to 42 days after birth
Uterine rupture	O71.0 Rupture of uterus before onset of labour O71.1 Rupture of uterus during labour	Start of pregnancy up to 42 days after birth
Eclampsia	O15 Eclampsia O15.0 Eclampsia in pregnancy O15.1 Eclampsia in labour O15.2 Eclampsia in the puerperium O15.9 Eclampsia, unspecified as to time period	Start of pregnancy up to 42 days after birth
Sepsis	O85 Puerperal sepsis O75.3 Other infection during labour (including sepsis during labour) A40 Streptococcal sepsis A40.0 Sepsis due to streptococcus, group A A40.1 Sepsis due to streptococcus, group B A40.2 Sepsis due to streptococcus, group D A40.3 Sepsis due to Streptococcus pneumoniae A40.8 Other streptococcal sepsis A40.9 Streptococcal sepsis, unspecified A41 Other sepsis A41.0 Sepsis due to Staphylococcus aureus A41.1 Sepsis due to other specified staphylococcus A41.2 Sepsis due to unspecified staphylococcus A41.3 Sepsis due to Haemophilus influenzae A41.4 Sepsis due to anaerobes A41.5 Sepsis due to other Gram-negative organisms A41.8 Other specified sepsis A41.9 Sepsis, unspecified (including septicaemia) A32.7 Listerial sepsis	Start of pregnancy up to 42 days after birth
Cerebral venous thrombosis	O87.3 Cerebral venous thrombosis in the puerperium I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic I67.6 Nonpyogenic thrombosis of intracranial venous system (including non-pyogenic thrombosis of cerebral vein and intracranial venous sinus)	Start of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (ICD-10 codes)	Codes	Time frame
Acute pancreatitis	K85 Acute pancreatitis K85.0 Idiopathic acute pancreatitis K85.1 Biliary acute pancreatitis K85.2 Alcohol-induced acute pancreatitis K85.3 Drug-induced acute pancreatitis K85.8 Other acute pancreatitis K85.9 Acute pancreatitis, unspecified K86.3 Pseudocyst of pancreas	Start of pregnancy up to 42 days after birth
Rupture of aortic aneurysm or dissection of aorta	I71.0 Dissection of aorta any part I71.1 Thoracic aortic aneurysm, ruptured I71.3 Abdominal aortic aneurysm, ruptured I71.5 Thoracoabdominal aortic aneurysm, ruptured I71.8 Aortic aneurysm of unspecified site, ruptured I72.2 Aneurysm and dissection of renal artery I72.3 Aneurysm and dissection of iliac artery I71.2 Thoracic aortic aneurysm, without mention of rupture I71.4 Abdominal aortic aneurysm, without mention of rupture I71.6 Thoracoabdominal aortic aneurysm, without mention of rupture I71.9 Aortic aneurysm of unspecified site, without mention of rupture	Start of pregnancy up to 42 days after birth
Diabetic ketoacidosis	E10.0 Diabetes mellitus with coma (including hyperglycaemic coma NOS, diabetic coma with or without ketoacidosis, diabetic hyperosmolar coma, diabetic hypoglycaemic coma) E10.1 Diabetes mellitus with ketoacidosis	Start of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (OPCS-4 codes)	Codes	Time frame
Respiratory support	E85.1 Invasive ventilation (Includes endotracheal intermittent positive pressure ventilation) E85.2 Non-invasive ventilation NEC (Includes continuous positive airway pressure, intermittent positive pressure ventilation NEC, Negative pressure ventilation, Bilevel positive airway pressure, High flow continuous positive airway pressure) E42.1 Permanent tracheostomy E42.2 Cricothyroidostomy E42.3 Temporary tracheostomy (includes tracheostomy NEC, Traccheostomy, Placement of tracheostomy tube) E42.8 Other specified (Exteriorisation of trachea) E42.9 Unspecified (Exteriorisation of trachea) E85.6: Continuous positive airway pressure E85.8: Other specified ventilation support E85.9: Unspecified ventilation support E89.9: Unspecified other respiratory support E89.8: Other specified other respiratory support Y73.3: Ventilatory support Y73.1: Cardiopulmonary bypass Y73.2: Extracorporeal circulation NEC	Start of pregnancy up to 42 days after birth
Surgical evacuation of the uterus following birth	R28.1 Curettage of delivered uterus R28.8 Other specified (Instrumental removal of products of conception from delivered uterus) R28.9 Unspecified (Instrumental removal of products of conception from delivered uterus) Q10 Curettage of uterus Q10.1 Dilation of cervix uteri and curettage of products of conception from uterus Q10.2 Curettage of products of conception from uterus NEC Q10.3 Dilation of cervix uteri and curettage of uterus NEC Q10.8 Other specified Q10.9 Unspecified Q11 Other evacuation of contents of uterus Q11.1 Vacuum aspiration of products of conception from uterus NEC Q11.5 Vacuum aspiration of products of conception from uterus using rigid cannula Q11.6 Vacuum aspiration of products of conception from uterus using flexible cannula Q11.3 Evacuation of products of conception from uterus NEC	End of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (OPCS-4 codes)	Codes	Time frame
Dialysis	X40 Compensation for renal failure X40.1 Renal dialysis X40.2 Peritoneal dialysis NEC X40.3 Haemodialysis NEC X40.4 Haemofiltration X40.5 Automated peritoneal dialysis X40.6 Continuous ambulatory peritoneal dialysis X40.7 Haemoperfusion X40.8 Other specified X40.9 Unspecified X41.1 Insertion of ambulatory peritoneal dialysis catheter X42.1 Insertion of temporary peritoneal dialysis catheter	Start of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (OPCS-4 codes)	Codes	Time frame
Management of intra-abdominal or pelvic collection	T34.1 Open drainage of subphrenic abscess T34.2 Open drainage of pelvic abscess T34.3 Open drainage of abdominal abscess NEC T45.1 Image controlled percutaneous drainage of subphrenic abscess T45.2 Image controlled percutaneous drainage of pelvic abscess T45.3 Image controlled percutaneous drainage of abdominal abscess NEC T45.4 Image controlled percutaneous drainage of lesion of abdominal cavity NEC Y22 Drainage of organ NOC Y22.1 Aspiration of haematoma of organ NOC T34.8 Other specified (open drainage of peritoneum) T34.9 Unspecified (open drainage of peritoneum) T46.8: Other specified other drainage of peritoneal cavity T46.9: Unspecified other drainage of peritoneal cavity T96.3: Debridement of soft tissue NEC Y05.5: Debridement of organ NOC Y22.8: Other specified drainage of organ NOC Y22.9: Unspecified drainage of organ NOC Y25.1: Suture of laceration of organ NOC Y25.2: Resuture of organ NOC Y32.1: Re-exploration of organ and surgical arrest of postoperative bleeding NOC Y32.2: Re-exploration of organ and other repair of organ NOC Y32.3: Re-exploration of organ and packing of organ NOC Y32.8: Other specified re-exploration of organ NOC Y32.9: Unspecified re-exploration of organ NOC T30.1: Reopening of abdomen and re-exploration of intra-abdominal operation site and surgical arrest of postoperative bleeding T30.2: Reopening of abdomen and re-exploration of intra-abdominal operation site NEC T30.3: Reopening of abdomen NEC H03.1: Drainage of abscess of appendix H58.1: Drainage of ischiorectal abscess H58.3: Drainage of perirectal abscess	
Management of vulval or vaginal haematoma	P09.3 Evacuation of haematoma from vulva P27.1 Evacuation of haematoma from vagina	End of pregnancy up to 42 days after birth
Hysterectomy	Q07.4 Total abdominal hysterectomy NEC Q07.5 Subtotal abdominal hysterectomy R25.1 Caesarean hysterectomy	End of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (OPCS-4 codes)	Codes	Time frame
Interventional and surgical procedures to arrest major haemorrhage following birth	L70.2 Open embolisation of artery NEC L70.3 Ligation of artery NEC L71.3 Percutaneous transluminal embolisation of artery L93.3 Ligation of vein NEC L94.1 Percutaneous transluminal embolisation of vein L99.5: Percutaneous transluminal occlusion of vein NEC L53.1: Repair of iliac artery NEC L53.8: Other specified other open operations on iliac artery L53.9: Unspecified other open operations on iliac artery L54.3: Arteriography of iliac artery L66.3: Percutaneous transluminal occlusion of artery L72.1: Arteriography NEC L93.7: Repair of vein NEC L97.4: Operations on artery NEC L97.5: Operations on vein NEC L97.4: Operations on artery NEC L97.5: Operations on vein NEC Y78.1: Arteriotomy approach to organ using image guidance with fluoroscopy Y78.2: Arteriotomy approach to organ using image guidance with computed tomography Y79.3: Transluminal approach to organ through femoral artery Y78.8: Other specified arteriotomy approach to organ under image control Y78.9: Unspecified arteriotomy approach to organ under image control Y79.8: Other specified approach to organ through artery Y79.9: Unspecified approach to organ through artery	End of pregnancy up to 42 days after birth
Management of caesarean wound dehiscence	T28.3: Resuture of previous incision of anterior abdominal wall T28.8: Other specified other repair of anterior abdominal wall T28.9: Unspecified other repair of anterior abdominal wall	End of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (OPCS-4 codes)	Codes	Time frame
Repair of damage to bladder or urinary tract	M37.3: Repair of rupture of bladder M37.8: Other specified other repair of bladder M37.9: Unspecified other repair of bladder M73.6: Urethroplasty NEC M73.7: Repair of rupture of urethra NEC M73.8: Other specified repair of urethra M13.6: Percutaneous insertion of nephrostomy tube M18.2: Excision of segment of ureter M18.8: Other specified excision of ureter M18.9: Unspecified excision of ureter M19.1: Construction of ileal conduit M19.2: Creation of urinary diversion to intestine NEC M19.4: Cutaneous ureterostomy NEC M20.1: Bilateral replantation of ureter M20.2: Unilateral replantation of ureter M20.3: Replantation of ureter after urinary diversion M20.8: Other specified replantation of ureter M20.9: Unspecified replantation of ureter M21.1: Direct anastomosis of ureter to bladder M21.2: Anastomosis of ureter to bladder using flap of bladder M21.3: Ileal replacement of ureter M21.4: Colonic replacement of ureter M21.6: Ureteroureterostomy M22.1: Suture of ureter M22.2: Removal of ligature from ureter M22.8: Other specified repair of ureter M22.9: Unspecified repair of ureter M27.4: Ureteroscopic insertion of ureteric stent M27.7: Ureteroscopic dilation of ureter M27.8: Other specified therapeutic ureteroscopic operations on ureter M29.4: Endoscopic dilation of ureter M33.1: Percutaneous insertion of metallic stent into ureter M33.2: Percutaneous insertion of plastic stent into ureter M33.8: Other specified percutaneous ureteric stent procedures M33.9: Unspecified percutaneous ureteric stent procedures M73.4: Reconstruction of urethra M73.8: Other specified repair of urethra M73.9: Unspecified repair of urethra	End of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (OPCS-4 codes)	Codes	Time frame
Repair of damage to the intestine and management of intestinal obstruction	G58.1: Total jejunectomy and anastomosis of stomach to ileum G58.2: Total jejunectomy and anastomosis of duodenum to ileum G58.3: Total jejunectomy and anastomosis of duodenum to colon G58.4: Partial jejunectomy and anastomosis of jejunum to ileum G58.5: Partial jejunectomy and anastomosis of duodenum to colon G58.8: Other specified excision of jejunum G58.9: Unspecified excision of jejunum G69.1: Ileectomy and anastomosis of stomach to ileum G69.2: Ileectomy and anastomosis of duodenum to ileum G69.3: Ileectomy and anastomosis of ileum to ileum G69.4: Ileectomy and anastomosis of ileum to colon G69.8: Other specified excision of ileum G69.9: Unspecified excision of ileum G78.4: Closure of perforation of ileum G78.5: Exclusion of segment of ileum G78.6: Open intubation of ileum H06.1: Extended right hemicolectomy and end to end anastomosis H06.2: Extended right hemicolectomy and anastomosis of ileum to colon H06.9: Unspecified extended excision of right hemicolon H07.1: Right hemicolectomy and end to end anastomosis of ileum to colon H07.2: Right hemicolectomy and side to side anastomosis of ileum to transverse colon H07.3: Right hemicolectomy and anastomosis NEC H07.4: Right hemicolectomy and ileostomy HFQ H07.5: Right hemicolectomy and end to side anastomosis H07.8: Other specified other excision of right hemicolon H07.9: Unspecified other excision of right hemicolon H08.1: Transverse colectomy and end to end anastomosis H08.2: Transverse colectomy and anastomosis of ileum to colon H08.3: Transverse colectomy and anastomosis NEC H08.4: Transverse colectomy and ileostomy HFQ H08.5: Transverse colectomy and exteriorisation of bowel NEC H08.6: Transverse colectomy and end to side anastomosis H08.8: Other specified excision of transverse colon H08.9: Unspecified excision of transverse colon H09.1: Left hemicolectomy and end to end anastomosis of colon to rectum H09.2: Left hemicolectomy and end to end anastomosis of colon to colon	End of pregnancy up to 42 days after birth

	H11.2: Colectomy and side to side anastomosis of ileum to colon NEC H11.3: Colectomy and anastomosis NEC H11.4: Colectomy and ileostomy NEC H11.5: Colectomy and exteriorisation of bowel NEC H11.6: Colectomy and end to side anastomosis NEC H11.8: Other specified other excision of colon H11.9: Unspecified other excision of colon H29.1: Subtotal excision of colon and rectum and creation of colonic pouch and anastomosis of colon to anus H29.2: Subtotal excision of colon and rectum and creation of colonic pouch NEC H29.3: Subtotal excision of colon and creation of colonic pouch and anastomosis of colon to rectum H29.4: Subtotal excision of colon and creation of colonic pouch NEC H29.5: Subtotal excision of colon and anastomosis of colon to ileum H29.8: Other specified subtotal excision of colon H29.9: Unspecified subtotal excision of colon H33.1: Abdominoperineal excision of rectum and end colostomy H33.2: Proctectomy and anastomosis of colon to anus H33.3: Anterior resection of rectum and anastomosis of colon to rectum using staples H33.4: Anterior resection of rectum and anastomosis NEC H33.5: Rectosigmoidectomy and closure of rectal stump and exteriorisation of bowel H33.6: Anterior resection of rectum and exteriorisation of bowel H33.7: Perineal resection of rectum HFQ H33.8: Other specified excision of rectum H33.9: Unspecified excision of rectum T37.4: Repair of mesentery of small intestine T38.4: Repair of mesentery of colon H17.2: Open reduction of volvulus of caecum H17.3: Open reduction of volvulus of sigmoid colon H17.4: Open reduction of volvulus of colon NEC H17.5: Open relief of strangulation of colon H17.6: Open relief of obstruction of colon NEC H15.8: Other specified other exteriorisation of colon H15.9: Unspecified other exteriorisation of colon H15.1: Loop colostomy H15.2: End colostomy H13.1: Bypass of colon by anastomosis of ileum to colon H13.2: Bypass of colon by anastomosis of caecum to sigmoid colon H13.3: Bypass of colon by anastomosis of transverse colon to sigmoid colon H13.4: Bypass of colon by anastomosis of transverse colon to rectum H13.5: Bypass of colon by anastomosis of colon to rectum NEC H13.8: Other specified bypass of colon	

	H13.9: Unspecified bypass of colon H10.1: Sigmoid colectomy and end to end anastomosis of ileum to rectum H10.2: Sigmoid colectomy and anastomosis of colon to rectum H10.3: Sigmoid colectomy and anastomosis NEC H10.4: Sigmoid colectomy and ileostomy HFQ H10.5: Sigmoid colectomy and exteriorisation of bowel NEC H10.6: Sigmoid colectomy and end to side anastomosis H10.8: Other specified excision of sigmoid colon H10.9: Unspecified excision of sigmoid colon H05.1: Total colectomy and anastomosis of ileum to rectum H05.2: Total colectomy and ileostomy and creation of rectal fistula HFQ H05.3: Total colectomy and ileostomy NEC H05.8: Other specified total excision of colon H05.9: Unspecified total excision of colon G63.3: Closure of perforation of jejunum G72.1: Anastomosis of ileum to caecum G72.2: Anastomosis of ileum to transverse colon G72.3: Anastomosis of ileum to colon NEC G72.4: Anastomosis of ileum to rectum G72.5: Anastomosis of ileum to anus and creation of pouch HFQ G74.1: Creation of continent ileostomy G74.2: Creation of temporary ileostomy G74.3: Creation of defunctioning ileostomy G76.2: Open relief of strangulation of ileum G76.3: Open relief of obstruction of ileum NEC T30.5: Packing of abdominal cavity	

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (OPCS-4 codes)	Codes	Time frame
Management of acute coronary syndrome	K63.4: Coronary arteriography using two catheters K63.5: Coronary arteriography using single catheter K63.6: Coronary arteriography NEC K63.8: Other specified contrast radiology of heart K63.9: Unspecified contrast radiology of heart K65.1: Catheterisation of combination of right and left side of heart NEC K65.2: Catheterisation of right side of heart NEC K65.3: Catheterisation of left side of heart NEC K65.4: Catheterisation of left side of heart via atrial transeptal puncture K65.8: Other specified catheterisation of heart K65.9: Unspecified catheterisation of heart K75.1: Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery K75.2: Percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery K75.3: Percutaneous transluminal balloon angioplasty and insertion of 1-2 stents into coronary artery K75.4: Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC K75.8: Other specified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery K75.9: Unspecified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery L76.1: Endovascular placement of one metallic stent L76.2: Endovascular placement of one plastic stent L76.3: Endovascular placement of two metallic stents L76.4: Endovascular placement of two plastic stents L76.5: Endovascular placement of three or more metallic stents L76.6: Endovascular placement of three or more plastic stents L76.7: Endovascular placement of metallic stent with mechanical embolic protection L76.8: Other specified endovascular placement of stent L76.9: Unspecified endovascular placement of stent L89.1: Endovascular placement of two drug-eluting stents L89.2: Endovascular placement of two coated stents L89.3: Endovascular placement of three or more drug-eluting stents L89.4: Endovascular placement of three or more coated stents L89.5: Endovascular placement of one drug-eluting stent L89.6: Endovascular placement of one coated stent L89.8: Other specified other endovascular placement of stent L89.9: Unspecified other endovascular placement of stent	Start of pregnancy up to 42 days after birth

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (OPCS-4 codes)	Codes	Time frame
Interventional and surgical procedures to manage thromboembolism	L79.1: Insertion of filter into vena cava L12.4: Open embolectomy of pulmonary artery L13.1: Percutaneous transluminal embolectomy of pulmonary artery L96.1: Percutaneous mechanical thromboembolectomy L96.2: Percutaneous aspiration thromboembolectomy L96.8: Other specified percutaneous removal of thrombus from vein L96.9: Unspecified percutaneous removal of thrombus from vein L99.3: Percutaneous transluminal venous thrombolysis with reconstruction L99.4: Percutaneous transluminal venous thrombolysis NEC	Start of pregnancy up to 42 days after birth
Interventional and surgical procedures to manage major haemorrhage originating from the spleen	J69.1: Total excision of spleen and replantation of fragments of spleen J69.2: Total splenectomy J69.8: Other specified total excision of spleen J69.9: Unspecified total excision of spleen J70.1: Partial splenectomy J72.2: Embolisation of spleen J72.4: Repair of spleen J72.5: Banding of spleen	Start of pregnancy up to 42 days after birth
Interventional procedures to treat haemorrhagic or ischaemic stroke	L33.1: Excision of aneurysm of cerebral artery L33.2: Clipping of aneurysm of cerebral artery L33.3: Ligation of aneurysm of cerebral artery NEC L33.4: Obliteration of aneurysm of cerebral artery NEC L33.8: Other specified operations on aneurysm of cerebral artery L33.9: Unspecified operations on aneurysm of cerebral artery L34.3: Open embolectomy of cerebral artery L34.4: Open embolisation of cerebral artery L35.1: Percutaneous transluminal embolisation of cerebral artery L35.2: Arteriography of cerebral artery L35.3: Percutaneous transluminal insertion of stent into cerebral artery L35.4: Percutaneous transluminal embolectomy of cerebral artery L35.8: Other specified transluminal operations on cerebral artery L35.9: Unspecified transluminal operations on cerebral artery L96.1: Percutaneous mechanical thromboembolectomy L96.2: Percutaneous aspiration thromboembolectomy O01.1: Percutaneous transluminal coil embolisation of small aneurysm of artery O01.2: Percutaneous transluminal coil embolisation of medium aneurysm of artery O01.3: Percutaneous transluminal coil embolisation of large aneurysm of artery	Start of pregnancy up to 42 days after birth

	O01.4: Percutaneous transluminal coil embolisation of giant aneurysm of artery O01.8: Other specified transluminal coil embolisation of aneurysm of artery O01.9: Unspecified transluminal coil embolisation of aneurysm of artery O02.1: Percutaneous transluminal balloon assisted coil embolisation of three or more aneurysms of artery O02.2: Percutaneous transluminal balloon assisted coil embolisation of two aneurysms of artery O02.3: Percutaneous transluminal balloon assisted coil embolisation of single aneurysm of artery O02.8: Other specified transluminal balloon assisted coil embolisation of aneurysm of artery O02.9: Unspecified transluminal balloon assisted coil embolisation of aneurysm of artery O03.1: Percutaneous transluminal stent assisted coil embolisation of three or more aneurysms of artery O03.2: Percutaneous transluminal stent assisted coil embolisation of two aneurysms of artery O03.3: Percutaneous transluminal stent assisted coil embolisation of single aneurysm of artery O03.4: Percutaneous transluminal flow diverting stent assisted coil embolisation of three or more aneurysms of artery O03.5: Percutaneous transluminal flow diverting stent assisted coil embolisation of two aneurysms of artery O03.6: Percutaneous transluminal flow diverting stent assisted coil embolisation of single aneurysm of artery O03.8: Other specified transluminal stent assisted coil embolisation of aneurysm of artery O03.9: Unspecified transluminal stent assisted coil embolisation of aneurysm of artery O04.1: Percutaneous transluminal liquid polymer embolisation of aneurysm of artery O04.2: Percutaneous transluminal stent assisted liquid polymer embolisation of aneurysm of artery O04.3: Percutaneous transluminal flow diverting stent embolisation of aneurysm of artery O04.8: Other specified other transluminal embolisation of aneurysm of artery O04.9: Unspecified other transluminal embolisation of aneurysm of artery	

Table B5. (continued) Morbidity categories, timeframes and codes used in final composite outcome indicator used to identify events consistent with severe maternal morbidity

Morbid event category (OPCS-4 codes)	Codes	Time frame
Repair of aortic aneurysm rupture or aortic dissection	L18.1: Emergency replacement of aneurysmal segment of ascending aorta by anastomosis of aorta to aorta L18.2: Emergency replacement of aneurysmal segment of thoracic aorta by anastomosis of aorta to aorta NEC L18.3: Emergency replacement of aneurysmal segment of suprarenal abdominal aorta by anastomosis of aorta to aorta L18.4: Emergency replacement of aneurysmal segment of infrarenal abdominal aorta by anastomosis of aorta to aorta L18.5: Emergency replacement of aneurysmal segment of abdominal aorta by anastomosis of aorta to aorta NEC L18.6: Emergency replacement of aneurysmal bifurcation of aorta by anastomosis of aorta to iliac artery L18.8: Other specified emergency replacement of aneurysmal segment of aorta L18.9: Unspecified emergency replacement of aneurysmal segment of aorta L19.1: Replacement of aneurysmal segment of ascending aorta by anastomosis of aorta to aorta NEC L19.2: Replacement of aneurysmal segment of thoracic aorta by anastomosis of aorta to aorta NEC L19.3: Replacement of aneurysmal segment of suprarenal abdominal aorta by anastomosis of aorta to aorta NEC L19.4: Replacement of aneurysmal segment of infrarenal abdominal aorta by anastomosis of aorta to aorta NEC L19.5: Replacement of aneurysmal segment of abdominal aorta by anastomosis of aorta to aorta NEC L19.6: Replacement of aneurysmal bifurcation of aorta by anastomosis of aorta to iliac artery NEC L19.8: Other specified other replacement of aneurysmal segment of aorta L19.9: Unspecified other replacement of aneurysmal segment of aorta L26.5: Percutaneous transluminal insertion of stent into aorta L26.6: Transluminal aortic stent graft with fenestration NEC L26.7: Transluminal aortic branched stent graft NEC L25.4: Operations on aneurysm of aorta NEC L27.1: Endovascular insertion of stent graft for infrarenal abdominal aortic aneurysm L27.2: Endovascular insertion of stent graft for suprarenal aortic aneurysmL27.3: Endovascular insertion of stent graft for thoracic aortic aneurysm L27.4: Endovascular insertion of stent graft for aortic dissection in any position L27.5: Endovascular insertion of stent graft for aortic aneurysm of bifurcation NEC L27.6: Endovascular insertion of stent graft for aorto-uni-iliac aneurysm L27.8: Other specified transluminal insertion of stent graft for aneurysmal segment of aorta L27.9: Unspecified transluminal insertion of stent graft for aneurysmal segment of aorta L28.1: Endovascular insertion of stent for infrarenal abdominal aortic aneurysm L28.2: Endovascular insertion of stent for suprarenal aortic aneurysm L28.3: Endovascular insertion of stent for thoracic aortic aneurysm L28.4: Endovascular insertion of stent for aortic dissection in any position L28.5: Endovascular insertion of stent for aortic aneurysm of bifurcation NEC L28.6: Endovascular insertion of stent for aorto-uni-iliac aneurysm	Start of pregnancy up to 42 days after birth

	L28.8: Other specified transluminal operations on aneurysmal segment of aorta L28.9: Unspecified transluminal operations on aneurysmal segment of aorta O20.1: Endovascular placement of one branched stent graft O20.2: Endovascular placement of one fenestrated stent graft O20.3: Endovascular placement of one stent graft NEC O20.4: Endovascular placement of two stent grafts O20.5: Endovascular placement of three or more stent grafts O20.8: Other specified endovascular placement of stent graft O20.9: Unspecified endovascular placement of stent graft	
Surgical management of acute pancreatitis	J60.1: Drainage of pancreatic duct J57.6: Pancreatic necrosectomy J60.2: Open removal of calculus from pancreatic duct J60.3: Insertion of T tube into pancreatic duct J61.2: Drainage of cyst of pancreas into transposed jejunum J61.3: Drainage of cyst of pancreas into jejunum NEC J61.4: Drainage of cyst of pancreas NEC	Start of pregnancy up to 42 days after birth

Table B6. Constituent medical codes, read codes and read terms used to identify neonatal death

Neonatal death		
Medcode	Read code	Read term
2240	Q4z..12	Neonatal death
36564	Q48y700	Late neonatal death
28341	Q48y600	Early neonatal death
51323	R210z00	Sudden infant death syndrome NOS
57786	R210100	Crib death
94533	RyuC000	Sudden infant death syndrome
4302	R210000	Cot death
45750	Q4z..13	Newborn death
26679	Q4z..11	Infant death
48288	R210200	Nonspecific sudden infant death
9163	13M6.00	Death of daughter
13581	R210.00	Sudden infant death syndrome
5622	13MD.00	Death of child
27475	13M3.00	Sudden infant death
8218	13M5.00	Death of son
15465	13M2.00	Death of infant

Table B7. Constituent codes for pregnancy and birth characteristics

Anaesthetic intervention	
OPCS-4 code	
Y801 Inhalation anaesthetic using muscle relaxant	
Y802 Inhalation anaesthetic using endotracheal intubation NEC	
Y803 Inhalation anaesthetic NEC	
Y804 Intravenous anaesthetic NEC	
Y805 Rapid sequence induction of anaesthetic	
Y808 Other specified general anaesthetic	
Y809 Unspecified general anaesthetic	
Y811 Epidural anaesthetic using lumbar approach	
Y812 Epidural anaesthetic using sacral approach	
Y818 Other specified spinal anaesthetic	
Y819 Unspecified spinal anaesthetic	
Pregnancy induced hypertension (usage in searchable database = 20 weeks to 2 weeks postpartum)	
Medcode	Read term
70342	Transient hypertension of pregnancy + postnatal complication
20439	Transient hypertension of pregnancy
21526	Gestational hypertension
ICD-10 code	
O13 Gestational pregnancy induced hypertension	
Pre-eclampsia (usage in searchable database = 20 weeks to 2 weeks postpartum)	
Medcode	Read term
66860	Mild or unspecified pre-eclampsia - delivered with p/n comp
62916	Severe pre-eclampsia with postnatal complication
62919	Severe pre-eclampsia - delivered with postnatal complication
105933	Pre-eclampsia or eclampsia with hypertension + p/n comp
90577	Pre-eclampsia or eclampsia with hypertension - del+p/n comp
42947	Pre-eclampsia or eclampsia with hypertension - delivered
48347	Mild or unspecified pre-eclampsia with p/n complication
42088	Severe pre-eclampsia - delivered
49893	Mild or unspecified pre-eclampsia – delivered
59124	Mild or unspecified pre-eclampsia NOS
27800	Mild or unspecified pre-eclampsia - not delivered
57233	Mild or unspecified pre-eclampsia unspecified

53160	Pre-eclampsia or eclampsia with hypertension - not delivered
9429	Mild or unspecified pre-eclampsia
9067	Severe pre-eclampsia
16879	Mild pre-eclampsia
43664	Pre-eclampsia or eclampsia with pre-existing hypertension
67447	Severe pre-eclampsia - not delivered
93055	Pre-eclampsia or eclampsia + pre-existing hypertension NOS
47741	Pre-eclampsia or eclampsia with hypertension unspecified
40730	Severe pre-eclampsia NOS
14867	Mild pre-eclampsia
17805	Moderate pre-eclampsia
40686	Severe pre-eclampsia unspecified
8744	Pre-eclampsia, unspecified
9170	Hypertension complicating pregnancy/childbirth/puerperium
ICD-10 code	
O11 Pre-eclampsia superimposed on chronic hypertension O14 Pre-eclampsia O14.0 Mild to moderate pre-eclampsia O14.1 Severe pre-eclampsia O14.2 HELLP syndrome O14.9 Pre-eclampsia, unspecified	
Obstetric cholestasis (usage in searchable database = 20 weeks to 2 weeks postpartum)	
Medcode	Read term
22766	Toxic liver disease with cholestasis
26286	Cholestasis of pregnancy
18258	Liver disorder in pregnancy
36421	Liver disorder in pregnancy NOS
57419	Liver disorder in pregnancy - delivered
ICD-10 code	
O26.6 Liver disorders in pregnancy, childbirth and the puerperium Incl. Cholestasis (intrahepatic) in pregnancy and Obstetric cholestasis	
Gestational diabetes (usage in searchable database = 20 weeks to 2 weeks postpartum)	
Medcode	Read term
2664	Gestational diabetes mellitus
8446	Gestational diabetes mellitus
53167	Abnormal GTT during pregnancy - baby not yet delivered

49559	Diabetes mellitus during pregnancy - baby not yet delivered
34639	Diabetes mellitus during pregnancy - baby delivered
73557	Abnormal GTT in pregnancy/childbirth/puerperium NOS
ICD-10 code	
O24.4 Diabetes mellitus arising in pregnancy O24.9 Diabetes mellitus in pregnancy, unspecified	
Anaemia (usage in searchable database = at any point in the pregnancy)	
Medcode	Read term
1668	Iron deficiency anaemia of pregnancy
1771	Anaemia during pregnancy, childbirth and the puerperium
33634	Anaemia during pregnancy/childbirth/puerperium NOS
21119	Anaemia during pregnancy - baby not yet delivered
15633	Anaemia - unspecified whether in pregnancy or the puerperium

Table B8. Comparison of the prevalence of individual health conditions included in the study between all pregnancies in the cohort and by research quality status.

Health condition	All pregnancies in cohort (total N=906743)		Non-research quality pregnancies (total N=484652)		Research quality pregnancies (total N=422091)		p-value*
	n	%	n	%	n	%	
Conditions with no difference in prevalence based on research quality status							
Cardiac failure	120	0.01	66	0.01	54	0.01	0.734
Aortopathy	189	0.02	94	0.02	95	0.02	0.306
Pulmonary fibrosis	39	0.004	22	0.004	17	0.004	0.711
Sarcoidosis	318	0.04	160	0.03	158	0.04	0.262
Non-alcoholic steatohepatitis	374	0.04	190	0.04	184	0.04	0.305
Alcoholic liver disease	15	0.002	8	0.002	7	0.002	0.993
Hyperthyroidism	971	0.11	491	0.1	480	0.11	0.072
Adrenocortical insufficiency	71	0.01	32	0.01	39	0.01	0.157
Cerebrovascular disease	835	0.09	421	0.09	414	0.1	0.079
Ankylosing spondylitis	352	0.04	183	0.04	169	0.04	0.583
Eating disorder	16022	1.77	8591	1.77	7431	1.76	0.663
Cancer	283	0.03	142	0.03	141	0.03	0.270
Conditions with an increased prevalence among research quality pregnancies							
Hypertension	1637	0.18	696	0.14	941	0.22	<0.001
Ischaemic heart disease	532	0.06	197	0.04	335	0.22	<0.001
Valvular heart disease	1676	0.18	810	0.17	866	0.21	<0.001
Congenital structural heart disease	3847	0.42	1912	0.39	1935	0.46	<0.001
Asthma	43724	4.82	11896	2.45	31828	7.54	<0.001
Infective hepatitis	290	0.03	210	0.04	80	0.02	<0.001
Inflammatory bowel disease	4280	0.47	1888	0.39	2392	0.57	<0.001
Coeliac disease	1932	0.21	825	0.17	1107	0.26	<0.001
Dysfunctional uterine bleeding	15049	1.66	5663	1.17	9386	2.22	<0.001
Polycystic ovarian syndrome	33058	3.65	17008	3.51	16050	3.8	<0.001
Pelvic floor dysfunction	14092	1.55	4997	1.03	9095	2.15	<0.001
Hypothyroidism	16756	1.85	7534	1.55	9222	2.18	<0.001
Diabetes	5467	0.6	2479	0.51	2988	0.71	<0.001

Table B8. (continued) Comparison of the prevalence of individual health conditions included in the study between all pregnancies in the cohort and by research quality status.

Health condition	All pregnancies in cohort (total N=906743)		Non-research quality pregnancies (total N=484652)		Research quality pregnancies (total N=422091)		
	n	%	n	%	n	%	p-value*
Migraine	1740	0.19	323	0.07	1417	0.34	<0.001
Epilepsy	2854	0.31	776	0.16	2078	0.49	<0.001
Systemic Lupus Erythematosus	752	0.08	341	0.07	411	0.1	<0.001
Rheumatoid arthritis	2112	0.23	953	0.20	1159	0.27	<0.001
Depression	155618	17.16	72640	14.99	82978	19.66	<0.001
Anxiety	105641	11.65	50771	10.48	54870	13	<0.001
Solid organ transplant	147	0.02	66	0.01	81	0.02	0.038
Chronic renal failure	895	0.1	232	0.05	663	0.16	<0.001
Chronic pelvic pain	13178	1.45	6163	1.27	7015	1.66	<0.001
Fibromyalgia	2174	0.24	919	0.19	1255	0.3	<0.001
Chronic pain requiring prescription only medication	19948	2.2	5392	1.11	14556	3.45	<0.001
Irritable bowel syndrome	8137	0.9	3194	0.66	4943	1.17	<0.001
Myalgic encephalomyelitis	250	0.03	106	0.02	144	0.03	<0.001
Thromboembolism	4429	0.49	2246	0.46	2183	0.52	<0.001
Eczema	469	0.05	110	0.02	359	0.09	<0.001
Psoriasis	163	0.02	34	0.01	129	0.03	<0.001
Conditions with a decreased prevalence among research quality pregnancies							
Cystic fibrosis	104	0.01	42	0.01	62	0.01	0.008
Cirrhosis and liver failure	370	0.04	229	0.05	141	0.03	0.001
Leiomyoma	1358	0.15	822	0.17	536	0.13	<0.001
Schizophrenia	718	0.08	454	0.09	264	0.06	<0.001
Bipolar disorder	1886	0.21	1154	0.24	732	0.17	<0.001
Psychosis	296	0.03	175	0.04	121	0.03	0.05
Personality disorder	3773	0.42	2410	0.5	1363	0.32	<0.001
Learning disability	1947	0.21	1188	0.25	759	0.18	<0.001
Autism spectrum disorder	395	0.04	265	0.05	130	0.03	<0.001
HIV	487	0.05	311	0.06	176	0.04	<0.001
Thalassemia	2157	0.24	1218	0.25	939	0.22	0.005
Sickle cell anaemia	67	0.01	48	0.01	19	0.004	0.003

**Chi-squared test for differences in proportion comparing research quality pregnancies and non-research quality pregnancies*

Figure B1. Flow diagram of stage 1 data management (management of overlapping pregnancy episodes)

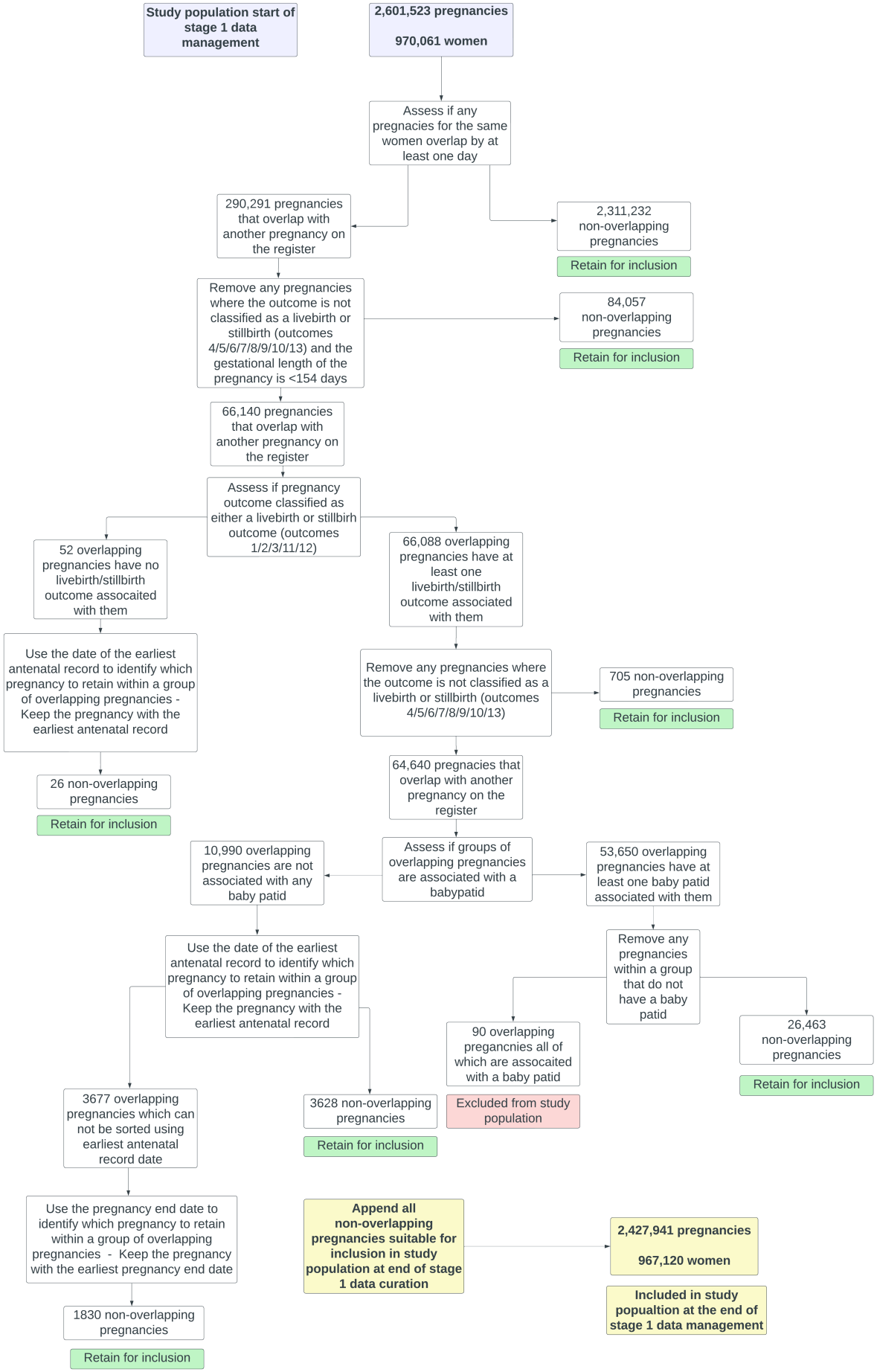


Figure B2. Flow diagram of stage 2 of data management (identification of the study population based on pregnancy outcome, gestational length, and study period parameters)

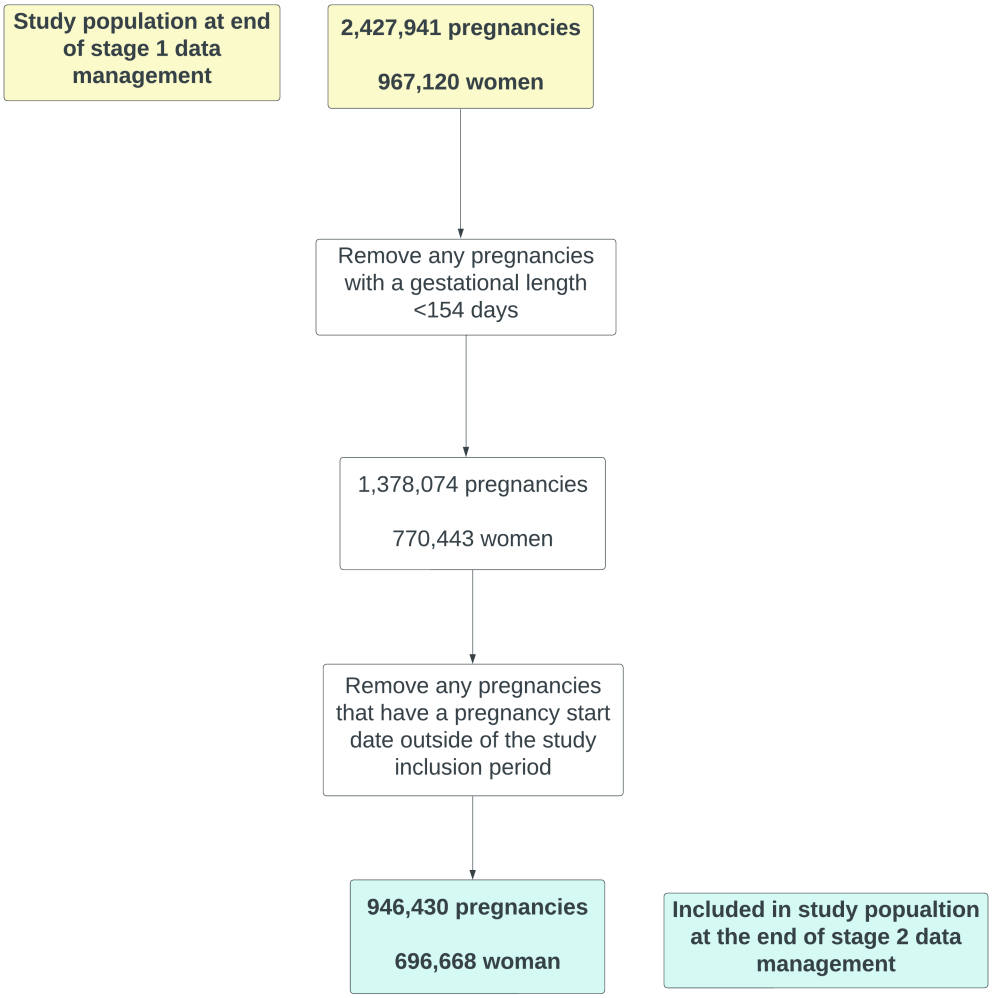


Figure B3. Flow diagram of stage 3 of data management (management of pregnancy episodes with improbable inter-pregnancy interval)

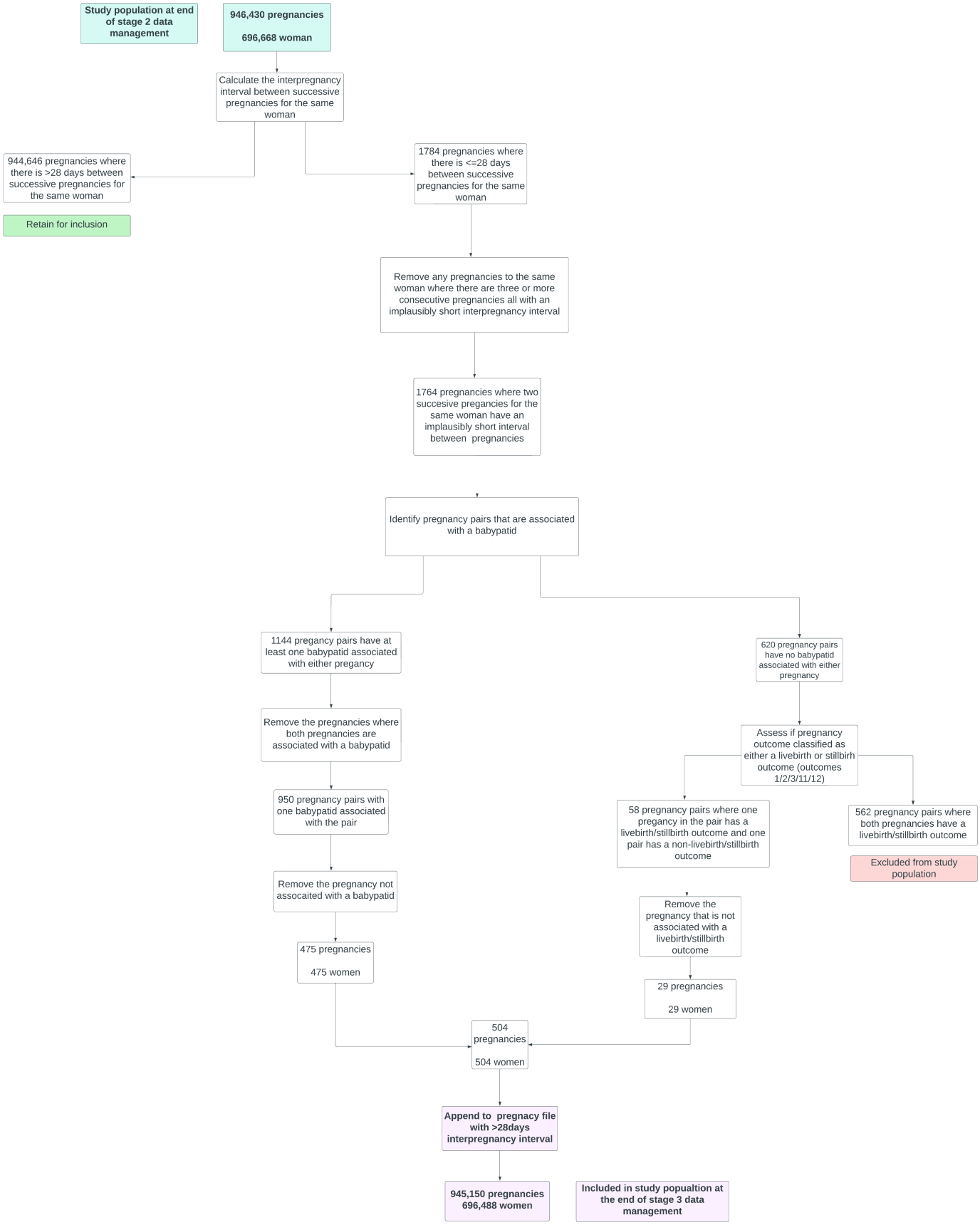


Figure B4. Flow diagram of stage 4 of data management (identification of study population using maternal age and minimum follow-up time parameters)

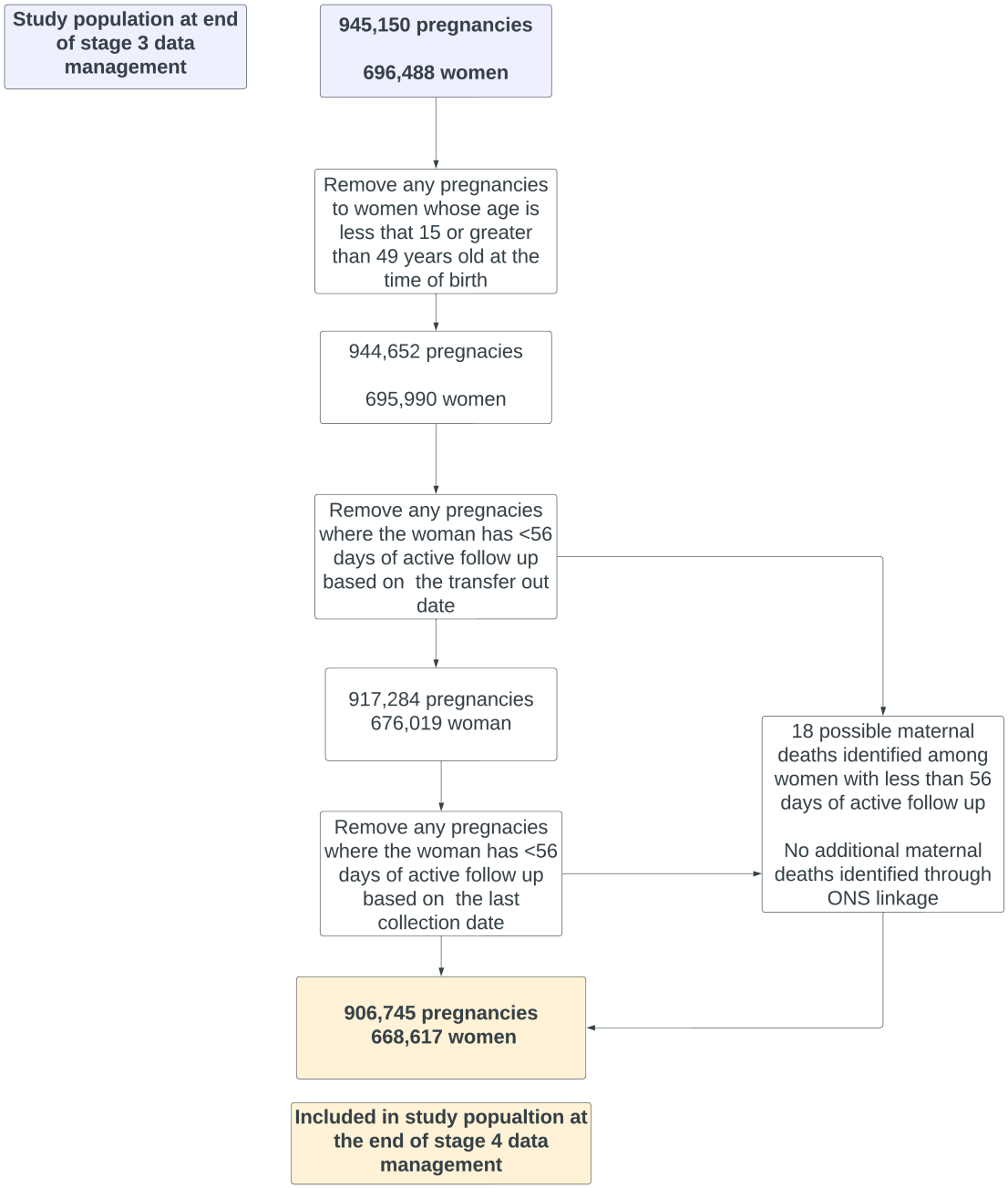
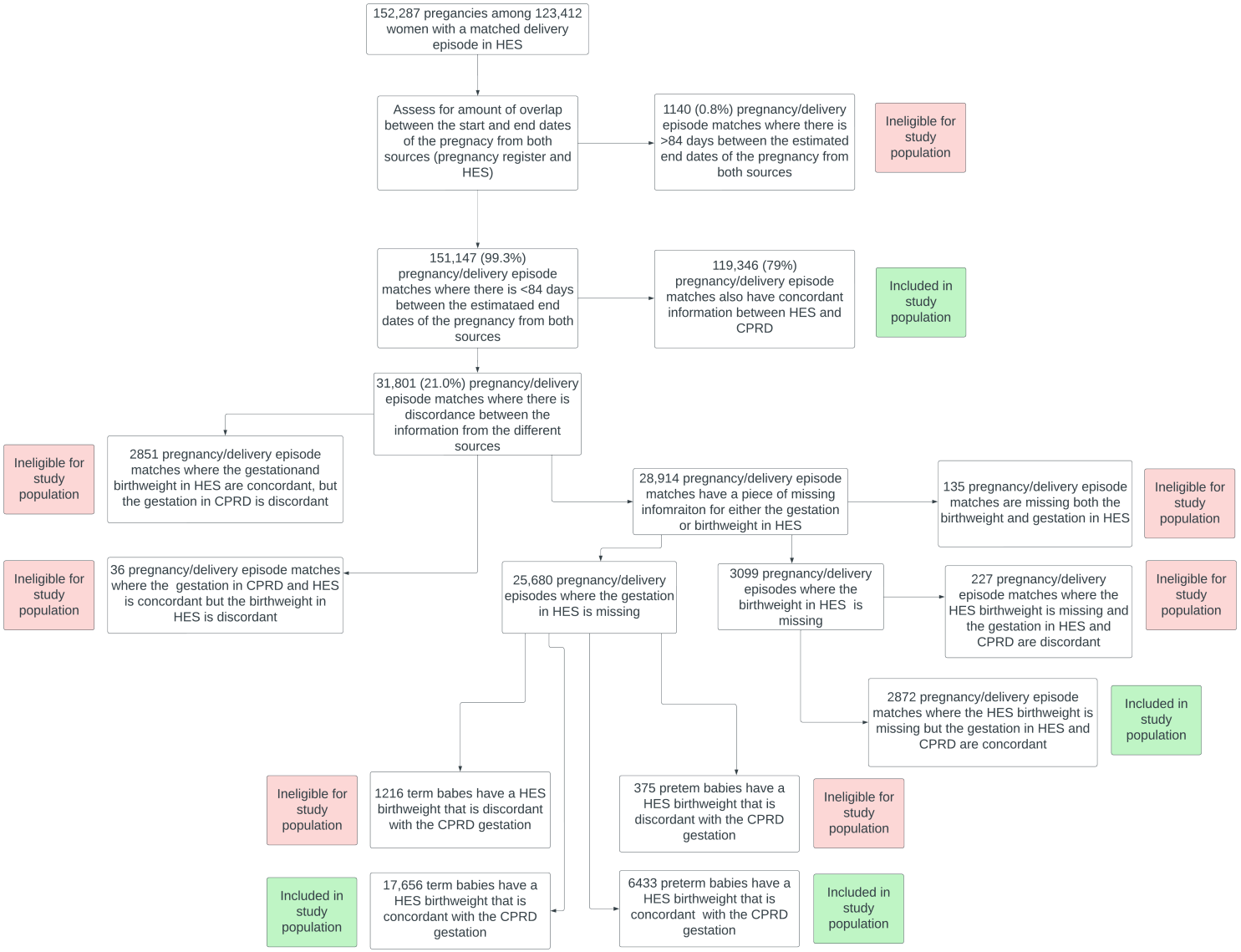


Figure B5. Flow diagram of the validation of the quality of matching process



Appendix C

Table C1. Social and demographic characteristics of the study population presented as a per woman analysis by MLTC status

Social and demographic characteristics	All pregnancies in study population total n=331517		Pregnancies among non-MLTC women total n=279192		Pregnancies among MLTC women total n=52325		Chi-squared test for differences in proportion**
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	
Maternal Age (n with data=331517)							
Less than 20 years	17144	5.2	16140	5.8	1004	1.9	<0.001
20- 34 years	240015	72.4	203447	72.9	36568	69.9	
35-39 years	59104	17.8	47924	17.2	11180	21.4	
More than 40 years	15254	4.6	11681	4.2	3573	6.8	
Smoking status (n with data=314253)							
Current smoker	81272	25.9	63775	24.2	17497	34.5	<0.001
Ex-Smoker	49898	15.9	39930	15.2	9968	19.6	
Non-smoker	183083	58.3	159797	60.6	23286	45.9	
Missing data (as a proportion of total n)	*17264*	*5.21*	*15690*	*5.6*	*1574*	*3.0*	
BMI category (n with data=243898)							
Underweight	9019	3.7	7469	3.7	1550	3.7	<0.001
Healthy Weight	124606	51.1	106233	52.7	18373	43.3	
Overweight	63121	25.9	52158	25.9	10963	25.9	
Obese	47145	19.3	35645	17.7	11507	27.1	
Missing data (as a proportion of total n)	*87619*	*26.43*	*77687*	*27.8*	*9932*	*19.0*	
Ethnicity (n with data=237165)							
White	210270	88.7	174421	87.7	35849	93.5	<0.001
Black/Black British	6216	2.6	5678	2.9	538	1.4	
Asian/Asian British	12936	5.5	11699	5.9	1237	3.2	
Mixed	2523	1.1	2189	1.1	334	0.9	
Other	5220	2.2	4826	2.4	394	1.0	
Missing data (as a proportion of total n)	*94352*	*28.5*	*80379*	*28.8*	*13973*	*26.7*	

Table C1. (continued) Social and demographic characteristics of the study population presented as a per woman analysis by MLTC status

Social and demographic characteristics	All pregnancies in study population total n=331517		Pregnancies among non-MLTC women total n=279192		Pregnancies among MLTC women total n=52325		Chi-squared test for differences in proportion**
	n	%	n	%	n	% (	
IMD Quintile (n with data=147421)							
1 (Most affluent)	29770	20.2	25477	20.6	4239	18.2	<0.001
2	28827	19.6	24412	19.7	4415	18.7	
3	29800	20.2	25034	20.2	4766	20.2	
4	28799	19.5	24018	19.4	4781	20.3	
5 (Most deprived)	30225	20.5	24870	20.1	5355	22.7	
*Missing data (as a proportion of total n)**	*40945*	*21.74*	*34526*	*21.8*	*6419*	*21.4*	

** IMD quintile only available for patients registered at English practices, total n =188366.*

*** Comparison of pregnancies among MLTC women and pregnancies among non-MLTC women*

Table C2: Prevalence of MLTC by year of study directly standardised for maternal age using the age structure in 2007 as the reference population

Age Group	Characteristic	Year of Study										
		2007	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
15 to 19 years	Estimate of population	2630	2605	2395	2248	1996	1745	1426	1148	913	772	696
	Number with MLTC	149	137	139	134	109	120	109	72	65	56	44
	Crude rate (per 100000 persons)	5565.4	5259.1	5803.8	5960.9	5060.9	6867.8	7643.8	6271.8	7119.4	7253.9	4540.8
	Age-specific rate (per 100000 standard population)	-	315.54	348.2	357.7	303.7	412.1	458.6	376.3	427.2	435.2	272.4
20 – 34 years	Estimate of population	32487	33194	34028	33910	33713	31601	29179	25558	21766	18924	17238
	Number with MLTC	4612	4879	4945	5712	5382	5181	4759	4363	3755	3372	3144
	Crude rate (per 100000 persons)	14196.4	14698.4	14532.1	16844.6	15964.2	16395.1	16309.7	17071	17251.7	17817.6	18238.8
	Age-specific rate (per 100000 standard population)	-	10435.6	10317.8	11959.7	11334.6	11640.5	11579.9	12120.4	12248.7	12650.5	12949
35-39 years	Estimate of population	8594	8584	8579	8332	7903	7624	7269	6617	5686	5090	4712
	Number with MLTC	1408	1486	1544	1620	1526	1441	1440	1341	1143	1087	927
	Crude rate (per 100000 persons)	16383.5	17311.3	17997.4	19443.1	19309.1	18900.8	19810.2	20266	20102	21355.6	19673.2
	Age-specific rate (per 100000 standard population)	-	3289.1	3419.5	3694.2	3668.7	3591.2	3763.9	3850.5	3819.4	4057.6	3737.9

Table C2. (continued) Prevalence of MLTC by year of study directly standardised for maternal age using the age structure in 2007 as the reference population

Age Group	Characteristic	Year of Study										
		2007	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**
40 – 49 years	Estimate of population	2044	2023	2121	2050	2159	2023	1835	1601	1361	1175	1044
	Number with MLTC	430	426	430	446	493	496	500	382	360	310	264
	Crude rate (per 100000 persons)	21037.2	21057.8	20273.5	21756.1	22834.6	24518	27248	23860.1	26451.1	26383	25287.4
	Age-specific rate (per 100000 standard population)	-	1052.9	1013.7	1087.8	1141.73	1225.9	1362.4	1193	1322.6	1319.2	1264.4
Total population	Estimate of population	45755	46406	47123	46540	45771	43993	39709	34924	29726	25961	23619
	Number with MLTC	6599	6928	7058	7372	7510	7238	6808	6158	5323	4825	4379
	Crude rate (per 100000 persons)	14422.5	14929.1	14977.8	15840.1	16407.7	16452.6	17144.7	17632.6	17906.9	18585.6	18540.2
Age standardised rate MLTC per 100000 standard population		-	15093.1	15099.2	17099.4	16468.7	16869.7	17164.8	17540.2	17817.9	18462.5	18223.65

Age standardisation using population age-distribution in 2007 as the reference:
<20 years 6%
20-34 years 71%
35-39 years 19%
40 + years 5%

Table C3. Prevalence of MLTC by region directly standardised for maternal age using the age structure in South East as the reference population

Age Group	Characteristic	Year of Study											
		North East	North West	Yorkshire and the Humber	East Midlands	West Midlands	East of England	London	South East	South West	Wales	Scotland	Northern Ireland
<20 years	Estimate of population	367	2019	304	346	1435	730	745	2582	1213	3084	4383	1366
	Number with MLTC	18	134	14	34	73	49	44	179	83	197	219	90
	Crude rate (per 100000 persons)	4904.6	6636.9	4605.3	9826.6	5087.1	6712.3	5906.0	6276.3	6482.6	6837.8	4996.6	6588.6
	Age-specific rate (per 100000 standard population)	147.1	199.2	138.2	294.8	152.6	201.4	177.2	-	194.5	205.1	149.9	197.7
20 – 34 years	Estimate of population	3894	29377	4832	4571	22746	15287	19778	52291	20279	45508	71683	21802
	Number with MLTC	689	5184	580	854	3580	2428	2228	8578	3464	7807	10571	3541
	Crude rate (per 100000 persons)	17693.9	17646.5	12003.3	18683	15739	15882.8	11265.0	16404.4	17081.7	17155.2	14746.9	16241.6
	Age-specific rate (per 100000 standard population)	12562.6	12529	8522.3	13264	11174.7	11276.8	7998.2	-	12128	12180.2	10470.3	11531.5

Age standardisation using population distribution in South East region as the reference:
<20 years 3%
20-34 years 71%
35-39 years 21%
40+ years 4%

Table C3. (continued) Prevalence of MLTC by region directly standardised for maternal age using the age structure in South East as the reference population

Age Group	Characteristic	Year of Study											
		North East	North West	Yorkshire and the Humber	East Midlands	West Midlands	East of England	London	South East	South West	Wales	Scotland	Northern Ireland
35-40 years	Estimate of population	675	6159	987	960	5099	4746	7973	14192	4552	9573	17840	5232
	Number with MLTC	133	1372	163	216	1043	910	1156	2761	998	2023	3201	987
	Crude rate (per 100000 persons)	19703.7	22276.3	16514.7	22500	27515.2	19174	14511.4	19454.6	21924.4	21132.4	17942.8	18864.7
	Age-specific rate (per 100000 reference population)	4137.8	4678	3468.1	4725	5778.2	4026.5	3047.3	-	4604	4437.8	3768	3961.6
40 – 49 years	Estimate of population	177	1553	200	222	1278	1180	2220	3823	1102	2249	4251	1181
	Number with MLTC	45	414	34	60	306	261	396	893	291	584	948	305
	Crude rate (per 100000 persons)	25423.7	26658.1	17000	27027	23943.7	22118.6	17837.8	23358.6	26406.5	25967.1	22300.6	25825.6
	Age-specific rate (per 100000 standard population)	1016.9	1066.3	680	1081.1	957.7	884.7	713.5	-	1056.3	1038.7	892	1033
Total population	Estimate of population	5113	39108	5973	6099	30558	21943	30716	73888	27146	60414	98157	29583
	Number with MLTC	885	7104	791	1164	5002	3648	3884	12411	4836	10611	14939	4923
	Crude rate (per 100000 persons)	17308.8	18165.1	13242.9	19085.1	16368.9	16624.9	12644.9	16797	17814.8	17563.8	15219.5	16641.3
Age standardised rate MLTC per 100000 standard population (95% CI)		17864.4	18472.5	12808.6	19364.8	18063.2	16389.4	11935.9	-	17982.7	17861.8	15280.2	16723.8

Appendix D

Table D1. Pregnancy and birth characteristics of the study population as a per woman analysis for all pregnancies and by MLTC status

Pregnancy and birth characteristics	**Pregnancies to all women in the study population** **total n=121211**		**Pregnancies among non-MLTC women** **total n=101779**		**Pregnancies among MLTC women** **total n=19432**		Chi-squared test for differences in proportion** p-value
	n	%	n	%	n	%	
Parity (n with data=121211)							
Primiparous	60374	49.8	52318	51.4	8056	41.5	<0.001
Multiparous	60837	50.2	49461	48.6	11376	58.5	
Previous caesarean birth for multiparous women (n with data=60837)							
No	50302	82.7	40957	82.8	9345	82.2	0.093
Yes	10535	17.3	8504	17.2	2031	17.9	
Booking gestation (n with data=94359)							
Booked at <10+0 weeks gestation	36495	38.7	29916	37.8	6579	43.1	<0.001
Booked at > 10+0 weeks gestation	57864	61.3	49479	62.12	8692	56.9	
Missing (as a proportion of total n)	*26852*	*22.2*	*22691*	*22.3*	*4161*	*21.4*	
Obstetric co-morbidity in pregnancy (n with data=121211)							
No	98045	80.9	82762	81.3	15283	78.7	<0.001
Yes	23166	19.1	19017	18.7	4149	21.3	
Onset of labour method for women with a trial of vaginal birth (n with data=101856)							
Spontaneous onset of labour	74811	73.5	64316	74.5	10549	67.5	<0.001
Induction of labour	27045	26.6	21984	25.5	5061	32.5	
*Missing (as a proportion of total n for women with a trial of vaginal birth)**	*6626*	*6.1*	*5396*	*5.9*	*1227*	*7.3*	
Mode of birth (n with data=118130)							
Vaginal birth	73313	62.1	61976	62.5	11337	59.8	<0.001
Assisted vaginal birth (including breech)	15899	13.5	13713	13.8	2186	11.5	
Elective caesarean birth	12732	10.8	10083	10.2	2649	14.0	
Emergency caesarean birth	16186	13.7	13410	13.5	2776	14.7	
Missing (as a proportion of total n)	*3081*	*2.5*	*2597*	*2.6*	*484*	*2.5*	

Table D1. (continued) Pregnancy and birth characteristics of the study population as a per woman analysis for all pregnancies and by MLTC status

Pregnancy and birth characteristics	**Pregnancies to all women in the study population total n=121211**		**Pregnancies among non-MLTC women total n=101779**		**Pregnancies among MLTC women total n=19432**		Chi-squared test for differences in proportion**
	n	%	n	%	n	%	p-value
Anaesthetic intervention at birth (n with data=115676)							
No anaesthetic/local anaesthetic	65629	56.7	55788	57.5	9841	53.0	<0.001
Regional anaesthetic	14904	36.2	34737	35.8	7167	38.6	
General anaesthetic	8143	7.0	6567	6.8	1576	8.5	
Missing (as a proportion of total n)	*5535*	*4.6*	*4687*	*4.6*	*848*	*4.4*	
Gestation at birth (n with data=121211)							
Birth at less than 37+0 weeks gestation	5630	4.6	4380	4.3	1250	6.4	<0.001
Birth at 37+0 weeks gestation and above	115581	95.4	97399	95.7	18182	93.6	
Birthweight less than the 10th centile for sex and gestation at birth (n with data=118863)							
No	107561	90.5	90441	90.7	17120	89.5	<0.001
Yes	11307	9.5	9306	9.3	2001	10.5	
Missing (as a proportion of total n)	*2343*	*1.9*	*2032*	*2.0*	*311*	*1.6*	
Birthweight less than the 3rd centile for sex and gestation at birth (n with data=118868)							
No	115017	96.8	96615	96.9	18402	96.2	<0.001
Yes	3851	3.2	3132	3.1	719	3.8	
Missing (as a proportion of total n)	*2343*	*1.9*	*2032*	*2.0*	*311*	*1.6*	
Maternal admission to critical care (n with data=121211)							
No	120704	99.6	101391	99.6	19313	99.4	<0.001
Yes	507	0.4	388	0.4	119	0.6	

** total n =108479, women coded as giving birth by elective caesarean section excluded from this group*

*** Comparison of MLTC women and non-MLTC women*

Table D2. Proportions of births and ongoing pregnancies occurring across six different gestational timeframes based on MLTC status

Gestational timeframe	Proportion of ongoing pregnancies				Proportion of pregnancies where the woman has given birth				Chi-squared test for difference in proportion p-value*
	Non-MLTC women Total n=122070		MLTC women Total n=24237		Non-MLTC women Total n=122070		MLTC women Total n=24237		
	n	%	n	%	n	%	n	%	
22 to 27+6 weeks	121806	99.8	24174	99.7	264	0.2	63	0.3	0.189
22 to 31+6 weeks	121227	99.3	23993	99.0	843	0.7	244	1.0	<0.001
22 to 36+6 weeks	116931	95.8	22720	93.7	5139	4.2	1517	6.3	<0.001
22 to 38+6 weeks	98001	80.3	18049	74.5	24069	19.7	6188	25.5	<0.001
22 to 40+6 weeks	21398	17.5	3464	14.3	100672	82.5	20773	85.7	<0.001
22 to 41+6 weeks	3257	2.7	508	2.1	118813	97.3	23729	97.9	<0.001

**Comparison of non-MLTC women and MLTC women for the proportion of pregnancies where the woman has given birth*

Table D3. Multivariable regression models investigating the association between MLTC and severe adverse maternal and perinatal outcomes

Severe maternal morbidity	**Model C base model** Crude HR (95% CI) Total n=105819	p-value	**Model C adjusted model [1]** Adjusted HR (95% CI) Total n=105819	p-value	**Model D base model** Crude HR (95% CI) Total n=113931	p-value	**Model D adjusted model [2]** Adjusted HR (95% CI) Total n=113931	p-value
All MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
MLTC	1.63 (1.46-1.82)	<0.001	1.58 (1.41-1.77)	<0.001	1.62 (1.45-1.81)	<0.001	1.66 (1.48-1.86)	<0.001
Complexity of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
2 conditions MLTC	1.38 (1.21-1.59)	<0.001	1.36 (1.18-1.57)	<0.001	1.44 (1.26-1.65)	<0.001	1.47 (1.29-1.69)	<0.001
3+ conditions MLTC	2.17 (1.85-2.54)	<0.001	2.07 (1.76-2.43)	<0.001	2.04 (1.73-2.41)	<0.001	2.08 (1.76-2.46)	<0.001
Type of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
Physical health MLTC	2.15 (1.71-2.7)	<0.001	2.01 (1.59-2.51)	<0.001	2.1 (1.67-2.64)	<0.001	2.05 (1.63-2.58)	<0.001
Mental health MLTC	1.13 (0.91-1.4)	0.248	1.15 (0.92-1.41)	0.216	1.17 (0.95-1.44)	0.138	1.21 (0.98-1.49)	0.076
Mixed MLTC	1.78 (1.55-2.03)	<0.001	1.71 (1.48-1.97)	<0.001	1.77 (1.54-2.03)	<0.001	1.81 (1.57-2.08)	<0.001
Stillbirth	**Model C base model** Crude HR (95% CI) Total n=105782	p-value	**Model C adjusted model [1]** Adjusted HR (95% CI) Total n=105782	p-value	**Model D base model** Crude HR (95% CI) Total n=113891	p-value	**Model D adjusted model [2]** Adjusted HR (95% CI) Total n=113891	p-value
All MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
MLTC	1.23 (0.94-1.6)	0.128	1.13 (0.87-1.49)	0.352	1.13 (0.86-1.47)	0.389	1.08 (0.82-1.42)	0.582
Complexity of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
2 conditions MLTC	1.21 (0.88-1.65)	0.234	1.14 (0.83-1.56)	0.426	1.1 (0.80-1.51)	0.562	1.06 (0.77-1.46)	0.716
3+ conditions MLTC	1.27 (0.83-1.95)	0.272	1.14 (0.74-1.76)	0.560	1.19 (0.76-1.85)	0.448	1.12 (0.71-1.74)	0619
Type of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
Physical health MLTC	1.45 (0.81-2.6)	0.206	1.37 (0.76-2.47)	0.287	0.95 (0.47-1.92)	0.883	0.94 (0.47-1.9)	0.869
Mental health MLTC	1.03 (0.64-1.66)	0.917	0.97 (0.60-1.57)	0.9	1.08 (0.69-1.7)	0.744	1.03 (0.65-1.63)	0.909
Mixed MLTC	1.28 (0.92-1.79)	0.145	1.17 (0.83-1.63)	0.375	1.2 (0.85-1.69)	0.291	1.15 (0.81-1.62)	0.432

Table D3. (continued) Multivariable regression models investigating the association between MLTC and severe adverse maternal and perinatal outcomes

Neonatal death	**Model C base model** Crude HR (95% CI) Total n=105455	p-value	**Model C adjusted model [1]** Adjusted HR (95% CI) Total n=105455	p-value	**Model D base model** Crude HR (95% CI) Total n=113533	p-value	**Model D adjusted model [2]** Adjusted HR (95% CI) Total n=113533	p-value
All MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
MLTC	2.09 (1.3-3.36)	0.002	1.83 (1.13-2.97)	0.011	2.26 (4.45-3.52)	<0.001	2.2 (1.40-3.45)	0.001
Complexity of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
2 conditions MLTC	2.08 (1.21-3.59)	0.008	1.88 (1.08-3.29)	0.02	2.21 (1.32-3.69)	0.002	2.17 (1.28-3.66)	0.004
3+ conditions MLTC	2.12 (1.0-4.43)	0.05	1.72 (0.82-3.63)	0.153	2.37 (1.18-4.77)	0.016	2.25 (1.12-4.52)	0.022
Type of MLTC								
Non-MLTC (reference group)	1	-	1	-	1	-	1	-
Physical health MLTC	2.89 (1.15-7.22)	0.023	2.32 (0.94-5.7)	0.06	2.76 (1.11-6.87)	0.029	2.86 (1.08-6.63)	0.034
Mental health MLTC	1.9 (0.86-4.18)	0.11	1.8 (0.81-3.97)	0.147	1.76 (0.80-3.84)	0.158	1.17 (0.78-3.77)	0.18
Mixed MLTC	1.98 (1.08-3.64)	0.027	1.7 (0.93-3.1)	0.085	2.42 (1.40-4.19)	0.002	2.34 (1.36-4.03)	0.002

[1] Model C adjusted for maternal age, ethnicity, smoking status, socioeconomic status and maternal BMI

[2] Model D adjusted for maternal age, ethnicity, smoking status and socioeconomic status

Appendix E

Table E1. Multivariable regression models investigating the association between MLTC and maternal mental health outcomes for pregnancies with complete data for all potential confounding covariates

Acute psychosis	**Model C base model** Crude HR (95% CI) Total n=105819	p=value	**Model C adjusted model [1]** Adjusted HR (95% CI) Total n=105819	p=value
All MLTC				
Non-MLTC (reference group)	1	-	1	-
MLTC	5.61 (3.28-9.83)	<0.001	6.38 (3.62-11.23)	<0.001
Complexity of MLTC				
Non-MLTC (reference group)	1	-	1	-
2 conditions MLTC	6 (3.32 -0.84)	<0.001	6.74 (3.68-12.34)	<0.001
3+ conditions MLTC	4.88 (2.18-10.91)	<0.001	5.54 (2.43-12.65)	<0.001
Type of MLTC				
Non-MLTC (reference group)	1	-	1	-
Physical health MLTC	**		**	
Mental health MLTC	10.74 (5.73-20.11)	<0.001	13.89 (7.24-26.64)	<0.001
Mixed MLTC	4.26 (2.12-8.57)	<0.001	5.06 (2.46-10.39)	<0.001
Self-harm	**Model C base model** Crude HR (95% CI) Total n=105819	p=value	**Model C adjusted model [1]** Adjusted HR (95% CI) Total n=105819	p=value
All MLTC				
Non-MLTC (reference group)	1	-	1	-
MLTC	4.19 (3.3-5.33)	<0.001	4.02 (3.14-5.15)	<0.001
Complexity of MLTC				
Non-MLTC (reference group)	1	-	1	-
2 conditions MLTC	3.15 (2.35-4.23)	<0.001	3.06 (2.27-4.11)	<0.001
3+ conditions MLTC	6.43 (4.79-8.67)	<0.001	6.16 (4.53-8.36)	<0.001
Type of MLTC				
Non-MLTC (reference group)	1	-	1	-
Physical health MLTC	1.35 (0.6-3.06)	0.471	1.6 (0.7-3.62)	0.263
Mental health MLTC	4.79 (4.4-6.69)	<0.001	4.4 (3.13-6.19)	<0.001
Mixed MLTC	4.6 (3.49-6.09)	<0.001	4.36 (3.28-5.8)	<0.001

Table E1. (continued) Multivariable regression models investigating the association between MLTC and maternal mental health outcomes for pregnancies with complete data for all potential confounding covariates

Active postnatal CMHD	**Model C base model** Crude HR (95% CI) Total n=105819	p=value	**Model C adjusted model [1]** Adjusted HR (95% CI) Total n=105819	p=value
All MLTC				
Non-MLTC (reference group)	1	-	1	-
MLTC	4.24 (4.11-4.38)	<0.001	3.86 (3.73-3.99)	<0.001
Complexity of MLTC				
Non-MLTC (reference group)	1	-	1	-
2 conditions MLTC	3.66 (3.51-3.8)	<0.001	3.37 (3.24-3.5)	<0.001
3+ conditions MLTC	5.61 (5.37-5.86)	<0.001	5.01 (4.79-5.24)	<0.001
Type of MLTC				
Non-MLTC (reference group)	1	-	1	-
Physical health MLTC	1.09 (0.96-1.22)	0.182	1.13 (1.0-1.3)	0.053
Mental health MLTC	4.99 (4.77-5.23)	<0.001	4.46 (4.25-4.67)	<0.001
Mixed MLTC	4.77 (4.59-4.96)	<0.001	4.27 (4.1-4.43)	<0.001

[1] *Model C adjusted for maternal age, ethnicity, smoking status, socioeconomic status and maternal BMI*

**Hazards ratio not estimated due to no outcome events within strata

Table E2. Rate of active postnatal CMHD per 1000 years of person time based on different categorisations of MLTC and whether any pre-existing health conditions were physical or mental health conditions.

MLTC status and type of pre-existing health condition	Rate per 1000 years of person time (95% CI)
Non-MLTC, no health conditions	49.7 (48.3-51.1)
Non-MLTC, one physical health condition	64.3 (61.0-68.7)
Non-MLTC, one mental health condition	211.5 (205.6-217.6)
MLTC comprised of 2 conditions, physical health conditions only	83.0 (73.9-93.2)
MLTC comprised of 2 conditions, mental health conditions only	350.1 (337.3-363.2)
MLTC comprised of 2 conditions, mixed physical and mental health conditions	260.4 (249.2-272.1)
MLTC comprised of 3+ conditions, physical health conditions only	79.5 (59.1-106.8)
MLTC comprised of 3+ conditions, mental health conditions only	490.7 (433.7-555.1)
MLTC comprised of 3+ conditions, mixed physical and mental health conditions	425.8 (410.2-441.2)

Table E3. Rate of self-harm per 1000 years of person time based on different categorisations of MLTC and whether any pre-existing health conditions were physical or mental health conditions.

MLTC status and type of pre-existing health condition	Rate per 1000 years of person time (95% CI)
Non-MLTC, no health conditions	1.2 (1.0-1.5)
Non-MLTC, one physical health condition	1.2 (0.8-1.7)
Non-MLTC, one mental health condition	3.7 (3.0-4.6)
MLTC comprised of 2 conditions, physical health conditions only	1.6 (0.7-3.6)
MLTC comprised of 2 conditions, mental health conditions only	5.2 (3.9-6.9)
MLTC comprised of 2 conditions, mixed physical and mental health conditions	3.9 (2.7-5.5)
MLTC comprised of 3+ conditions, physical health conditions only	3.3 (0.8-13.3)
MLTC comprised of 3+ conditions, mental health conditions only	15.3 (8.2-28.4)
MLTC comprised of 3+ conditions, mixed physical and mental health conditions	7.3 (5.9-9.3)