Multimorbidity in pregnancy: Epidemiology and core outcome set

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Lay summary

What is the problem?

Women may live with two or more long-term conditions before getting pregnant. These can be both physical conditions (like diabetes or raised blood pressure), and mental health conditions (such as depression or anxiety). They may have to take several medications and see different health care professionals to manage their different health conditions. Recent studies show that women with two or more long-term conditions are more at risk of pregnancy complications, such as giving birth prematurely. However, there is not much information out there to help pregnant women and their health care professionals make informed decisions.

Researchers measure outcomes to know whether a new intervention works or how a health condition affects a person. If different studies measure different outcomes, then we cannot combine and compare the results. To address this, we need a core outcome set. This is a standard set of outcomes that are so important they should be reported in all studies for a given health condition. To make sure researchers are capturing outcomes that matter to stakeholders, core outcome sets should be developed with people living with the conditions and health care professionals.

What was done?

The first part of this thesis described how many pregnant women in the United Kingdom have two or more long-term conditions in 2018. It also described their sociodemographic and lifestyle characteristics. The study used anonymised routine health records in general practices and hospitals.

The second part of this thesis developed a core outcome set to guide future studies for pregnant women with two or more long-term conditions. This involved four steps. First, we looked at what types of outcomes have researchers been measuring. Second, we conducted focus groups

and asked stakeholders what outcomes were important to them. This created a long list of potential outcomes. Third, stakeholders completed surveys to choose which outcomes to include. Finally, stakeholders met to discuss which outcomes should be included in the final core outcome set. Stakeholders included women with two or more long-term conditions with experience of pregnancy or planning a pregnancy, their partners and health care professionals.

What were the findings?

One in five pregnant women had two or more long-term physical or mental health conditions in the United Kingdom in 2018. They were more likely to be older, had more previous pregnancies, smoked and had higher body weight. Amongst those with two or more long-term conditions, seven in ten had at least one mental health condition.

The final core outcome set included 11 core outcomes. The five maternal outcomes were: (i) maternal death, (ii) severe maternal morbidity (life threatening consequences of childbirth), (iii) change in existing long-term physical or mental health conditions, (iv) quality and experience of care and (v) development of new mental health conditions. The six child outcomes were: (i) survival of baby, (ii) gestational age at birth, (iii) neurodevelopmental conditions/impairment, (iv) quality of life, (v) birth weight, and (vi) separation of baby from mother for health care needs.

What does this mean?

Having two or more long-term conditions before pregnancy is very common in the United Kingdom. We next need to investigate the consequences of multiple long-term conditions for the pregnant women's health, pregnancy, and child. We also need to develop interventions and health services that will deliver optimal outcomes for these women and their babies. Future studies will be guided by the core outcome set developed in this thesis.

Abstract

Background: Women are increasingly entering pregnancy with two or more long-term physical or mental health conditions. This can impact on the outcomes for the pregnant women and her offspring. This thesis aims to (i) describe the epidemiology of multimorbidity in pregnancy in the United Kingdom (UK) and (ii) develop a core outcome set for studies of pregnant women with multimorbidity.

Methods: The epidemiological study used an observational study design utilising routine health records in the UK. This included primary care records (Clinical Practice Research Datalink [CPRD, UK] and Secure Anonymised Information Linkage [SAIL, Wales]); and secondary care records with linked community prescriptions (Scottish Morbidity Records [SMR]).The study population was pregnant women and the exposure was pre-existing multimorbidity (2 or more long-term conditions). Multimorbidity was operationalised by 79 long-term conditions selected by a multidisciplinary team. Logistic regression was performed to examine the association of maternal multimorbidity with sociodemographic factors.

The core outcome set development consisted of four stages: (i) systematic literature search, (ii) focus groups with stakeholders in the UK, (iii) international Delphi surveys, and (iv) virtual consensus meetings.

Results: Amongst women pregnant in 2018 in the UK, the prevalence of multimorbidity was 44.2% (95% CI 43.7–44.7%), 46.2% (45.6–46.8%) and 19.8% (18.8– 20.8%) in CPRD, SAIL and SMR respectively. When limited to health conditions that were active in the year before pregnancy, the prevalence of multimorbidity was still high (24.2% [23.8–24.6%], 23.5% [23.0–24.0%] and 17.0% [16.0 to 17.9%] in the respective datasets). Logistic regression showed that pregnant women with multimorbidity were more likely to be older (CPRD England, adjusted OR 1.81 [95% CI 1.04–3.17] 45–49 years vs 15–19 years), multigravid (1.68 [1.50–1.89]

gravidity ≥ five vs one), have raised body mass index (1.59 [1.44–1.76], body mass index 30+ vs body mass index 18.5–24.9) and smoked preconception (1.61 [1.46–1.77) vs non-smoker).

For the core outcome set development study, 26 studies were included in the systematic literature search (2017 to 2021) reporting 185 outcomes. Three virtual focus groups (n=22) were conducted from December 2021 to March 2022 in the United Kingdom. Thematic analysis of the focus groups added 28 outcomes. Two hundred and nine stakeholders completed the first Delphi survey. One hundred and sixteen stakeholders completed the second Delphi survey where 45 outcomes reached *Consensus In* (≥70% of all participants rating an outcome as *Critically Important*). After two rounds of consensus meetings (first meeting n=13, second meeting n=17), the final core outcome set included 11 outcomes: The five maternal outcomes were: maternal death, severe maternal morbidity, change in existing long-term conditions (physical and mental), quality and experience of care, and development of new mental health conditions. The six child outcomes were: survival of baby, gestational age at birth, neurodevelopmental conditions/impairment, quality of life, birth weight, and separation of baby from mother for health care needs.

Conclusion: Multimorbidity is highly prevalent in pregnant women in the United Kingdom. We developed a core outcome set to guide future studies for pregnant women with multimorbidity. The next step would be to quantify the association between maternal multimorbidity and outcomes for the women, the pregnancy, and their offspring.

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Alternative thesis format

This thesis is formatted in line with the University of Birmingham alternative thesis guide: https://intranet.birmingham.ac.uk/as/studentservices/graduateschool/documents/public/rsa/alternative-format-thesis-guidelines.pdf

Inclusivity statement

Where the words 'women', 'maternal', or 'mother' are used, these also refer to people who do not identify as women but have been pregnant or may be pregnant in the future.

List of publications, manuscripts and conferences

Published manuscripts

1. **Lee SI**, Azcoaga-Lorenzo A, Agrawal U, et al. Epidemiology of pre-existing multimorbidity in pregnant women in the UK in 2018: a population-based cross-sectional study. BMC Pregnancy and Childbirth. 2022;22(1):120.
2. **Lee SI**, Eastwood K-A, Moss N, et al. Protocol for the development of a core outcome set for studies of pregnant women with pre-existing multimorbidity. BMJ Open. 2021;11(10):e044919.
3. **Lee SI**, Hanley S, Vowles Z, et al. Key outcomes for reporting in studies of pregnant women with multiple long-term conditions and their children: a qualitative study. BMC Pregnancy and Childbirth. 2023; in print.

Manuscript in submission to peer reviewed journals

1. **Lee SI**, Hanley S, Vowles Z, et al. The development of a core outcome set for studies of pregnant women with multimorbidity. BMC Medicine; under review.

Other related manuscripts published during this PhD

1. **Lee SI**, Hope H, O'Reilly D, et al. Maternal and child outcomes for pregnant women with pre-existing multiple long-term conditions: protocol for an observational study in the UK. BMJ Open 2023;13(2):e068718. doi: 10.1136/bmjopen-2022-068718
2. Anand A, Phillips K, Subramanian A, **Lee SI**, et al; MuM-PreDiCT Group. Prevalence of polypharmacy in pregnancy: a systematic review. BMJ Open. 2023 Mar 6;13(3):e067585. doi: 10.1136/bmjopen-2022-067585.
3. Subramanian A, Azcoaga-Lorenzo A, Anand A, … **Lee SI**, et al; MuM-PreDiCT Group. Polypharmacy during pregnancy and associated risk factors: a retrospective

analysis of 577 medication exposures among 1.5 million pregnancies in the UK, 2000-2019. BMC Med. 2023 Jan 16;21(1):21. doi: 10.1186/s12916-022-02722-5.

4. Singh M, Crowe F, Thangaratinam S,… **Lee SI**, et al. Association of pregnancy complications/risk factors with the development of future long-term health conditions in women: overarching protocol for umbrella reviews. BMJ Open. 2022 Dec 29;12(12):e066476. doi: 10.1136/bmjopen-2022-066476.

Conference abstracts

1. **Lee SI**, Azcoaga-Lorenzo A, Agrawal U, et al. Epidemiology of pre-existing multimorbidity in pregnant women in the UK in 2018: a cross-sectional study. The Lancet. 2021;398(S7). Available from: https://doi.org/10.1016/S0140-6736(21)02550-2
2. **Lee SI**, Plachcinski R, Moss N, et al. Core outcomes for studies of pregnant women with multimorbidity: Clinician focus group. BJOG. 2022;129(S1):120. Available from: https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.15_17178

Oral presentations

1. UK Multiple Long Term Conditions Symposium 2022
2. UK Public Health Science Conference 2021, ***runner up prize***

Poster presentations

1. Society of Academic Primary Care South West Regional Meeting 2023, Birmingham
2. Royal College of Obstetricians and Gynaecologists World Congress 2022, London
3. MacDonald Obstetric Medicine Conference 2022, Birmingham
4. British Maternal and Fetal Medicine Society Conference 2022, Birmingham
5. Medical Research Council Midlands Early Career Researchers Posters 2022, Birmingham
6. Biochemical Society Early Career Life Scientists' Virtual Symposium 2021
7. West Midlands Academic Trainees Virtual Conference 2021

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List of abbreviations

aOR	Adjusted odds ratio
BMI	Body mass index
BNF	British national formulary
CDC	Centres for Disease Control and Prevention
CI	Confidence intervals
CINAHL	Cumulated Index to Nursing and Allied Health Literature
CKD	Chronic kidney disease
CMHD	Common mental health disorder
COMET	Core outcome measures in effectiveness trials
COS	Core outcome set
COSMIN	Consensus-based standards for the selection of health measurement instruments
COS-STAR	Core Outcome Set Standards for Reporting
CROWN	Core outcomes in women's and newborn health
CPRD	Clinical Practice Research Datalink
DM	Diabetes mellitus
EDS	Ehlers's Danlos syndrome
FG	Focus group
FGR	Fetal growth restriction
GORD	Gastroesophageal reflux disease
GP	General practitioner
HCP	Health care professionals
HELLP	Haemolysis, elevated liver enzymes and low platelets
HIC	Health informatics centre
HR	Hazard ratio
IAPT	Improving access to psychological therapies
IBS	Irritable bowel syndrome
ICD	International disease classification of disease
ICU	Intensive care unit
IMD	Index of multiple deprivation
IQR	Interquartile range
LGBTQ+	Lesbian, gay, bisexual, transgender, queer and others
MBRRACE-UK	Mothers and babies: Reducing risk through audits and confidential enquiries across the UK
MICE	Multiple imputation with chain equation
NCCHD	National Community Child Health Database
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NIHR	National Institute for Health and Care Research
NIMATS	Northern Ireland Maternity System
NMPA	National Maternal and Perinatal Audit
OPCS	Operating procedures codes
OR	Odds ratio
P	Partner
PCOS	Polycystic ovarian syndrome
PPI	Patient and public involvement

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PREM	Patient reported experience measures
PROM	Patient reported outcomes measures
PROMIS SFFAC102	Patient Reported Outcomes Measurement Information System Sexual Function and Satisfaction
QR	Quick response
Ref	Reference
RR	Relative risk
SAIL	Secure Anonymised Information Linkage
SCBU	Special care baby unit
SFGR	Severe fetal growth restriction
SMI	Severe mental illness
SMM	Severe maternal morbidity
SMR	Scottish Morbidity Records
SOP	Standard operating procedures
SPIRIT	Standard protocol items: Recommendations for interventional trials
UK	United Kingdom
USA	United States of America
VBAC	Vaginal birth after previous caesarean section
W	Women
WHOQoL-BREF	World Health Organization Quality of Life Brief Version

Chapter 1: Introduction

Chapter overview

This chapter will start with an introduction to multimorbidity and why this thesis focuses on multimorbidity in pregnancy. This is followed by an appraisal of the existing literature for the epidemiology of multimorbidity in pregnancy, and the rationale for a study based in the United Kingdom. The chapter then explores outcomes and guidelines for pregnant women with long-term conditions, to highlight future research need for pregnant women with multimorbidity. Finally, the chapter introduces the concept of core outcome set and outlines the need for a core outcome set for studies of pregnant women with multimorbidity.

1.1 Multimorbidity

What is multimorbidity?

Multimorbidity is defined as the co-existence of two or more conditions of long duration in a person, including: (i) physical non-communicable conditions; (ii) mental health conditions; or (iii) infectious conditions such as human immunodeficiency virus or hepatitis C.[1] Unlike the concept of comorbidity, multimorbidity does not focus on a primary index condition.[1] However the two terms are often used interchangeably in the literature.

In concordant multimorbidity, health conditions co-exist in a person due to common aetiology and may be managed with similar treatment.[1] Examples include coronary heart disease and cerebrovascular disease, with the common aetiology being hypertension.[1] In discordant multimorbidity, health conditions are unrelated and may require different management strategies, for example, mental and physical health conditions.[1]

Multimorbidity or multiple long-term conditions

The United Kingdom Taskforce on Multiple Conditions found the term 'multimorbidity' was not deemed acceptable by some people.[2] The term was perceived negatively, it suggests multimorbidity is a single condition and do not capture the complexities associated with living with multiple conditions.[2] The National Institute of Health and Care Research has moved towards using the term 'multiple long-term conditions' as it was better understood and preferred by patients, carers and the public.[3] This issue was also discussed by the MuM-PreDiCT parent and public involvement advisory group for research in multimorbidity in pregnancy, where the term 'two or more long-term conditions' was suggested at least for public facing study documents. However, 'multimorbidity' is still commonly used in the literature. Throughout this thesis, both terms will be used, with later studies using the term 'multiple long-term conditions', reflecting the shift in this field.

Challenges of multimorbidity

Current health care systems and guidelines are oriented around single health conditions.[4] To manage multiple long-term conditions in a holistic way requires generalist skills.[4] However the health care workforce is increasingly subspecialised.[4] Specialists are faced with the complexity of following multiple guidelines developed for single health conditions; patients with multimorbidity are faced with frequent and complex interactions with different health care services.[4 5] The consequences of these challenges include: reduced adherence to complex management regimes, increased risk of drug interactions and adverse effects with polypharmacy and increased susceptibility to failures of care delivery.[5]

Epidemiology of multimorbidity

United Kingdom

In Scotland, Barnett et al's seminal paper reported a 23% point prevalence of multimorbidity in patients of all ages in 2007.[6] This study covered a third of the Scottish population using primary care data and defined multimorbidity with 40 conditions.[6] Despite the wide coverage, the findings may not be applicable to other nations in the United Kingdom due to the different sociodemographic characteristics of the population, especially to more ethnically diverse areas. In addition, more contemporaneous data is needed.

In England, the point prevalence of multimorbidity was 27% for adults aged ≥18 years in 2012.[7] This study used primary care routine health data and defined multimorbidity with 36 conditions.[7] A more recent study, also using primary care data for adults in England, reported a rise of multimorbidity from 31% in 2004 to 53% in 2019.[8] The higher prevalence is likely due to the study defining multimorbidity with 211 conditions.[8]

International

Two recent systematic reviews reported on the prevalence of multimorbidity globally. Ho et al (2022) searched nine databases and included 193 studies. Prevalence of multimorbidity in all ages ranged from 2.7% to 95.6%, with a pooled prevalence of 42.4% (95% confidence intervals [CI] 38.9% to 46.0%).[9] Chowdhury et al (2023) searched four databases and included 126 studies, but limited the population to adults in community settings.[10] The prevalence of multimorbidity ranged from 4.0% to 92.8%, the pooled prevalence was 37.2% (95% CI 34.9% to 39.4%).[10] Both reviews reported high levels of heterogeneity, with I^2 around 99% and large ranges in the reported prevalence. Ho et al additionally conducted meta-regression which showed that participants' mean age and the number of conditions used to define multimorbidity

accounted for 47.8% of heterogeneity in the prevalence.[9] The latter will be discussed further in Chapter 1.3.

Risk factors

Risk factors for multimorbidity include advancing age, socioeconomic deprivation and being female.[6 8 11 12] Globally, the incidence and prevalence of multimorbidity are increasing due to an ageing world population, increase in obesity and urbanisation.[8 13-15] This is significant because systematic reviews have demonstrated that multimorbidity is associated with poorer quality of life, higher mortality and higher health care cost and utilisation.[16-18]

Multimorbidity and quality of life

Makovski et al's systematic review on multimorbidity and quality of life comprehensively searched four databases and meta-analysed 39 studies.[17] The mean decrease in quality of life for each additional long-term condition ranged from −1.55% (95% CI: −2.97% to − 0.13%) for the mental health component of the Short Form Health Surveys to −4.37% (95% CI: −7.13% to −1.61%) for World Health Organization Quality of Life Brief Version (WHOQoL-BREF) physical health domain.[17]

Multimorbidity and mortality

Nunes et al meta-analysed 26 studies and found that multimorbidity was associated with mortality in adults aged ≥60 years, with a hazard ratio (HR) of 1.44, 95% CI 1.34 to 1.55.[16] A dose response relationship was observed.[16] With every additional long-term condition, the hazard of death increased by 20% (95% CI 1.10 to 1.30).[16] The risk of death (HR) was 1.73 (95% CI 1.41 to 2.13) and 2.72 (95% CI 1.81 to 4.08) for people with two and three or more conditions, respectively.[16] However, this review only searched Pubmed and may not have included all relevant studies. Only five studies included in the meta-analysis adjusted for confounders, therefore effect sizes may be biased.

Multimorbidity and health care cost and utilisation in the United Kingdom

Using routine health records, Cassell et al's studied health care utilisation in adults with multimorbidity in England over a four year period (2012-2015).[7] Just over half of general practice consultations (53%) and hospital admissions (56%) were attributable to adults with multimorbidity, despite constituting a quarter of the study sample.[7] However, all health care utilisations were weighted equally, the authors commented that additional analysis on length of consultations and hospitalisations would provide a more comprehensive picture.[7]

Soley-Bori et al's systematic review assessed the impact of multimorbidity on health care costs and utilisation in the United Kingdom.[18] The review included 17 studies and found that multimorbidity increased total health care costs, hospital costs, care transition costs, primary care use, dental care use, emergency department use and hospitalisations.[18] The largest estimate was observed in patients with ≥four physical conditions: the odds for unplanned, potentially preventable hospitalisations was 14 times that of patients with no physical conditions (odds ratio [OR] 14.38 [95% CI 11.87 to 17.43].[18]

Although Soley-Bori et al's review only searched one database (Medline), this was complemented with searches of the grey literature and a bidirectional citation searching to completion method. The latter involved screening the references and citations of included studies, with the advantage of identifying additional parallel topics that are relevant to the research question.[19]

Key approaches for managing multimorbidity

A multimorbidity study that examined 28 health conditions using hospital admission data found over 60000 unique combinations of health conditions.[20] This illustrates the magnitude of heterogeneity in multimorbidity and the challenges of establishing an all-encompassing guideline. Instead, the English National Institute for Health and Care Excellence guideline

focused on the general approach to managing multimorbidity, with emphasis on holistic, personalised and coordinated care.[21]

Research priorities for multimorbidity

Given its increasing global burden, multimorbidity has been recognised as a priority for global research by The Academy of Medical Sciences.[1] In their report, the working group's research priorities were understanding the epidemiology of multimorbidity and evaluating the optimal health care systems for people with multimorbidity. However, given the latter would be a huge undertaking, the expert group suggested focusing on discrete populations such as pregnant women.[22]

The report also identified an evidence gap in multimorbidity in younger adults.[1] Although multimorbidity is often described in the older population, it can also affect younger adults and women of reproductive age. A United Kingdom primary care-based study found a higher absolute number of people with multimorbidity in those aged <65 years old, despite a higher rate in those aged >65 years.[6]

Why should we focus on pregnant women?

Pregnant women are under-served and under-researched in clinical research.[23] A 2021 United Kingdom report highlighted the absence of drug development trials in pregnant women.[24] A clear example is the exclusion of pregnant women from most Covid-19 clinical trials during the pandemic.[25] The following subchapters will outline the rationale for studying multimorbidity in pregnant women.

1.2 Multimorbidity in pregnancy

General pregnancy trends

In England and Wales, there has been a downward trend in the number of conceptions and conception rate over the past decade. The number of conceptions for women of all ages decreased from over 909109 conceptions in 2011 to 824983 conceptions in 2021.[26] The conception rate for women aged 15 to 44 years decreased from 80.4 conceptions per 1,000 women in 2011 to 71.5 per 1,000 women in 2021.[26] The Office for National Statistics used birth registration and abortion notification data to produce these statistics.[26] The legal requirement to register births in the United Kingdom means birth statistics from the Office for National Statistics are considered the gold standard. However, pregnancies that ended with miscarriages or illegal abortions are not captured, and therefore the true number of conceptions would be underestimated.[26]

Globally, the total fertility rates (the average number of children born to a female over their reproductive life span if exposed to current age-specific fertility rates) halved from 4.7 live births in 1950 to 2.4 live births in 2017.[27] Despite substantial variation across countries, total fertility rates decreased across all 195 countries included in this Global Burden of Disease study.[27] Nevertheless, annual live births globally have remained stable between 133.5 million and 141.7 million per year over the last 25 years.[27]

Increase in maternal age

In England and Wales, the standardised mean age of mothers who gave birth increased from 26.7 years in 1970 to 30.9 years in 2021.[28] The highest number of conception (249073) and conception rates (116.2 per 1000 women) were observed in women aged 30 to 34 years in 2021 in England and Wales.[26] In the last decade (2011-2021), women aged 35 to 39 years and >40

years were the only age groups with an increase in conception rate (increase by 4% and 20% respectively).[26]

Increase in maternal obesity

In Northern Ireland, a population-based study reported that maternal obesity (body mass index ≥30kg/m^2 measured at ≤16 weeks gestation) increased from 19% in 2010 to 23% in 2017 for singleton pregnancies.[29] Using nationally representative data from 34 English maternity units, Heslehurst et al found that first trimester maternal obesity increased from 8% in 1989 to 16% in 2007.[30] More recent data from the English Maternity Services Dataset showed that 18% of women were obese at the time of booking in 2017.[31] Although this dataset has national coverage, it is relatively new and subjected to data flow issues from providers.[31] In addition, 19% of the records had missing data for maternal body mass index.[31]

Increase in maternal long-term conditions

In a Danish population based study, the prevalence of maternal long-term conditions increased from 3.71% in 1989 to 15.76% in 2013.[32] The prevalence of maternal long-term conditions was ascertained as having at least one of 23 categories of non-malignant and non-acute major health conditions before childbirth.[32] The most prevalent health conditions were chronic lung disease (including asthma, 1.73%), thyroid disorders (1.50%) and anxiety and personality disorders (1.33%).[32]

This study used the Danish birth registry linked to the national patient registry (inpatient, outpatient and emergency contacts).[32] This means pregnancies that do not lead to a birth would not be captured. As some long-term conditions increase the risk of miscarriage,[33 34] the reported prevalence of maternal long-term conditions may be underestimated. The secondary care-based dataset would also not capture health conditions that were managed conservatively in primary

care. The findings with data up to 2013 may not be generalisable to present day United Kingdom, which has a population with different sociodemographic characteristics and a different health care system. As the prevalence was aggregated as one or more long-term conditions, data for multimorbidity (two or more long-term conditions) in pregnancy was not available. However, the observed increase in prevalence of single long-term condition is likely to translate to an increase in multimorbidity in pregnancy and be applicable to high income countries.

Increasing importance of multimorbidity in pregnancy

The previous sections demonstrated that despite a downward trend in the overall numbers and rates of pregnancy, pregnancy rates are increasing in older women in England and Wales. With rising maternal age, pre-pregnancy obesity and prevalence of long-term conditions, multimorbidity in pregnancy is becoming increasingly important.[35-38] Both advanced maternal age and obesity are known independent risk factors for adverse pregnancy outcomes;[38 39] multimorbidity is likely to have an additional impact. The next section will look at existing literature describing the epidemiology of multimorbidity in pregnancy.

Epidemiology of multimorbidity in pregnancy

The prevalence of maternal multimorbidity (two or more long-term conditions) ranged from 0.5% of births to 27% of reproductive aged women (Table 1.1).[40 41] The number of eligible conditions used to define multimorbidity ranged from seven to 25.[42 43] One study based in a tertiary hospital in the United Kingdom reported 21% of women who gave birth had two or more medical conditions.[44]

Table 1.1: Summary of selected studies reporting the prevalence of multimorbidity in pregnancy

Article	Country	Study design	Setting	Data source	Number of eligible conditions to define multimorbidity (2+ conditions)	Prevalence of multimorbidity
1. Kersten 2014[45]	Germany	Observational	Population based, birth registration	Self-reported and medical records	-	8% women who gave birth
2. Cunningham 2017[46]	United States	Observational	Hospital	Medical records	10	8% women with low-risk pregnancy who gave birth
3. Admon 2017[40] Admon 2018[47]	United States	Observational	Hospital	Medical records	8	0.5% births in years 2005-2006, 0.8% births in years 2013 to 2014
4. D'Arcy 2019[44]	United Kingdom	Observational	Hospital	Medical records	-	21% women who gave birth
5. Brown 2020[43]	United States	Observational	Hospital	Medical records	25 conditions from 29 Elixhauser comorbidity measures	14% births
6. Field 2020[48]	United States	Observational	Hospital	Medical records	15	24% women who gave birth
7. Puri 2020[42]	India	Observational	Population based	National survey: self-reported and measured diagnosis	7	3.5% women of reproductive age
8. Harris 2021[41]	Australia	Observational	Population based, hospital	Self-reported and administrative data	10	27% and 18% of women of reproductive age from the 1973-78 and 1989-95 cohorts respectively in 2020
9. Pati 2022[49]	India	Observational	Antenatal clinics	Self-reported	18	15% pregnant women
10. Stanhope 2022[50]	United States	Observational	Hospital	Medical records	11	10% births
11. Nakanishi 2023[51]	Japan	Observational	Population based, community	Self-reported, medical records, interviews	23	6.3% pregnant women with singleton pregnancies and live births

Appraisal of current literature on the epidemiology of multimorbidity in pregnancy

Most of the studies were conducted in the United States, with only one conducted in the United Kingdom. This limits the applicability of study findings to maternity services in the United Kingdom given the different health care system and population characteristics. In addition, none of the studies used primary care records to ascertain maternal multimorbidity. This means health conditions that are managed in primary care and do not require hospital admission will not be captured.

Most of the studies used the number of births in hospital as the denominator, few studied pregnant women attending antenatal clinics. In hospital-based studies, women with pregnancy losses managed in the community may not be captured. Some long-term conditions can predispose women to miscarriages and for some women, termination of pregnancy may be necessary for medical reasons.[52 53] Therefore studies that only included pregnant women who have given birth may under-estimate the prevalence of maternal multimorbidity in pregnancy, compared to studies that included all pregnant women regardless of the pregnancy outcome.

Most of the studies used medical records as the data source for ascertaining maternal multimorbidity. This avoids misclassification and recall bias, limitations which self-reporting of medical history is susceptible to. However, observational studies using routinely collected data may not provide details on psychological and social morbidities, compared to cross sectional and prospective cohort studies that systematically administer measurement tools to capture these.

As observed in other multimorbidity studies, there are variations in how maternal multimorbidity is measured, especially in terms of what conditions are included. Previous studies have shown that the number of conditions used to define multimorbidity can impact on the prevalence of multimorbidity.[9] This will be discussed further in Chapter 1.3.

Rationale for an epidemiological study for this PhD thesis

Building upon existing literature, there is a clear need for a comprehensive descriptive study of multimorbidity in pregnancy in the United Kingdom. This will improve the understanding of how multimorbidity is distributed and which long-term conditions and combination of long-term conditions are most prevalent in pregnant women in the United Kingdom. This information will be useful for planning services for preconception care and long-term conditions management. The proposed study will also examine the utility of using primary care, secondary care, and community prescription data in studying multimorbidity in pregnancy.

1.3 Measuring multimorbidity

Challenges in measuring multimorbidity

A key issue in multimorbidity research is the huge variation in how multimorbidity is defined and measured.[1] Key considerations include: the minimum number of conditions used to define multimorbidity, counting individual conditions or categories of health conditions by body system, the list of conditions to be included (e.g. medical diagnoses, biopsychosocial factors such as socioeconomic factors and health behaviours) and using simple counts or weighted measures.[1 54] For instance, the English National Institute for Health and Care Excellence multimorbidity guidelines additionally considers symptom complexes (e.g. chronic pain), sensory impairment (e.g. sight or hearing loss), alcohol and substance misuse in defining multimorbidity.[21]

These issues can affect the measured prevalence of multimorbidity.[54] Methods that result in very high prevalence of multimorbidity may negate the utility of its measurement in planning health care resources.[54] Therefore some studies have used the concept of complex multimorbidity, defined as three or more conditions from three or more body systems.[8 54]

Number of conditions used to define multimorbidity

As observed in Ho et al's systematic review, the number of conditions included to measure multimorbidity ranged widely from two to 285 (median 17, interquartile range 11 to 23).[55] The prevalence of multimorbidity increases with the number of conditions included to measure it.[9] This dose response relationship was observed in Ho et al's systematic review.[9] The pooled multimorbidity prevalence for studies using <9 conditions was 31% compared to 88% in studies using ≥44 conditions to measure multimorbidity.[9]

MacRae et al investigated this impact using one routine health record dataset, by varying the number of conditions included to measure multimorbidity from two to 80.[56] The prevalence of

multimorbidity increased from 5% (when measured with two conditions) to 41% (when measured with 80 conditions).[56] Crucially a ceiling effect was observed with 52 conditions, where additional conditions had little impact on the prevalence.[56] The number of conditions required for the ceiling effect was higher in younger age group (71 for age <nine years compared to 29 for >80 years), and generally above 50 for the reproductive age.[56] Due to the large variation in prevalence depending on how multimorbidity was measured, the authors recommended using a standardised approach with existing condition lists.[56] However, existing condition lists are not specific to a pregnant population.

Multimorbidity indices

Stirland et al's systematic review identified 35 indices that measure multimorbidity beyond disease counts in a community setting.[57] The study recommends 12 multimorbidity indices for use in future research, based on exposure variables available (e.g. diagnoses or medications) and outcomes of interest (e.g. mortality, hospital admission, health care costs and quality of life).[57] Most importantly, the authors concluded that no single index can definitively measure multimorbidity in all settings, given the heterogeneity of research methodology in multimorbidity.[57]

Consensus on measuring multimorbidity

A recent international Delphi consensus study including professional and public panels addressed these uncertainties.[58] The consensus recommended that multimorbidity should be defined as the co-occurrence of two or more long-term conditions, individual conditions should be counted instead of categories by body systems and conditions that are downstream complications should be counted separately from the primary health condition (e.g. diabetic retinopathy and diabetes).[58] Simple count was preferred when measuring prevalence whilst weighted measures (multimorbidity indices) are preferred for outcome prediction.[58] Though

considered a useful concept, consensus on how complex multimorbidity should be measured was not reached.[58] The study reached consensus on 24 health conditions that should always be included, and 35 conditions that should usually be included in multimorbidity measures.[58]

Ho et al's international Delphi consensus study also recommended the following criteria when considering what conditions to include in defining multimorbidity: (i) conditions lasting 12 months or more; (ii) medical diagnoses; (iii) currently active; (iv) permanent in effect; (v) requiring current treatment, care or therapy; (vi) requiring surveillance; and (vii) remitting-relapsing conditions requiring ongoing treatment or care.[58]

Measuring multimorbidity in pregnancy

McCauley et al's systematic review described how and what different types of maternal multimorbidity were measured in low and middle income countries.[59] The review included physical, psychological and social morbidities (e.g., domestic violence, food insecurity) in its definition of maternal multimorbidity during pregnancy and after childbirth.[59] The most commonly reported physical, psychological and social morbidities were anaemia, human immunodeficiency virus infection, depression and domestic violence respectively.[59]

None of the included studies measured physical morbidities with validated questionnaires or international disease classifications.[59] Eighteen data collection tools were used to assess psychological and social morbidities, one example being the Edinburgh Postnatal Depression Score questionnaire.[59] It concluded that there was a lack of comprehensive and routine measurement of the burden of maternal multimorbidity and a lack of standardised measurement tools.[59]

Social risk factors in pregnant women

As outlined in Chapter 1.1, multimorbidity usually encompasses physical and mental health (psychological) conditions.[1] McCauley et al's systematic review additionally considered social

morbidities in conceptualising maternal multimorbidity in low-middle income countries, such as domestic violence and food insecurity.[59] In the 2020 MBRRACE national maternal mortality and morbidity review, many of the women who died of suicide or substance misuse had multiple adversity (e.g. history of childhood or adult trauma, care leavers).[60]

In England, the National Institute for Health and Care Excellence recognises these social risk factors and produced a guideline for pregnant women with complex social factors.[61] Exemplar populations included women who misuse substances, recent migrants, asylum seekers or refugees, women aged under 20 and women who experienced domestic abuse.[61] This was later expanded to include: mental health and personality disorders, women with no social support, human trafficking and child sexual exploitation, female genital mutilation, gender queer and gender reassignment.[62]

Maternal multimorbidity index

For maternal health research using administrative health records, Aoyama et al's systematic review identified three comorbidity indices: Obstetric / Maternal Comorbidity Index, Charlson Comorbidity Index and Elixhauser Comorbidity Index.[63] Only the Obstetric / Maternal Comorbidity Index was derived and validated in pregnant and postpartum women.[63] It was developed in the United States, with modest predictive ability for end organ injury or 30 day mortality of hospitalised pregnant women (c-statistic 0.68, 95% confidence interval 0.65 – 0.67).[63 64] The 20 health conditions in the Maternal Comorbidity Index included pregnancy related conditions such as pre-eclampsia, previous caesarean section, placenta previa and multiple gestation.[64]

Defining multimorbidity in pregnancy in this thesis

For this thesis, the definition of multimorbidity in pregnancy was guided by the recommendations from Ho et al's international Delphi consensus study[58] and the English

National Institute for Health and Care Excellence multimorbidity guidelines.[21] Conceptually, the definition of multimorbidity in pregnancy would be similar to multimorbidity for the general population. However, some long-term conditions may lack relevance for pregnant women. For instance, Ho et al's core list of conditions defining multimorbidity included neurodegenerative conditions that are more prevalent in older adults, such as dementia and Parkinson's disease.[58] This difference was also reflected in Kuan et al's epidemiological study of 308 health conditions across the life course.[65] Common mental health conditions, skin conditions and atopic conditions were most common in reproductive age women, whilst cancer, cardiometabolic and degenerative conditions were most common in older aged adults.[65]

Additional considerations include whether conditions that arise from pregnancy, such as gestational diabetes and gestational hypertension, should be included. However, in preparation for future outcome studies, it is important to distinguish between exposure (multimorbidity) and pregnancy outcomes. In addition, focusing on pre-pregnancy long-term conditions is more helpful in understanding the impact of long-term conditions on maternity care provision and planning for long-term conditions management and preconception care.[66] More detailed information on how the measurement of multimorbidity in pregnancy was operationalised is described in Chapter 3.

1.4 Outcomes for pregnant women with single long-term conditions

Examining the epidemiology of multimorbidity in pregnancy provides information on where preventative measures and preconception care provision is most needed. The next step is to understand the consequences of maternal multimorbidity on the pregnant women and their offspring. Pre-existing medical conditions are known risk factors for adverse pregnancy outcomes and maternal death.[34 67-71] Examining pregnancy outcomes in women with single

long-term conditions can provide some initial understanding of how multimorbidity may impact on pregnancy outcomes. Here we look at physiological changes in pregnancy and its implications for long-term conditions, some examples of adverse outcomes for pregnant women with single long-term conditions and examine the rising importance of indirect maternal deaths.

Physiological changes in pregnancy

Women's body undergo significant physiological changes during pregnancy to meet the needs of the growing fetus and to prepare the women's body for childbirth.[72 73] This includes changes to the cardiovascular system (e.g. increase in cardiac output to deliver nutrients to the fetus), haematological system (e.g. hypercoagulable state for haemostasis following birth), glucose metabolism system (e.g. insulin resistance to facilitate glucose transfer to the fetus) and the immune system (to tolerate a genetically incompatible fetoplacental unit).[72 73]

These major physiological changes can unmask underlying long-term conditions, interact with pre-existing predisposition for ill health and pre-existing long-term conditions and precipitate pregnancy complications.[72] For instance, autoimmune conditions such as rheumatoid arthritis and multiple sclerosis may improve during pregnancy and relapse after childbirth.[72] The cardiovascular changes during and immediately after labour predispose women with existing cardiovascular compromise to pulmonary oedema.[73] These challenges may be compounded in pregnant women with multimorbidity, resulting in an increased risk of adverse outcomes for the pregnancy and the long-term health of the women and her offspring.

Adverse pregnancy outcomes and impact of pregnancy on pre-existing health conditions

Three exemplar conditions, cardiac conditions, epilepsy and chronic kidney disease, are presented here to illustrate the impact of long-term conditions on pregnancy outcomes. Cardiac

conditions and epilepsy are both leading indirect causes of maternal death in the MBRRACE-UK national maternal mortality review report.[60]

Cardiac conditions

A meta-analysis reported that pregnant women with cardiomyopathy are at greater risk of major adverse cardiovascular events during pregnancy (OR 206.64, 95% CI 192.09 to 222.28) and in-hospital mortality (OR 126.67, 95% CI 43.01 to 373.07) than women with no heart disease.[67] An international registry of pregnant women with cardiac disease (2007-2018) reported an overall mortality of 0.6% with 17% and 21% experiencing obstetric and fetal complications respectively; 11% experienced heart failure and 2% experienced arrhythmia.[74]

Epilepsy

A meta-analysis found that pregnant women with epilepsy had higher risk of miscarriage (OR 1.54, 95% CI 1.02 to 2.32), antepartum haemorrhage (1.49, 1.01 to 2.20), postpartum haemorrhage (1.29, 1.13 to 1.49), hypertensive disorders (1.37, 1.21 to 1.55), any preterm birth (<37 weeks gestation; 1.16, 1.01 to 1.34), and fetal growth restriction (1.26, 1.20 to 1.33).[34]

Chronic kidney disease

A systematic review reported that pregnant women with chronic kidney disease had higher risk of pre-eclampsia (OR 10.36, 95% CI 6.28 to 17.09), preterm birth (5.72, 3.26 to 10.03), small for gestational age/ low birth weight (4.85, 3.03 to 7.76), caesarean section (2.67, CI 2.01 to 3.54), and offspring death (a composite of stillbirth, fetal death and neonatal death, 1.80, 1.03 to 3.13).[69]

A retrospective cohort study of six tertiary renal centres in the United Kingdom included pregnant women with pre-existing chronic kidney disease stages 3-5.[71] The live birth rate was 98%, 56% of babies were born preterm, with chronic hypertension as the strongest predictor.[71]

The effect of pregnancy was equivalent to 1.7, 2.1 and 4.9 years of kidney disease in stages 3a, 3b and 4-5, respectively, and advanced the need for renal replacement therapy by 2.5 years.[71]

Maternal deaths

Maternal deaths (pregnancy related deaths) can be divided into direct and indirect deaths.[75] Direct deaths are caused by obstetric complications such as obstetric haemorrhage and pre-eclampsia.[75] Indirect deaths are caused by pre-existing health conditions, or conditions that developed during pregnancy; these conditions are not due to direct obstetric causes but may have been aggravated by the physiologic effect of pregnancy.[75] An example would be death from pre-existing cardiac conditions exacerbated by pregnancy.[75]

Indirect maternal deaths: United Kingdom

In the latest United Kingdom national maternal mortality review (MBRRACE-UK 2018-2020), half of maternal deaths (52%) were due to indirect causes.[60] Cardiac conditions and neurological conditions (epilepsy and stroke) were consistently the top two most common indirect causes of maternal deaths in the last two MBRRACE-UK reports.[60 76] Other common indirect causes of maternal deaths included psychiatric conditions (substance use or alcohol) and malignancies (breast, ovarian and cervical cancers).[60]

Indirect maternal deaths: Global

More than a quarter (28%) of all maternal deaths worldwide (2003-2009) can be attributed to indirect causes, according to a World Health Organisation systematic review.[77] Similar figures were observed in both developed (25%) and developing regions (28%).[77] Pre-existing medical conditions as an indirect cause accounted for 15% of all deaths worldwide, 20% in developed regions and 15% in developing regions.[77] A gradual increase in the proportion of maternal deaths attributable to indirect causes was observed from 9% (1990) to 10% (2013) in a Global Burden of Disease study.[78]

Increasing importance of indirect maternal deaths

These statistics demonstrate that indirect causes of maternal deaths are important in both developed and developing countries and are on the rise. Non communicable diseases are gaining importance in developing countries going through epidemiological transition,[79] with the four main conditions being cardiovascular disease, cancers, chronic respiratory diseases and diabetes.[80] Souza et al described an 'obstetric transition' where with advancement in socioeconomic development and health care, the challenges in maternity care shift from lack of access, infrastructure and skilled workforce to maintaining quality of care; the main causes of maternal deaths shifts from direct to indirect causes.[81 82] As better obstetric care and targeted intervention lead to a reduction in direct causes of death,[77] health system reengineering is needed to meet the needs of the increasing number of pregnant women with pre-existing medical conditions.[78]

1.5 Outcomes for pregnant women with multimorbidity

Systematic review

Having looked at outcomes for pregnant women with single long-term conditions, we will now examine existing evidence for pregnant women with multimorbidity. A recent systematic review (2021) by Brown et al examined the association between pre-pregnancy multimorbidity and maternal outcomes.[66] Seven studies were included, with three studying specific combinations of comorbidities; all studies were based in North America.[66] The review found an increased risk of severe maternal morbidity or mortality, hypertensive disorders of pregnancy and acute health care use in the perinatal period in pregnant women with multimorbidity.[66] A dose response relationship was observed between increasing numbers of long-term conditions and risk of adverse maternal outcomes.[66] Heterogeneity of the included

studies precluded a meta-analysis,[66] but amongst the results, having three or more conditions was associated with severe maternal morbidity (adjusted OR 9.1, 95% CI 8.7 to 9.6);[43] having seven to 32 aggregated diagnosis group pre-pregnancy was associated with three or more perinatal emergency department visits (7.59, 7.39 to 7.78).[83]

Since the systematic review, two new studies were published reporting pregnancy outcomes for pregnant women with multimorbidity. A retrospective cohort study based in a single hospital in United States (n=14255 singleton births from 2015-2021) found that maternal multimorbidity (two or more conditions) was associated with increased risk of severe maternal morbidity (adjusted risk ratio 2.9, 95% CI 2.5 to 3.0) and 90-day postpartum readmission (2.2, 1.7 to 2.9).[50] The single study site limits the generalisability of study findings, and may miss readmissions to other hospitals.[50]

A prospective birth cohort from the Japanese Environment and Children's Study (n=86885 singleton pregnant women) found maternal multimorbidity was associated with preterm birth (adjusted odds ratio [aOR] 1.50, 95% CI 1.33 to 1.69), low birth weight (1.49, 1.35 to 1.63) and small for gestational age (1.33, 1.20 to 1.46).[51] The disease profile in this Asian country differs from western countries, once again limiting generalisability of study findings to the United Kingdom. For instance, the most prevalent chronic condition was maternal underweight (16%) whilst only 0.7% had psychiatric disorders.[51]

Studies in the United Kingdom

In the United Kingdom, two conference abstracts reported the outcomes for pregnant women with multimorbidity. D'Arcy et al's study of a tertiary hospital (n=6406 women giving birth in 2016) found that maternal multimorbidity was associated with increased odds of pre-eclampsia (adjusted OR 1.56, 95% CI 1.06 to 2.16), obstetric cholestasis (1.79, 1.08 to 3.0), thromboembolism (10.34, 3.74 to 28.5), emergency caesarean section (1.7, 1.38 to 2.12),

preterm birth (1.68, 1.29 to 2.29), and having a low birthweight baby (1.45, 1.19 to 1.93).[44] Azcoaga-Lorenzo et al's study of two regions in Scotland (2014-2018, n=26328 singleton births) using hospital and community prescription data found that maternal multimorbidity was associated with preterm birth before 37 weeks gestation (adjusted OR 1.67, 95% CI 1.51 to 1.84).[84] Both studies may have limited generalisability to the rest of the United Kingdom due to single or regional study location.

Severe maternal morbidity

Many of the studies of multimorbidity in pregnancy from the United States studied severe maternal morbidity.[66] This is a composite measure that indicates a life threatening diagnosis or the need for a lifesaving procedure around the time of childbirth.[85] These are unintended outcomes of labour and childbirth that result in significant short and long-term consequences to the women's health.[86] The Centres for Disease Control and Prevention (CDC) definition is often used and consists of 21 indicators.[87] Examples include acute heart failure / pulmonary oedema, air and thrombotic embolism, blood products transfusion and hysterectomy.[87] The CDC definition uses International Disease Classification of Disease (ICD) version 10 which allows for population level surveillance using hospital administrative data.[87]

There is currently no consensus for how severe maternal morbidity should be defined and measured.[86] A study reported low concordance between seven United States definitions, which were variations of the CDC definition and Bateman's index of end organ injury.[64 87 88] Globally different definitions for severe maternal mortality have been developed and used in different countries.[89] In high income countries, this included the EURO-PERISTAT,[90] EPIMOMS[91] and a validated Australian maternal mortality outcome indicator.[89 92] The latter was adapted for use in a study using English hospital administrative data (26 indicators).[93]

Sparse evidence quantifying outcomes for pregnant women with multimorbidity

Brown et al's systematic review revealed the lack of literature quantifying outcomes for pregnant women with multimorbidity.[66] Only four of the included studies examined multimorbidity and not specific combinations of comorbidities. Most studies were conducted in the United States. Maternal outcomes studied were often short-term outcomes in the peripartum period. For pregnant women with multimorbidity and their clinicians to make informed decisions on the preconception and pregnancy care plan, more research is needed on the associated risk of pregnancy. To ensure future studies measure outcomes that are clinically relevant and meaningful to pregnant women with multimorbidity, a core outcome set is needed. This will be discussed further in subchapters 1.7 and 1.8.

1.6 Management of pregnant women with long-term conditions and multimorbidity

Preconception care

The preconception period can be defined as the time when pregnancy is being planned, or at any time in the life course leading up to pregnancy.[94 95] A woman's health during this period can impact on pregnancy and long-term health outcomes for her and her child.[94 96] Preconception care provides biomedical, behavioural and social health interventions to optimise maternal health during this time period.[97] It is an important public health intervention to reduce perinatal morbidity and mortality.[98] However, as 45% of pregnancies are unplanned, there are huge missed opportunities.[99] This window of opportunity is particularly important for women with pre-existing long-term conditions and multimorbidity.

A recent umbrella review on preconception exposures found high certainty evidence that preconception folate supplementation reduces the risk of neural tube defect and pregnancy termination for fetal anomaly.[100] The review also found that raised maternal body mass index

and interpregnancy weight gain are associated with adverse pregnancy and birth outcomes, whilst maternal physical activity reduced the risk of pre-eclampsia and gestational diabetes.[100] Therefore key priorities for preconception care include: folic acid supplementation, supporting those with lifestyle risk factors (e.g. smoking, obesity, alcohol and substance misuse), reviewing genetic risks, medication history, obstetric history and optimising the control of pre-existing long-term conditions.[101 102]

Preconception care stratified by risk

Raghuraman et al proposed risk stratifying women into low, moderate and high risk to guide preconception care provision.[98] Women with low risk require routine preconception care and general health promotion (e.g. advice on folate supplement and healthy lifestyle such as smoking cessation and weight management).[98] Women with moderate risk require optimisation of their long-term conditions.[98] Women with severe medical conditions such as end-stage kidney disease, active cancer and class IV cardiac condition are at extremely high risk of severe maternal morbidity and mortality, and thus need to be fully informed of the risk before getting pregnant.[98]

For women with pre-existing long-term conditions, referral to specialists may be required for preconception care. The criteria for referral is set out by the English National Institute for Health and Care Excellence preconception care guideline for health conditions such as epilepsy, diabetes, cardiac, renal, thyroid, rheumatological and mental health conditions.[103] Therefore, understanding the burden of pre-existing multimorbidity in the pregnant population is important for planning the provision of preconception care.

Example: preconception care for women with diabetes mellitus

To reduce adverse maternal and offspring outcomes, preconception care for women with diabetes mellitus aims to optimise glycaemic control to a HbA1c of below 48 mmol/mol

(6.5%).[104 105] Women with diabetes should also undergo retinal and renal assessment to screen for complications prior to conception.[104 105] A systematic review that included mostly observational studies found that preconception care for women with type one or type two diabetes mellitus reduced the risk of congenital anomaly by 71%, preterm birth by 15%, perinatal mortality by 54%, small for gestational age by 48%, and neonatal admission to intensive care by 25%.[106]

Preconception care for other long-term conditions

A systematic review (2023) that included six studies found that preconception care improved the outcomes for women with various long-term conditions, including epilepsy, cardiovascular disease, inflammatory bowel disease and autoimmune rheumatic disorders.[107] Medication review was included as part of the preconception care intervention in most of the included studies, given the teratogenicity of some of the medications needed to manage the long-term conditions.[107] Preconception care resulted in better disease control during pregnancy, better medication adherence, folic acid intake and smoking cessation.[107] Preconception care also reduced rates of small for gestational age, low birth weight, preterm birth, congenital anomaly and miscarriage.[107] However, women who accessed preconception care were more likely to be younger, nulliparous, had shorter disease duration, higher education or job security and undergone in vitro fertilisation, highlighting possible inequality of access.[107]

Maternity care policy

In 2016, a national review of maternity services was conducted in England, producing a five year forward view in the Better Births report.[108] This sets out the vision for maternity services with the following seven tenets: personalised care, continuity of carer, safer care, better postnatal and perinatal mental health care, multi-professional working, working across boundaries, and a fair payment system for maternity services.[108] The Maternity Transformation

Programme was then established in 2017 to implement Better Births' vision, through locally led transformation (Local Maternity Systems) with support at national levels.[109] [110] The National Health Service Long Term Plan (2019) aimed to halve stillbirth, maternal and neonatal mortality and serious brain injury by 2025, improve access to perinatal mental health care, and ensure continuity of carer for pregnant women.[111] However the latter has been suspended following the Ockendon report (2022, an independent review of a local maternity hospital) until safe minimum staffing levels can be demonstrated.[112] The Ockenden report also listed immediate and essential actions to improve care and safety in maternity services in England.[112] This included ensuring women with pre-existing medical conditions have access to specialist preconception care and a robust pathway to manage complex pregnancies.[112]

The National Maternal and Perinatal Audit conducts annual audits in maternity services across England, Wales and Scotland.[113] It evaluates the care processes and outcomes to identify good practice and areas for improvement.[113] All maternal deaths in the United Kingdom are reported to MBRRACE, the national maternal mortality review team, which produces annual reports on lessons learned.[60] The latest enquiry focused on the health and care needs of pregnant women with multimorbidity, this will be discussed further in Chapter 8.[60]

Maternal Medicine Network

Recognising the rising importance of medical conditions that pre-date or arise in pregnancy and puerperium, the National Health Service in England outlined the service specification for the Maternal Medicine Network in 2021, with an emphasis on a multidisciplinary team approach.[114] A three tiered care system was suggested based on the complexity of the medical problem and local expertise: management by the local unit, shared care between the local unit and maternal medicine centre, and management by the maternal medicine centre.[114]

An example referral pathway from the London Maternal Medicine Network was provided.[114] For instance, pregnant women with uncomplicated asthma, uncomplicated rheumatoid arthritis, and migraine can be managed with local expertise; asthma and rheumatological conditions managed with biologics and idiopathic intracranial hypertension can be managed locally with support from the maternal medicine centre; cystic fibrosis, active lupus nephritis, and progressive brain tumour should have care led by the maternal medicine centre.[114]

Guidelines for the care of pregnant women with long-term conditions

The English National Institute for Health and Care Excellence guideline for the intrapartum care of women with pre-existing medical conditions includes recommendations on cardiac conditions, bleeding disorders, subarachnoid haemorrhage, asthma, long-term systemic steroids use, obesity and chronic kidney disease.[115] Other relevant guidelines are listed in the Maternal Medicine Network service specification and included diabetes, hypertension, renal disease, congenital heart disease, myasthenia gravis, multiple sclerosis and haematological conditions in pregnancy.[114]

The guidelines demonstrate the complexity of risk management and care planning required due to the interplay between the pre-existing medical condition, its management, and the requirements of childbirth. For instance, women with mechanical heart valves take anticoagulation to prevent blood clots from forming.[115] Careful timing of when the anticoagulant should be switched to a safer alternative temporarily is planned around when the women is likely to need regional anaesthesia or caesarean section.[115] Women with advanced kidney disease may need dialysis to prolong the pregnancy.[115] Certain medications may be contraindicated due to the pre-existing conditions, such as non-steroidal anti-inflammatory drugs in chronic kidney disease.[115] In high risk pregnancies, a planned caesarean section or birth before 38 weeks may be discussed with the women.[115]

Regardless of the pre-existing conditions, the overarching principles are early information provision, shared decision making and multidisciplinary care.[115] Information provision should include how the medical condition may affect women's intrapartum care, how labour and birth may affect their medical conditions, and how their medical condition and its management may affect the baby.[115] Guidelines recommend that the multidisciplinary team should include the following health professionals as appropriate: midwife, obstetrician, obstetric physician, obstetric anaesthetist, clinician with expertise in the condition, surgeon, critical care specialist, neonatologist, general practitioner, perinatal psychiatrist and allied health professionals.[114 115]

Experience of pregnancy and maternity care for women with long-term conditions

There is currently no qualitative study focusing specifically on the experience of pregnant women with multimorbidity. Most qualitative studies focused on women with single conditions.[116 117] These qualitative studies are important as they give voices to women to share their lived experience of navigating pregnancy and maternity care with their long-term conditions.

Risk perception

Ralston et al's systematic review (2021) extensively searched eleven databases and included eight qualitative studies exploring risk perceptions of pregnancy in women with long-term conditions.[116] Included studies covered a broad range of health conditions, such as epilepsy, type one diabetes and congenital heart disease.[116] Women felt there was a lack of information on risk to mother and baby and wanted more information about the teratogenicity of medications.[116] Their perception of risk were compartmentalised to risk to self and risk to baby, and influenced by psychosocial factors.[116] Women's pregnancy related behaviour were impacted by their perceived risk.[116] They were constantly engaged in a balancing act for their health and pregnancy related decision making and the emotions they experienced.[116]

Self-management

Jakubowski et al's systematic review (2022) searched two databases and included 16 qualitative studies exploring women's experience of self-managing long-term conditions during pregnancy.[117] Women's prime motivation for self-management of their long-term conditions were their babies' health.[117] Barriers for self-management were anxiety, lack of understanding of their conditions and lack of support from families and health care professionals.[117] However, the review only identified studies on diabetes self-management, reflecting the gap in the literature.

Maternity care needs and experience

A recent interview study by Hansen et al included women with single and multiple long-term conditions.[118] It explored maternity care needs and experiences of women with high risk pregnancies recruited from one tertiary hospital in Denmark.[118] The study included 14 participants and 18 medical conditions; eight participants had one long-term conditions, six participants had two or more long-term conditions.[118]

Although it was not possible to isolate the findings for women with multiple long-term conditions only, the study provided useful insights. The three main themes were: (i) chronic condition as determining pregnancy care; (ii) childbearing woman as messenger and interpreter; and (iii) feelings of abandonment after giving birth.[118] Participants spoke about fragmented care by the different health care teams who focused on the long-term conditions they specialised in.[118] They also spoke about the lack of: continuity, holistic care, breastfeeding support, support to interpret clinical information, and information to prepare them for the postpartum recurrence or progression of their long-term conditions.[118] Their long-term conditions limited their choices for their pregnancy.[118]

Despite only recruiting from one hospital, they recruited participants from different clinical settings (outpatients and inpatients) to capture experiences along the clinical pathway.[118] Their maximum variation sampling criterion based on participants' medical history resulted in a study sample with a broad range of health conditions (n=18).[118] However, all but one participant were of Danish ethnic background, and all had education beyond tertiary level.[118] Therefore, the study may not capture the experience of pregnant women with multiple long-term conditions with the added challenge of social risk factors.[118]

Extension to the care for pregnant women with multimorbidity

Multimorbidity is likely to add to the complexity for care of the pregnant women across all stages of pregnancy. The number of specialists team involved in their care is likely to increase. Therefore, coordination of appointments, investigations and medication regime is required. Although there are currently no guidelines for the care of pregnant women with multimorbidity, future guidance is likely to embrace the general principles of providing care to people with multimorbidity and pregnant women with pre-existing medical conditions, such as shared decision making and coordinated care.

To inform guideline development, interventional studies are needed to evaluate the optimum maternity care pathway for pregnant women with multimorbidity. Selection of relevant outcomes to measure is of great importance. The next subchapter will discuss how a core outcome set can address this.

1.7 Core outcome set

Outcomes

Outcomes are variables, events or end points measured in a study to understand the impact of an intervention or an exposure on the health or wellbeing of the population of interest.[119] For a given health condition, many outcomes can be measured. For example, in a study trialling treatment for asthma, researchers can choose to measure asthma perceived control using patient questionnaire, hospitalisation or pulmonary function tests.[119] However, for effective use of study resources, researchers have to select outcomes that are of the greatest therapeutic importance and relevance to stakeholders.[119 120]

Poorly selected, collected and reported outcomes

The usefulness of research findings can be hindered when outcomes are poorly selected, collected and reported.[120] In systematic reviews, meta-analyses may not be feasible if there is heterogeneity in the included studies, this can occur when studies that address the same clinical question reported different outcomes.[121] Just over half of Cochrane systematic reviews in neonatology for the years 2006-2010 were inconclusive, with heterogeneity amongst the common reasons for this.[122]

Outcome selections may be driven by consideration of sample size, costs and resources.[120] However, outcomes selected on such basis may have limited relevance to service users and providers if their views were not considered,[120] and may not translate to improvement in clinical care.[121] For example, even though live births would be considered an important outcome in infertility intervention trials, in a systematic review of in vitro fertilisation trials, only 37% of the included articles reported this outcome.[120 123] Even amongst studies that did

measure live births, there were variations on how the numerator and denominator were defined.[120]

Selective outcome reporting bias can occur when researchers choose to publish a subset of the original recorded outcome variables on the basis of the results.[120 124] Statistically significant outcomes are more likely to be reported than non-significant outcomes.[125] This can lead to the overestimation of treatment effect.[124] A review found that a third of Cochrane systematic reviews contained at least one trial with high suspicion of selective reporting bias and after accounting for this, the conclusions of some of the reviews changed from evidence of benefit to no evidence of benefit.[121 124]

Core outcome set

The problems with poorly selected, collected and reported outcomes can be addressed with core outcome sets to standardise outcome reporting in studies of a given health condition.[120] This is a set of outcomes that is expected to be collected and reported as minimum in all studies of a specific health conditions or trial population.[120] Core outcome sets aim to improve the consistency of reporting and facilitate pooling of results.[120] It is constructed following robust consensus science method with a diverse range of stakeholders.[120]

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement is an evidence based recommendation for the minimum content of a clinical trial protocol.[126] It recommends the incorporation of core outcome sets in trials when one is available.[126] However, a review assessing the uptake of core outcome sets in randomised controlled trials found this varied between 0% for gout to 82% for rheumatoid arthritis.[127] Efforts are ongoing to increase uptake of core outcome sets in studies.[128]

Core outcome sets in pregnancy and childbirth

In the field of women's and newborn health, the Core Outcomes in Women's and Newborn Health (CROWN) initiative is supported by over 80 journals committed to publishing and disseminating core outcomes to improve women's and newborn's health.[129] As of May 2022, the Core Outcome Measures in Effectiveness Trials (COMET) database contains 440 published and 421 ongoing core outcome sets.[128] Duffy et al's systematic review of core outcome sets relevant to women's and newborn health reported four published core outcome sets as of January 2017.[130] A more recent systematic review of core outcome sets related to pregnancy and childbirth found 27 published core outcome sets and 42 ongoing core outcome set development studies as of June 2021.[131] More than half (67%) of the published core outcome sets were published during 2018-2021, indicating an acceleration of core outcome set development for studies in pregnancy and childbirth in recent years.[131]

1.8 Core outcome set for multimorbidity in pregnancy

As discussed in subchapters 1.5 and 1.6, research is needed to quantify the outcomes and to evaluate interventions and care pathways for pregnant women with multimorbidity. The selection of what outcomes to measure and report would be best guided by a core outcome set for studies of pregnant women with multimorbidity, due to reasons outlined in subchapter 1.7. Currently no such core outcome set exists. There are however core outcome sets for multimorbidity[132] and for pregnancy in general.[133 134]

Core outcome set for multimorbidity

Smith et al's core outcome set for multimorbidity consists of 17 outcomes, with the highest ranking outcomes being: health-related quality of life, mental health outcomes and mortality;

other outcomes were related to patient-reported impacts and behaviours, physical activity and function, consultation and health system related.[132]

Core outcome sets for pregnancy in general

Devane et al's core outcome set for maternity care comprises 48 outcomes, it covers the antenatal, intrapartum and postnatal period.[133] The core outcome set included children's outcomes such as congenital anomaly; health care utilisation outcomes such as maternal and neonatal admission to intensive care unit; and experience based outcomes such as maternal satisfaction.[133]

Nijagal et al's core outcome set for pregnancy and childbirth comprises 24 outcomes to evaluate care during pregnancy and up to six month postpartum.[134] This included outcomes for survival, severe maternal morbidity, neonatal morbidity, patient reported health status, breastfeeding, role transition, mental health, satisfaction with care, health care responsiveness and birth experience. Case-mix factors and timeline for measurement were also recommended alongside the core outcome set.[134] To overcome the variation in how severe maternal morbidity is defined, the study group selected four outcomes that represent the common endpoints of the leading causes of preventable maternal deaths globally (hypertensive disorder of pregnancy, venous thromboembolism, sepsis and haemorrhage).[134] These were: admission to an intensive care unit, maternal length of stay, postpartum readmission and postpartum blood transfusion.[134]

Why is a core outcome set specific to pregnant women with multimorbidity needed?

Following qualitative studies of pregnant women with one or more long-term condition, experience based outcomes such as communication with health professionals, shared decision making and treatment burden were deemed important,[118] and are indeed included in the core outcome set for multimorbidity.[132] However, the latter lacks pregnancy related outcomes.[132]

Similarly, although the core outcome set for pregnancy is likely to be applicable to pregnant women with multimorbidity, it does not have multimorbidity related outcomes.[133 134]

If these existing core outcome sets were to be applied to studies for pregnant women with multimorbidity, two different core outcome sets will be needed. Moreover, the stakeholders involved in the development of these existing core outcome sets are unlikely to represent pregnant women with multimorbidity. Therefore, to advance the field in multimorbidity in pregnancy, a core outcome set specific to this population is needed.

1.9 Aims and objectives

Aims

This PhD thesis has two aims:

(i) to understand the epidemiology of pre-existing multimorbidity in pregnant women; and

(ii) to develop a core outcome set for studies of pregnant women with multimorbidity.

Objectives

The objectives for this PhD thesis are:

(i) to describe the epidemiology of pre-existing multimorbidity in pregnant women in the United Kingdom (*Chapter 3)*;

(ii) to examine the utility of primary and secondary care routine health records in studying the epidemiology of pre-existing multimorbidity in pregnant women *(Chapter 3)*;

(iii) to develop a study protocol for a core outcome set for studies of pregnant women with multimorbidity *(Chapter 4)*;

(iv) to identify types of outcomes reported in existing literature for pregnant women with multimorbidity *(Chapter 5)*;

(v) to explore outcomes that are important to women with multimorbidity who have been pregnant or planning to be pregnant, their partners and health care professionals *(Chapter 6)*; and

(vi) to develop a core outcome set for studies of pregnant women with multimorbidity using consensus methods *(Chapter 7)*.

Chapter 2: General methods

Chapter overview

Overall, five methods were employed in this thesis: (i) observational study using routinely collected data, (ii) systematic literature search, (iii) focus groups, (iv) Delphi surveys and (v) consensus meeting. Method (i) was used to describe the epidemiology of multimorbidity in pregnant women. Methods (ii) to (v) were used to develop a core outcome set for studies of pregnant women with multimorbidity. More detailed information is presented in the respective methods section of subsequent chapters. This chapter presents the rationale for each method used and outlines the patient and public involvement for this thesis.

2.1 Observational study: rationale for using routinely collected data

Observational study methods

Chapter 3 aims to estimate the prevalence of pre-existing multimorbidity in pregnant women in the United Kingdom. To achieve this, observational data can potentially be collected through cross sectional surveys, prospective cohorts or routinely collected data.

Cross sectional surveys

Cross sectional surveys would involve recruiting a nationally representative sample of pregnant women and asking participants to self-report their medical history. Limitations for self-reporting surveys include responder bias and recall bias. Pregnant women with long-term conditions, who had negative experience of maternity care or negative outcomes may be more motivated to participate in the surveys. They may also be more likely to recall their medical history. This may result in an overestimation of the prevalence of multimorbidity. Compared

to objective measures, the reliability of self-reported medical history depends on the participants' health literacy and adequate clinician-patient communication of their diagnosis.[135] However, this method is more likely to capture medical conditions that patients do not present to clinicians with and self-manage at home.[135]

Prospective cohorts

The baseline medical history of a prospective cohort can also provide information on the prevalence of multimorbidity in pregnancy. This could be through establishing a new cohort of pregnant women or through secondary analysis of established population cohorts, such as mothers in the Born in Bradford cohort.[136] The advantage of a prospective cohort study is the systematic collection of exposure and outcome data from participants over a long period of time.

However, similar to surveys, misclassification errors may occur if the participant's medical history is collected through self-reporting.[135] This can be circumvented by corroborating the reported medical history with participants' medical records.[135] Nevertheless, setting up a prospective cohort is resource intensive and this can limit the size of the cohort. In addition, many longitudinal cohorts were established decades ago.[136] Whilst these provide invaluable follow up data for outcome studies, it cannot provide contemporaneous prevalence data for pre-pregnancy multimorbidity.

Routinely collected data

In contrast, routinely collected electronic health records offer contemporaneous data on the prevalence of a health condition, with the added advantage of large sample sizes, low study costs and rapid study completion.[137] However, such data are collected for administrative and clinical care purposes, and not with the primary intention of research.[137] Therefore, not all relevant variables may have been collected and the data quality may vary, leading to

misclassification errors.[137] The presence of a record also relies on patient-clinician encounters and many factors influence whether a person seeks medical help.[138] Nevertheless, routine data are generally suited for studying long-term conditions where repeated medical consultation is required.[138] In particular, health conditions that are covered by financial incentive programmes for general practitioners in England (the Quality and Outcomes Framework) are usually well documented.[139]

2.2 Core outcome set: Overall method

Core outcome sets are developed following robust consensus science methods.[120] The first step is to conduct a systematic review to catalogue a long list of potential outcomes reported in published studies.[120] Previous systematic reviews conducted for the development of core outcome sets have identified variation in outcomes reported in their respective area of research.[140 141] However, outcomes reported in published studies, especially those that predate the emphasis of patient and public involvement in research, may reflect the interest of researchers and clinical academics more than people living with the conditions and their family.[120 142] Therefore, the second step involves using qualitative research to ensure inclusion of outcomes that are relevant to key stakeholders, especially those living with the conditions.[120] The next stage is to reduce the long list of potential outcomes through consensus science methods.[120] Prioritisation of the outcomes are usually achieved through Delphi surveys.[120] Participants are asked to rate the importance of each outcome and reflect on the results before re-rating in sequential surveys.[120] This iterative process aims to converge opinions to reach a consensus.[120] Structured consensus meetings can then be used to resolve disagreement and to finalise the core outcome set.[120]

The methods used to develop a core outcome set for studies of pregnant women with multimorbidity is reported in a published protocol in Chapter 4. Here we outline the rationale for the chosen methods.

2.2.1 Rationale for systematic literature search

The systematic literature search in Chapter 5 followed the standards of a systematic review for the search strategy and study selection. Four electronic databases were searched. Articles were screened against eligibility criteria following the concept of population, exposure, outcomes, and study type. However, at the data extraction stage, only data relevant to developing a core outcome set was extracted. Study effect size was not extracted, and the quality of the included studies was not assessed. Therefore, this was not a systematic review. A systematic review synthesising the latest evidence would have contributed to the literature in this field and identified evidence gaps. Although a recent systematic review already synthesised the latest evidence for maternal outcomes, the review did not include children's outcomes.[66] However, performing a systematic review would have gone beyond the aim of the study, which was to inform the development of a Delphi survey for a core outcome set.

2.2.2 Rationale for focus groups

Qualitative research can be incorporated into the core outcome set development through interviews, focus groups, or secondary analysis of qualitative datasets.[142 143] Consultation with an advisory group comprised of key stakeholders can be considered as an alternative method.[142 143] The systematic literature search in Chapter 5 did not identify any qualitative studies. Since the completion of the search, there has only been one interview study of pregnant women with

one or more long-term conditions published.[118] Therefore a secondary analysis of qualitative datasets of pregnant women with multimorbidity would not have been possible. Although the MuM-PreDiCT consortium does have an advisory group with key stakeholders, advisory group consultation is not qualitative research and will not produce results of similar robustness.[142]

Focus group methodology was chosen as it allowed for synergistic discussion and sharing of different experiences amongst participants with different backgrounds within the same stakeholder group. This is pertinent as multimorbidity in pregnancy is highly heterogenous. Participants have the opportunity to listen, discuss, agree and disagree with other people's views on why an outcome is important.[143] In the case for health care professionals, the group discussion allowed them to consider the perspective of colleagues from different specialties. The alternative would be to conduct individual interviews. This method would have allowed more in depth exploration of the experience and journey of patients, and for the researcher to interpret and extract outcomes from the participants' account.[143] Focus groups have been reported to identify fewer outcomes than interviews.[143] A way to account for this was the opportunity to suggest additional outcomes in the first round of the Delphi survey.

2.2.3 Rationale for Delphi surveys

Delphi surveys are commonly used in core outcome set development.[142] In a recent systematic review of core outcome sets for pregnancy and childbirth, most studies conducted Delphi surveys followed by a consensus meeting to finalise the core outcome set.[131] Only one study did not conduct a survey.[131] Delphi surveys involve sequential surveys administered to converge opinions of different stakeholder groups.[142] This is achieved by sharing individual and aggregate results of the previous survey with participants.[142] Participants are asked to

review these results before repeating the survey and may answer the survey differently once they have considered the views of other stakeholders.[142]

The technique allows highly structured group interaction, but without face-to-face communication.[144] The benefits include flexibility with the time and place of completion, ability to include large number of participants, avoiding dominant participants from influencing the decisions, preserving anonymity and thereby minimises social desirability bias, and consensus is determined by a prespecified criteria.[144 145] However, it can be difficult to retain participants throughout the multiple rounds of survey which can take place over a long period of time.[144] Verbal clarification with other participants is also not possible.[145]

2.2.4 Rationale for consensus meeting following principles of nominal group technique

The nominal group technique is an alternative to Delphi surveys. It also involves a highly structured group interaction but unlike Delphi surveys, it is conducted face-to-face. The technique was originally developed by Van de Ven and Delbecq,[146] and involves four stages: silent generation, round robin, clarification and voting.[144] The benefits include completion within one session, allowing all participants to have their views heard in turn, and avoiding the issues with dominating personalities.[144 145] However, nominal group technique can be challenging to administer, especially when coordinating the availability of all participants.[144 145] For effective discussion, the number of participants that can take part in one meeting should be capped.[144] For the core outcome set development in Chapter 7, both consensus methods were used. The long list of outcomes was prioritised with Delphi surveys; the nominal group technique was employed in the first consensus meeting to discuss borderline outcomes.

2.3 Patient and public involvement

This PhD is embedded in a wider project by the MuM-PreDiCT consortium. As such, the PhD work has extensive patient and public involvement from the MuM-PreDiCT patient and public involvement advisory group. MuM-PreDiCT's patient and public involvement consists of a three tiered system: tier one includes two experienced maternity service user representatives as project co-investigators (RP and NM); tier two includes thirteen women with multimorbidity and experience of pregnancy, with a range of medical conditions, demographics and geographical representation; tier three involves wider engagement with charities and local maternity services.[147] This PhD work mainly involved tier one and tier two members. Tier one co-investigators attended study planning meetings. Dedicated meetings that last 90 minutes were held in the evenings with tier two members when there were specific study queries requiring their input.

Table 2.1 outlines how patient and public involvement was incorporated in this PhD and what changes were made as a result. They were involved across different stages of a study, from study design, study conduct, data analysis and interpretation to dissemination of findings. Patient and public involvement co-investigator RP and NM are co-authors on all the manuscripts.

Table 2.1: Patient and public involvement in the conduct of this PhD

Stage of study	Activity	Support to participate	Impact
Chapter 3: Epidemiology of multimorbidity in pregnancy			
Study design	Two tier one PPI co-investigators participated in workshops to identify long-term conditions defining multimorbidity in pregnant women. The list was reviewed by tier two members.	Lay explanation of each long-term condition shared in a word document before the meeting.	Example changes: retinal detachment was included as this was commonly discussed in pregnancy groups.
Data analysis	Reviewed and interpreted the findings, debated over the relative importance of common mild conditions versus rare severe conditions.	Presented findings to PPI advisory group.	Additional analysis of multimorbidity in pregnant women with conditions which are leading indirect causes of maternal death. PPI wrote a blog piece summarising the discussion of common mild conditions versus rare severe conditions.[148]
Dissemination	Commented on manuscript and research posters.	Shared the research poster with PPI advisory group.	Simplified infographics with less content will be prepared, with key information to be conveyed decided by PPI advisory group. PPI lead is using study findings to raise awareness of multimorbidity in pregnancy during stakeholder engagement events.
Chapter 4: Core outcome set protocol			
Study design	Tier one coinvestigators participated in the writing of the study protocol.	Involvement in research planning meetings, shared manuscript draft.	PPI co-investigator NM produced a figure summarising PPI in the core outcome set development which is included in the published protocol.
Ethics	Reviewed study materials prior to submission to ethics application.	Shared study materials.	Amendment to the wording in the study materials.

Stage of study	Activity	Support to participate	Impact
Chapter 6: Focus group (core outcome set)			
Study design: stakeholders	Discussed how best to include and recruit partners.	Discussed queries in PPI advisory group meeting.	Recruited partners through women with multimorbidity. One focus group was dedicated to women and their partner who attended together to keep the discussion focused.
Study design: topic guide	Pilot tested the topic guide.	Test run the group discussion using the initial topic guide.	Altered the topic guide completely as the initial guide was not drawing out discussion on outcomes. The initial topic guide prompted discussion of their experience and patient journey, but the discussion focused on solutions. The new topic guide provided an explanation of what is an outcome and asked an open question on what outcomes are important.
Study design: recruitment material	Reviewed the study invitation and study poster.	Shared the study recruitment materials.	Added images that are more inclusive (e.g., disabled women, partners, family members), wording was changed, QR codes were added.
Study conduct: recruitment	Advised on recruitment channels and shared study adverts with their network.	Study poster and an invitation template was shared.	Study adverts were shared with women and patient groups that PPI were members of.
Data analysis	Cross checked researchers' interpretation of the qualitative dataset.	Anonymised transcript was shared with a tier one PPI co-investigator. Selected themes and anonymised quotes were presented to PPI advisory group members.	Contributed to the labelling of themes and ensured the overall narrative of the focus group was reflective of the transcript.

Stage of study	Activity	Support to participate	Impact
Chapter 7: Delphi surveys (core outcome set)			
Study design: Delphi surveys	Four PPI members participated in workshops to review the initial list of outcomes for inclusion in the Delphi surveys. Pilot tested the online Delphi survey and reviewed the plain English summary for the outcomes.	Lay explanation of the outcomes was shared before the workshop and alongside the Delphi survey.	Some outcomes such as placenta insufficiency that were initially omitted were subsequently included. Wording was changed for the Delphi survey. Advised on which sociodemographic questions to include and wording to use.
Study conduct: recruitment	Shared the survey link within their network.	Shared the study poster and survey link.	Survey was shared with women and patient groups that PPI were members of.
Chapter 7: Consensus meetings (core outcome set)			
Study conduct	Participated in study planning meetings.	Shared the proposed meeting agenda.	Following PPI co-investigator's suggestion, I arranged premeetings and post meeting debriefs with participants, provided information pack for ease of reference during the meeting, changed the structure and length of the meeting.
Study participation	Participated in the consensus meeting as PPI representatives.	Lay explanation for the outcomes and explanation of how the meeting will be conducted were shared before the meeting.	Contributed to the consensus meeting discussion and helped reached consensus for the core outcome set.
Data analysis	Reviewed the study findings.	Study findings and key issues that arose in the meeting was discussed.	Advised on how best to present the study findings in the manuscript, contributed to the discussion on how to resolve the divergent views from the meeting.

PPI: patient and public involvement; QR: quick response

Chapter 3: Epidemiology of multimorbidity in pregnant women in the United Kingdom

Chapter overview

Following the principles of how to measure multimorbidity and addressing the evidence gap discussed in Chapter 1, this chapter will use routine health records to meet *Objective 1:* describe the epidemiology of pre-existing multimorbidity in pregnant women in the United Kingdom. Using three different datasets from different health care settings, this chapter will also meet *Objective 2:* examine the utility of primary and secondary care routine health records in studying the epidemiology of pre-existing multimorbidity in pregnant women. The published manuscript is presented as follows.

Published manuscript

Lee SI, Azcoaga-Lorenzo A, Agrawal U, et al. Epidemiology of pre-existing multimorbidity in pregnant women in the UK in 2018: a population-based cross-sectional study. *BMC pregnancy and childbirth* 2022;22(1):120. doi: 10.1186/s12884-022-04442-3

Personal contribution

- Study design
- Compiled Read codes and drug codes for Clinical Practice Research Datalink (CPRD) and the Secure Anonymised Information Linkage Databank (SAIL)
- Developed the disease phenomes with the clinical team
- Applied for data access approval from CPRD
- Analysed the CPRD dataset
- Applied for access to the SAIL dataset and replicated the analysis
- Liaised with the Scottish team to harmonise the dataset and analysis
- Presented results to the patient and public involvement advisory group and conducted additional analysis as advised
- Wrote the first draft of the manuscript and submitted for publication, conducted additional analysis addressing reviewers' comments

Title: Epidemiology of pre-existing multimorbidity in pregnant women in the UK in 2018: a population-based cross-sectional study

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3.1 Abstract

Background

Although maternal death is rare in the United Kingdom, 90% of these women had multiple health/social risk factors. This study aims to estimate the prevalence of pre-existing multimorbidity (two or more long-term physical or mental health conditions) in pregnant women in the United Kingdom (England, Northern Ireland, Wales, and Scotland).

Study design

Pregnant women aged 15-49 years with a conception date 1/1/2018 to 31/12/2018 were included in this population-based cross-sectional study, using routine healthcare datasets from primary care: Clinical Practice Research Datalink (CPRD, United Kingdom, n=37,641) and Secure Anonymized Information Linkage databank (SAIL, Wales, n=27,782), and secondary care: Scottish Morbidity Records with linked community prescribing data (SMR, Tayside and Fife, n=6,099). Pre-existing multimorbidity preconception was defined from 79 long-term health conditions prioritised through a workshop with patient representatives and clinicians.

Results

The prevalence of multimorbidity was 44.2% (95% CI 43.7%-44.7%), 46.2% (45.6%-46.8%) and 19.8% (18.8%-20.8%) in CPRD, SAIL and SMR respectively. When limited to health conditions that were active in the year before pregnancy, the prevalence of multimorbidity was still high (24.2% [23.8%-24.6%], 23.5% [23.0%-24.0%] and 17.0% [16.0% to 17.9%] in the respective datasets). Mental health conditions were highly prevalent and involved 70% of multimorbidity (CPRD: multimorbidity with ≥one mental health condition/s 31.3% [30.8%-31.8%]).

After adjusting for age, ethnicity, gravidity, index of multiple deprivation, body mass index and smoking, logistic regression showed that pregnant women with multimorbidity were more

likely to be older (CPRD England, adjusted OR 1.81 [95% CI 1.04-3.17] 45-49 years vs 15-19 years), multigravid (1.68 [1.50-1.89] gravidity ≥ five vs one), have raised body mass index (1.59 [1.44-1.76], body mass index 30+ vs body mass index 18.5-24.9) and smoked preconception (1.61 [1.46-1.77) vs non-smoker).

Conclusion

Multimorbidity is prevalent in pregnant women in the United Kingdom, they are more likely to be older, multigravid, have raised body mass index and smoked preconception. Secondary care and community prescribing dataset may only capture the severe spectrum of health conditions. Research is needed urgently to quantify the consequences of maternal multimorbidity for both mothers and children.

3.2 Background

Multimorbidity is having two or more long-term health conditions.[149] Although well studied in other disease area, there is currently sparse literature for multimorbidity in pregnant women. Pregnant women with multimorbidity are at increased risk of adverse outcomes for mother and child.[44 150] Although maternal death is rare in the United Kingdom (UK), ninety percent of women who died during/within a year after pregnancy had multiple health and social risk factors.[151]

Multimorbidity increases health care burden for patients, for instance, needing to attend multiple health care appointments and being on multiple medications.[149] These challenges increase during pregnancy, with the addition of specialist antenatal clinic appointments and monitoring, and concerns regarding how medications may affect the developing fetus.

Despite this, there is a dearth of basic information on the prevalence and types of pre-existing health conditions affecting pregnant women. Better understanding of the epidemiology of multimorbidity in pregnant women could help policy makers and health care providers plan services to prevent women from developing multimorbidity, for early detection and optimal management of health conditions prior to conception, and tailor maternity services to pregnant women with multimorbidity.

In the UK, most people are registered with a general practitioner (GP), the gatekeepers to primary care and specialist referrals. In secondary care, health care utilization administrative data are recorded for reimbursement. Thus, both provide good data sources for multimorbidity and pregnancy research.

This study aims to describe the epidemiology of pre-existing multimorbidity in pregnant women. It also seeks to understand the utility of routine health care datasets in the study of

multimorbidity in pregnant women, by using three datasets from different health care settings and across the four UK nations (England, Northern Ireland, Scotland, and Wales).

3.3 Methods

Study design and study period

This was a cross sectional analysis of the prevalence of pre-existing multimorbidity prior to the start of pregnancy in the UK across three separate databases. We included index pregnancies where the conception date was between 1/1/2018 and 31/12/2018.

Inclusion and exclusion criteria

Women aged 15-49 years with a conception date in 2018 were eligible. Last menstrual period or gestational day 0 was considered the conception date.[152] When a woman had more than one pregnancy episode in 2018, the first recorded pregnancy in that year was included (not necessarily the first ever pregnancy). Women whose data did not meet standard quality checks were excluded (Additional File 3.1).

Data sources

This study used three datasets from different health settings, covering all four nations in the UK: Clinical Practice Research Datalink, (CPRD, England, Northern Ireland, Scotland, and Wales), Secure Anonymized Information Linkage (SAIL, Wales) and Scottish Morbidity Records (SMR, Scotland).

Primary care

CPRD GOLD contains anonymized, longitudinal medical records for over 19 million patients in the UK (England, Northern Ireland, Scotland and Wales) from over 940 participating general practices; it currently covers 4% of UK GP practices and is widely acknowledged to be representative of the UK population.[153] It includes data on demographics, diagnoses and prescriptions.[153] Linkage to area based deprivation index was available for patients in England. Within CPRD GOLD, the CPRD Pregnancy Register is an algorithm that takes information from maternity, antenatal and delivery health records to detect pregnancy episodes and their outcomes.[152]

The SAIL databank is a whole population level database in Wales. It is a repository of anonymized health and socio-economic administrative data and provides linkage at an individual level.[154] It holds data for 4.8 million people and covers 80% of Welsh GP practices.[154] Within SAIL, the National Community Child Health Dataset was used to detect pregnancies and was linked to the Welsh Longitudinal General Practice dataset and the Welsh Demographic Service dataset for diagnoses, prescriptions and demographics data respectively.

Secondary care and community prescriptions

SMR data was available from two Scottish regional health boards: National Health Service (NHS) Tayside and NHS Fife.[155] A dataset was created linking the Scottish Maternity Records (SMR02) to data from Hospital Admissions (SMR01), Mental Health Inpatients (SMR04), Accident and Emergency, and the Demography and Death registry. This covered diagnoses and demographic data for all inpatient stays and day cases for residents in the two regions. The dataset was also linked to the Prescribing Information System for data on all medications dispensed in the community. Pregnancies were detected from maternity records or pregnancy-related hospital admissions.

Definition of multimorbidity

Multimorbidity was defined by the presence of two or more pre-existing long-term physical or mental health conditions prior to the index pregnancy. We defined long-term conditions as conditions that have ongoing significant impact on patients, including conditions that are relapsing and remitting in nature.

One of the wider research aims is to mitigate the effect of multimorbidity on adverse pregnancy outcomes. As pregnancy related conditions (e.g., gestational diabetes and pregnancy induced hypertension) will be subsequently studied as maternal outcomes, they were not included in the definition of pre-existing multimorbidity.

An exhaustive list of long-term health conditions was first identified from existing literature,[65] [151] [156] in particular based on the work commissioned by Health Data Research UK on multimorbidity conceptualization [156] and health conditions that were leading indirect cause of death in the UK maternal mortality report (MBRRACE).[151] This list and phenome definitions were refined and harmonized through workshops with our research advisory group, consisting of patient and public representatives, clinicians from general practice, obstetrics, maternal medicine, psychiatry, public health, and data scientists. Seventy-nine health conditions were selected on the following basis: (i) prevalence; (ii) potential to impact on pregnancy outcomes; (iii) considered important by women; and (iv) recorded in the study datasets.

Diagnoses of these 79 long-term health conditions were determined from Read Codes version 2 (primary care datasets) and the International Classification of Disease 10th version (secondary care datasets) [157]. The validity of diagnostic coding has previously been shown to be good in primary care records and generally health conditions under payment for performance schemes, such as Quality Outcomes Framework, are well coded.[158] Code lists and phenome definitions used are available in Additional Files 3.2 and 3.3.

Data analysis

The primary analysis was the prevalence of pre-existing multimorbidity in pregnant women. The denominator was the total number of index pregnancies identified in 2018, regardless of the pregnancy outcome. Additional analysis was performed for multimorbidity with at least one mental health conditions and active multimorbidity. Active multimorbidity limits common transient/episodic conditions (e.g., mental health, dermatological and atopic conditions, and headaches) to those that were active in the 12 months preceding index pregnancy (Additional File 3.3).

Multivariable logistic regression was performed to examine the association of multimorbidity with maternal age (five-yearly categories), ethnicity, deprivation quintiles (patient level Index of Multiple Deprivation [IMD] for all three datasets), latest maternal pre-pregnancy body mass index (BMI) categories, latest pre-pregnancy smoking status, and gravidity (total number of pregnancies up to and including index pregnancy). Obesity was considered a covariate (BMI categories) instead of a health condition. For CPRD, practice level IMD was available for all four nations, but patient level IMD was only available for England, therefore, the regression analysis was limited to England. We then described the prevalence of individual health conditions, and the prevalence of mutually exclusive multimorbidity combinations.

Missing data were assigned to separate categories and included in the analyses. Sensitivity analysis was performed for CPRD (England), where missing ethnicity was substituted with data from linked hospital administrative data, and missing patient level IMD was substituted with practice level IMD.

Study results were presented for each dataset separately. Data were not combined as there was a possibility of patient overlap between CPRD (Wales, Scotland) with both SAIL (Wales) and

SMR (Scotland). Deduplication was not possible as the datasets are anonymized, and only aggregated data were exported within the permission of the data access approval.

Post hoc analysis

As our study found no association of recorded multimorbidity with social deprivation, we conducted a post hoc analysis in the CPRD cohort, with the list of conditions used to define multimorbidity in a seminal paper that found this association.[6] We also examined the association of selected health conditions with deprivation and ethnicity. Guided by our patient representatives, we analysed the prevalence of multimorbidity for selected health conditions to illustrate the burden of multimorbidity. The selected health conditions were: i) the top ten most common individual health conditions in this study, and ii) leading causes of maternal deaths.[151]

Analysis was performed using STATA 16 and R. The study is reported in accordance with the RECORD guideline (Additional File 3.4).

3.4 Results

Study population

Overall, there were 37,641 (CPRD), 27,782 (SAIL) and 6,099 (SMR) pregnant women aged 15-49 years included in the analysis in 2018. Additional Figure 3.1 presents the flow chart for the study population selection. The characteristics of the study cohort is presented in Table 3.1 and Additional Table 3.1. Most of the study participants were 20-34 years old, of White ethnicity, of normal weight or were overweight pre-pregnancy and were non-smoker pre-pregnancy. Linkage to area-based data for patient level IMD was available for 75% of the CPRD study cohort in England. There were more affluent women in the primary care dataset but vice versa for SMR.

Multimorbidity

The prevalence of pre-existing multimorbidity in pregnant women was 44.2% (95% confidence intervals [CI] 43.7% to 44.7%), 46.2% (45.6% to 46.8%) in CPRD and SAIL respectively (primary care dataset) but was halved in SMR's secondary care and community prescription dataset, 19.8% (18.8% to 20.8%).

Over seventy percent of pregnant women with multimorbidity had mental health condition/s: 31.3% (30.8% to 31.8%), 33.7% (33.1% to 34.2%) and 14.6% (16.0% to 17.9%) of pregnant women had multimorbidity with at least one mental health conditions in CPRD, SAIL and SMR respectively. The prevalence of active multimorbidity was half that of the primary analysis in primary care datasets, 24.2% (23.8% to 24.6%) and 23.5% (23.0% to 24.0%) for CPRD and SAIL respectively, but remained similar for SMR, 17.0% (16.0% to 17.9%). The percentage of pregnant women by the total morbidity count is available in Additional Table 3.2.

Characteristics associated with multimorbidity

The prevalence of pre-existing multimorbidity by the characteristics of pregnant women is presented in Additional Table 3.3. In the CPRD England study cohort (n=13,075), when all characteristics were adjusted for, increasing maternal age and gravidity remained significantly associated with multimorbidity (maternal age 45-49 years, aOR 1.8, 95% CI 1.0 to 3.2; gravidity ≥5, 1.7, 1.5 to 1.9); pregnant women with BMI 25 to 29.9 (aOR 1.2, 95% CI 1.1 to 1.3), BMI 30+ (1.6, 1.4 to 1.8), were smokers (1.6, 1.5 to 1.8) or ex-smokers (1.4, 1.3 to 1.6) had higher odds of multimorbidity. However, higher odds of multimorbidity were not observed in pregnant women of ethnic minority groups or from more deprived socioeconomic groups (Table 3.2). Findings were similar in the sensitivity analysis of CPRD (England) using

substituted data for missing ethnicity and IMD (Additional Table 3.4). In SAIL, the effect sizes of characteristics were generally similar to that in CPRD (England).

In SMR, after adjusting for all characteristics, higher odds of multimorbidity were observed only in those age 20-24 and 25-29 years, had gravidity of 3+, BMI 30+, were smokers and ex-smokers and those from more deprived socioeconomic groups. The odds of multimorbidity were not higher in ethnic minority groups (Table 3.2).

Post hoc analysis

Post hoc analysis was performed to explore whether the lack of association of multimorbidity with deprivation in our primary care datasets was, in part, due to the health conditions we used to define multimorbidity. Logistic regression was repeated in CPRD (England) with the list of 31 health conditions used to define multimorbidity in Barnet et al's seminal paper,[6] the adjusted variables were added in a step-wise manner. After adjusting for maternal age, ethnicity, and gravidity, increasing levels of deprivation were associated with higher odds of multimorbidity (most deprived quintile aOR 1.30, 95% CI 1.08 to 1.57). This association was attenuated and was no longer significant when raised BMI and smoking status were added to the model (aOR 1.05, 0.87 to 1.27, Additional Table 3.5, Figure 3.1).

To test this hypothesis further, we repeated the logistic regression in the CPRD (England) cohort by removing eight health conditions that were associated with being in less deprived socioeconomic groups. When adjusted for maternal age, ethnicity, and gravidity, multimorbidity (defined by 71 health conditions) was associated with deprivation (most deprived quintile aOR 1.26, 1.10 to 1.44). This association was attenuated and was no longer significant when raised BMI and smoking status were added (aOR 1.08, 0.94 to 1.24, Additional Table 3.6).

Individual health conditions

Table 3.3 presents the top 20 most prevalent health conditions in our study cohort. The top four most common health conditions across all three datasets were depression, anxiety (both known as common mental health disorders), allergic rhinoconjunctivitis and asthma, with the prevalence of common mental health disorders being consistently around 20%. The full list of prevalence for each health condition is presented in Additional Table 3.7.

Combinations of multimorbidity

Table 4 presents the top ten most common combinations of multimorbidity, the most prevalent combinations being *depression and anxiety* in primary care dataset (2.2% and 2.7% of pregnant women in CPRD and SAIL respectively) and *common mental health disorders and asthma* for SMR (3.2%). The presented prevalence is for mutually exclusive multimorbidity combinations, and therefore prevalence for *depression and anxiety* will not include women with depression, anxiety, and other health condition/s. When only considering physical conditions, the most common combination was *asthma and allergic rhinoconjunctivitis* (1.7%, 2.1% and 2.2% in CPRD, SAIL and SMR respectively).

Prevalence of multimorbidity in pregnant women with selected health conditions

These examples have been provided to illustrate the burden of using the CPRD (UK) pregnancy cohort in 2018. The featured health conditions were the leading causes of maternal deaths in the MBRRACE-UK report.[151]

Cardiovascular disease (ischemic heart disease, stroke/transient ischemic attack, heart failure, atrial fibrillation, congenital heart disease, valvular heart disease, cardiomyopathy, hypertension) affected 2.0% (745/37641) of pregnant women, of whom 80.1% (597/745) had multimorbidity. Less than one percent (246/37641) of pregnant women had a history of venous

thromboembolism, among whom 85.8% (211/246) had multimorbidity. Epilepsy affected 1.4% (543/37641) pregnant women, among whom 80.7% (438/543) had multimorbidity.

Prevalence of selected health conditions by social deprivation and ethnicity

Table 3.5 presents examples to illustrate the difference in the prevalence of individual health conditions by patient level social deprivation and ethnicity using CPRD (England). Mental health conditions, asthma and epilepsy increased with deprivation. In contrast, some of the common health conditions were more common in the affluent groups, including anxiety, migraine, irritable bowel syndrome, and polycystic ovarian syndrome. For ethnicity, mental health conditions, asthma, migraine, irritable bowel syndrome and psoriasis were more prevalent in White ethnic group; whilst allergic rhinoconjunctivitis and polycystic ovarian syndrome were more prevalent in ethnic minority groups.

3.5 Discussion

Main findings

This study used contemporaneous, routinely collected datasets to study the epidemiology of multimorbidity (defined as having two or more long-term physical or mental health conditions) in pregnant women in the UK. Two in five pregnant women had pre-existing multimorbidity. One in five pregnant women had multimorbidity that were active in the year before pregnancy. Seven in ten pregnant women with multimorbidity had a history of mental health condition/s. In women with conditions that are known to be leading causes of maternal death,[151] four in five had pre-existing multimorbidity. Pregnant women with multimorbidity were more likely to be older, multigravid, smoked or have raised BMI preconception.

Strengths and limitations

This study utilized electronic health records which provided a rich source of data and is generalizable across different settings. It avoided misclassification bias associated with self-reported surveys. However, as with all research that use routine health records, it is subjected to residual confounding and can be limited by the quality and consistency of data entry by clinicians and administrators.[159] We have attempted to improve the accuracy of health conditions ascertainment through the design of our phenome definitions (e.g., using additional age limit and phenomes by prescriptions).

The definition of multimorbidity used in this study was based on simple counting of conditions, without weightings. There is currently no single multimorbidity index that can measure multimorbidity in all settings definitively.[57] The only currently available validated comorbidity index in maternal health research was developed using secondary care data and only included 20 conditions,[160] in comparison to the 79 conditions prioritized by our multidisciplinary group and patient representatives. Obesity was analysed as a covariate (BMI categories) in this study; the prevalence of multimorbidity would be higher if obesity was considered a long-term health condition.

Utility of the different datasets

Compared with CPRD and SAIL primary care datasets, the prevalence of non-life-threatening health conditions such as allergic rhinoconjunctivitis, migraine, irritable bowel syndrome and, ultimately, multimorbidity was lower in the Scottish secondary care with linked community prescription dataset.

This is likely to reflect that health conditions seen in primary care encompass the whole severity spectrum. Some common conditions, such as anxiety or depression, may only present to primary care, some of which are managed conservatively without prescribed medications. In

contrast, the Scottish secondary care and community prescription database would only capture the severe spectrum of a condition that requires hospital attendance or regular prescriptions and may under-estimate the prevalence of multimorbidity. This confirms that primary care health records may be a more comprehensive data source to study pre-existing multimorbidity in pregnant women, and to identify the target at risk population for preconception intervention.

Similar findings were observed in both CPRD, and SAIL add to the validity of these findings. Whilst CPRD offered the benefit of representing data from all four UK nations, SAIL offered a more complete coverage at a population level in Wales with good follow up throughout an individual's lifetime even when they change GP practices.

Our study highlighted a shortfall in the recording of ethnicity and preconception body mass index, and to a lesser extent, smoking status preconception for pregnant women in routine health records. Patient level data for social deprivation was limited by the availability of data linkage in CPRD. Although sensitivity analysis in the CPRD (England) dataset with substituted ethnicity and IMD showed similar findings with the primary analysis, the interpretation of the association analysis should be taken with caution. In SAIL, pregnancy episodes were detected from the National Community Child Health database (NCCHD), and this does not include pregnancies that resulted in early pregnancy loss; hence the gravidity data generated from this database is likely to be an under-estimation. Historical data from the SMR datasets were available from 2005-2019. This meant that if a pregnant woman had a history of a health condition prior to this time period, it may not be captured. This limitation is more likely to affect older women in the SMR pregnancy cohort and may partially account for the lack of association of maternal age with multimorbidity. Further limitations of each dataset are outlined in Additional File 3.5.

Results in the context of what is known

High prevalence of multimorbidity in pregnant women

The current evidence for the prevalence of multimorbidity in pregnant women is scarce and findings vary widely. This ranged between <10% to 35%.[44 150 161 162] The high prevalence of multimorbidity in pregnant women in this study is concerning as it is associated with adverse outcomes for mother and child.[44 150 151] In the latest MBRRACE UK maternal mortality enquiry report, 90% of maternal deaths up to one year post pregnancy occurred in women with multiple health and social risk factors.[151] MBRRACE has called for national guidance for the management of pregnant women with multiple morbidities and social factors.[163] Recently, the Ockenden report (a high profile UK independent inquiry of maternity services at a local hospital) highlighted the need for involvement of maternal medicine specialist and maternal mental health services for managing women with complex pregnancies.[164]

Clinical implications

Our study provided a current snapshot of how multimorbidity is distributed in the UK in terms of socio-demographics, the health conditions that constitute multimorbidity and the common combinations of health conditions in pregnant women. Mental health conditions were particularly prevalent and contributed to 70% of multimorbidity in pregnant women. Psychiatric causes were amongst the leading cause of maternal death in the UK.[151] Our findings further support the need for integration of mental health services with maternity services and equitable access to perinatal mental health services in the UK.[165]

Social deprivation, ethnicity and multimorbidity in pregnant women

Post hoc analysis found that some health conditions were more prevalent in affluent pregnant women (e.g., anxiety, irritable bowel syndrome), potentially masking the association of multimorbidity with social deprivation. When these conditions were removed, multimorbidity

was associated with social deprivation but this effect was not observed when BMI and smoking status were also adjusted for. This suggests that smoking and obesity may mediate the relationship between social deprivation and multimorbidity in pregnant women.

Many of the topmost common health conditions were more prevalent in White pregnant women, particularly mental health conditions. This may have contributed to the lack of association of ethnic minority groups with multimorbidity. Previous literature reported that people of ethnic minority are less likely to access/receive mental health support/treatment.[166] [167] In addition, stigma associated with mental health conditions was reported to be higher in ethnic minorities.[168]

Both observations mean that there could be health care access issues for some of the common health conditions, especially mental health conditions, for people from socially deprived and ethnic minority groups prior to pregnancy. In addition, it strengthens the importance of addressing smoking and obesity preconception especially in pregnant women with multimorbidity from socially deprived groups. Smoking and obesity are two well-known modifiable risk factors for adverse pregnancy outcomes,[169] [170] the added impact of multimorbidity is likely to compound this. Further research is required to quantify this, but interventions addressing smoking and obesity may help reduce adverse outcomes in pregnant women with multimorbidity.

Research implications

Despite the high prevalence of multimorbidity in pregnant women, and the associated adverse outcomes, there is currently a paucity of evidence in this field. The MuM-PreDiCT consortium is a multidisciplinary collaboration across all four nations in the UK, including women with lived experience of multimorbidity and pregnancy. Our next step is to quantify the impact of multimorbidity on pregnancy, maternal and offspring outcomes. This will provide crucial

information for women with multimorbidity who are planning a pregnancy and results from the outcome studies may require us to reconsider how we categorize high-risk pregnancy. The ultimate aim is to produce high quality evidence that would guide clinical practice to prevent pregnancy complications and to optimize long-term maternal and offspring health for pregnant women with multimorbidity.

Conclusion

A significant proportion of women enter pregnancy with pre-existing multimorbidity, especially with mental health condition/s. Amongst pregnant women with health conditions known to be leading causes of maternal death, prevalence of multimorbidity was high. Pregnant women with multimorbidity were more likely to smoke and have a raised BMI and support maybe required to address this. There may be health care access inequalities for some health conditions, especially mental health conditions in pregnant women from deprived or ethnic minority groups.

DECLARATIONS

Ethics approval and consent to participate

CPRD has ethics approval from the Health Research Authority to support research using anonymised patient data. The study has been approved by the Independent Scientific Advisory Committee for CPRD (reference: 20_181R) and by SAIL Information Governance Review Panel for SAIL databank. The Health Informatics Centre (HIC) at the University of Dundee provided a linked dataset within a Safe Haven environment for this study. Dataset was obtained under HIC Standard Operating Procedures (SOP). NHS Tayside Research Ethics Committee have approved these SOPs (18/ES/0126). The School of Medicine Ethics Committee, acting on behalf of the University of St Andrews Teaching and Research Ethics Committee approved this project. As the study data are de-identified, consent is not required. All methods were performed in accordance with the guidelines and regulations as stipulated by the respective data providers.

Consent for publication

As the study data are de-identified, consent for publication is not required.

Availability of data and materials

The data that support the findings of this study are available from CPRD, SAIL and the HIC at the University of Dundee but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Competing interests

None declared.

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Authors' contributions

Our authors list includes PPI co-investigators NM and RP. SIL, AAL, UA, JIK, HH, AS, AA, BT, CNP, CY, KAE, NM, PB, RP, ST, MB, DOR, KMA, SB, KN, CM conceived the study, identified the list of health conditions to define multimorbidity and defined the phenome; SB, JIK, CM, AAL, UA, KN, SIL, AS acquired the data and required approval; SIL led the data analysis and drafting of the manuscript with contribution from AS, AAL, UA, JIK, AFF, FC; AS, AA, KN, SIL, HH curated the Read codes, UA and AAL curated the ICD-10 codes; SIL, AAL, UA, JIK, AFF, HH, AS, AA, BT, CNP, CDM, CY, FC, GS, KAE, ZV, ML, NM, PB, RP, ST, MB, DOR, KMA, SB, KN, CM contributed to the interpretation of the data. AAL, UA, JIK, AFF, HH, AS, AA, BT, CNP, CDM, CY, FC, GS, KAE, ZV, ML, NM, PB, RP, ST, MB,

DOR, KMA, SB, KN, CM critically revised the manuscript for important intellectual content; all authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Patient Involvement

Our patient representatives comprised of two patient and public (PPI) co-investigators and a PPI advisory group of six women with lived experience of multimorbidity and pregnancy, with various long-term conditions. They were involved with selecting the 79 long-term health conditions used to define multimorbidity. They were also involved in interpreting the results, in particular, they noted that prevalent conditions may be on the milder spectrum and do not necessarily require specialist antenatal care. This led to additional analysis on health conditions that were leading causes of maternal death in the MBRRACE report.[151] Their feedback shaped how we presented and disseminated our findings to the public, including choosing the terminology of describing multimorbidity that they were comfortable with (two or more long-term conditions). Finally, our PPI co-investigators contributed to the preparation of this manuscript.

Table 3.1: Baseline characteristics of pregnant women in CPRD (UK), SAIL (Wales) and SMR (Scotland) in 2018

Characteristics	Frequency (percentage)					
	CPRD (UK)		SAIL (Wales)		SMR (Scotland)	
Total	37641	-	27782	-	6099	-
Nation						
England	13075	(34.74%)	-	-	-	-
Northern Ireland	2984	(7.93%)	-	-	-	-
Scotland	12559	(33.37%)	-	-	-	-
Wales	9023	(23.97%)	-	-	-	-
Age categories (5 yearly)						
15-19	2534	(6.73%)	1537	(5.53%)	422	(6.92%)
20-24	6604	(17.54%)	5360	(19.29%)	1147	(18.81%)
25-29	10204	(27.11%)	8617	(31.02%)	1830	(30.00%)
30-34	10723	(28.49%)	8081	(29.09%)	1746	(28.63%)
35-39	5970	(15.86%)	3549	(12.77%)	803	(13.17%)
40-44	1428	(3.79%)	603	(2.17%)	138	(2.26%)
45-49	178	(0.47%)	35	(0.13%)	13	(0.21%)
Gravidity						
1	11480	(30.50%)	13006	(46.81%)	1800	(29.51%)
2	9895	(26.29%)	9972	(35.89%)	1992	(32.66%)
3	6734	(17.89%)	3252	(11.71%)	1105	(18.12%)
4	4004	(10.64%)	1035	(3.73%)	580	(9.51%)
≥5	5528	(14.69%)	517	(1.86%)	618	(10.13%)
Missing	-	-	-	-	4	(0.07%)
Ethnicity						
Asian / South Asians*	1261	(3.35%)	418	(1.50%)	149	(2.44%)
Black	973	(2.58%)	178	(0.64%)	23	(0.38%)
Mixed	305	(0.81%)	121	(0.44%)	8	(0.13%)
Other	528	(1.40%)	229	(0.82%)	91	(1.49%)
White	20818	(55.31%)	17430	(62.74%)	4903	(80.39%)
Missing	13756	(36.55%)	9406	(33.86%)	925	(15.17%)
BMI (kg/m^2)						
Underweight (<18.5)	1217	(3.23%)	1287	(4.63%)	92	(1.51%)
Normal Weight (18.5-24.9)	14440	(38.36%)	9485	(34.14%)	1478	(24.23%)
Overweight (25-29.9)	8075	(21.45%)	5658	(20.37%)	1010	(16.56%)
Obese (30+)	7178	(19.07%)	5372	(19.34%)	1279	(20.97%)
Missing	6731	(17.88%)	5980	(21.52%)	2240	(36.73%)

Characteristics	Frequency (Percentage)		
	CPRD (UK)	SAIL (Wales)	SMR (Scotland)
Smoking			
Non-Smoker	22395 (59.50%)	10151 (36.54%)	3349 (54.91%)
Ex-smoker	5707 (15.16%)	8022 (28.87%)	863 (14.15%)
Smoker	8237 (21.88%)	6612 (23.80%)	1041 (17.07%)
Missing	1302 (3.46%)	2997 (10.79%)	846 (13.87%)
Patient level deprivation quintiles (IMD)	**Only available for England**[†]		
1, least deprived	2326 (17.79%)	6455 (23.23%)	722 (11.84%)
2	1835 (14.03%)	5460 (19.65%)	1039 (17.04%)
3	1878 (14.36%)	4779 (17.20%)	979 (16.05%)
4	1853 (14.17%)	4032 (14.51%)	1253 (20.54%)
5, most deprived	1908 (14.59%)	3832 (13.79%)	1344 (22.04%)
Missing	3275 (25.05%)	3224 (11.60%)	762 (12.49%)

[*] South Asian for CPRD, Asian for SAIL and SMR

[†] Aggregate IMD quintiles cannot be provided for UK as each nation has its specific IMD; data presented here is patient level IMD for England only (n=13075). Practice level IMD for all four UK nations in CPRD is available in Additional Table 3.1.

BMI: body mass index, CPRD: Clinical Practice Research Datalink, IMD: Index of Multiple Deprivation, SAIL: The Secure Anonymized Information Linkage databank, SMR: Scottish Morbidity Records

Table 3.2: Logistic regression for pre-existing multimorbidity by women's characteristics

Characteristics	CPRD (England), n=13075						SAIL (Wales), n=27782						SMR (Scotland), n=6099					
	Unadjusted OR (95% CI)			Adjusted OR (95% CI)			Unadjusted OR (95% CI)			Adjusted OR (95% CI)			Unadjusted OR (95% CI)			Adjusted OR (95% CI)		
Age categories (5 yearly)																		
15-19	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
20-24	1.60	(1.34	-1.90)	1.17	(0.97	-1.42)	1.64	(1.45	-1.85)	1.10	(0.96	-1.26)	1.48	(1.11	-1.94)	1.42	(1.05	-1.92)
25-29	1.80	(1.52	-2.12)	1.21	(1.01	-1.45)	1.93	(1.72	-2.17)	1.21	(1.06	-1.39)	1.36	(1.02	-1.81)	1.45	(1.07	-1.95)
30-34	1.84	(1.56	-2.17)	1.26	(1.05	-1.52)	2.19	(1.94	-2.46)	1.36	(1.19	-1.56)	1.18	(0.89	-1.58)	1.32	(0.97	-1.80)
35-39	1.95	(1.64	-2.32)	1.28	(1.06	-1.56)	2.54	(2.24	-2.89)	1.64	(1.42	-1.90)	1.23	(0.90	-1.69)	1.37	(0.97	-1.93)
40-44	2.55	(2.04	-3.20)	1.61	(1.26	-2.06)	3.19	(2.63	-3.88)	2.20	(1.77	-2.73)	1.04	(0.62	-1.75)	1.18	(0.68	-2.04)
45-49	2.98	(1.74	-5.11)	1.81	(1.04	-3.17)	3.88	(1.94	-7.76)	4.11	(1.83	-9.26)	1.56	(0.42	-5.87)	1.67	(0.45	-6.93)
Gravidity																		
1	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
2	1.07	(0.97	-1.18)	0.98	(0.89	-1.08)	1.20	(1.14	-1.26)	1.03	(0.97	-1.09)	1.09	(0.92	-1.30)	1.03	(0.86	-1.23)
3	1.35	(1.22	-1.50)	1.18	(1.06	-1.32)	1.51	(1.40	-1.63)	1.16	(1.07	-1.27)	1.30	(1.07	-1.58)	1.17	(0.95	-1.43)
4	1.52	(1.35	-1.72)	1.30	(1.15	-1.48)	1.89	(1.67	-2.15)	1.39	(1.21	-1.60)	1.77	(1.41	-2.21)	1.49	(1.17	-2.01)
≥5	2.11	(1.9	-2.35)	1.68	(1.50	-1.89)	2.73	(2.27	-3.29)	1.81	(1.48	-2.22)	2.70	(2.21	-3.34)	2.19	(1.75	-2.76)
Missing	-	-	-	-	-	-	-	-	-	-	-	-	1.75	(0.18	-16.88)	1.31	(0.13	-13.43)
Ethnicity																		
Asian /South Asian*	0.60	(0.52	-0.69)	0.66	(0.56	-0.77)	0.48	(0.39	-0.59)	0.53	(0.43	-0.66)	0.44	(0.26	-0.75)	0.51	(0.29	-0.87)
Black	0.76	(0.63	-0.91)	0.73	(0.61	-0.89)	0.31	(0.22	-0.43)	0.31	(0.22	-0.45)	0.78	(0.27	-2.31)	0.86	(0.29	-2.58)
Mixed	0.88	(0.67	-1.16)	0.95	(0.72	-1.26)	0.78	(0.54	-1.11)	0.86	(0.59	-1.27)	-	-	-	-	-	-
Other	0.55	(0.44	-0.70)	0.61	(0.48	-0.77)	0.31	(0.23	-0.42)	0.33	(0.24	-0.45)	0.66	(0.38	-1.15)	0.59	(0.33	-1.05)
White	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
Missing	0.85	(0.78	-0.93)	0.94	(0.86	-1.03)	0.61	(0.58	-0.65)	0.74	(0.70	-0.78)	0.62	(0.51	-0.75)	0.63	(0.52	-0.77)

	CPRD (England), n=13075						SAIL (Wales), n=27782						SMR (Scotland), n=6099					
Characteristics	**Unadjusted OR (95% CI)**			**Adjusted OR (95% CI)**			**Unadjusted OR (95% CI)**			**Adjusted OR (95% CI)**			**Unadjusted OR (95% CI)**			**Adjusted OR (95% CI)**		
BMI (kg/m^2)																		
Underweight (<18.5)	0.89	(0.73	-1.07)	0.91	(0.75	-1.10)	1.06	(0.94	-1.19)	1.08	(0.96	-1.22)	1.59	(0.96	-2.63)	1.27	(0.68	-1.93)
Normal Weight (18.5-24.9)	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
Overweight (25-29.9)	1.20	(1.10	-1.31)	1.16	(1.05	-1.27)	1.19	(1.11	-1.27)	1.17	(1.09	-1.25)	1.31	(1.06	-1.62)	1.33	(0.75	-2.16)
Obese (30+)	1.69	(1.53	-1.86)	1.59	(1.44	-1.76)	1.57	(1.47	-1.69)	1.51	(1.41	-1.62)	1.98	(1.64	-2.39)	1.90	(1.55	-2.28)
Missing	0.60	(0.54	-0.67)	0.73	(0.64	-0.82)	0.26	(0.24	-0.28)	0.61	(0.56	-0.67)	1.21	(1.02	-1.44)	1.24	(1.03	-1.49)
Smoking																		
Non-Smoker	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
Ex-Smoker	1.62	(1.47	-1.78)	1.43	(1.29	-1.57)	1.82	(1.71	-1.93)	1.58	(1.49	-1.68)	1.47	(1.22	-1.78)	1.32	(1.10	-1.60)
Smoker	1.69	(1.54	-1.84)	1.61	(1.46	-1.77)	2.19	(2.05	-2.33)	2.03	(1.90	-2.17)	2.54	(2.17	-2.95)	2.06	(1.79	-2.51)
Missing	0.31	(0.24	-0.41)	0.48	(0.36	-0.64)	0.07	(0.06	-0.08)	0.12	(0.10	-0.14)	1.16	(0.95	-1.41)	1.19	(0.96	-1.47)
Patient level deprivation quintiles (IMD)																		
1, least deprived	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-	Ref	-	-
2	0.95	(0.84	-1.07)	0.92	(0.81	-1.05)	0.87	(0.81	-0.93)	0.88	(0.82	-0.96)	1.33	(0.99	-1.77)	1.22	(0.92	-1.64)
3	1.00	(0.88	-1.13)	0.93	(0.82	-1.05)	0.90	(0.83	-0.97)	0.92	(0.85	-1.00)	1.89	(1.40	-2.45)	1.56	(1.17	-2.07)
4	0.98	(0.87	-1.11)	0.90	(0.79	-1.02)	0.78	(0.72	-0.84)	0.87	(0.79	-0.95)	2.67	(2.06	-3.49)	2.18	(1.67	-2.87)
5, most deprived	0.96	(0.85	-1.09)	0.88	(0.77	-1.00)	0.88	(0.82	-0.96)	0.90	(0.83	-0.99)	2.49	(1.89	-3.19)	1.77	(1.34	-2.34)
Missing	0.90	(0.81	-1.00)	0.86	(0.77	-0.96)	0.80	(0.74	-0.88)	0.90	(0.82	-0.99)	1.82	(1.36	-2.44)	1.65	(1.23	-2.23)

[*] South Asian for CPRD, Asian for SAIL and SMR

Adjusted for maternal age, gravidity, ethnicity, BMI, smoking status, patient level IMD.

BMI: body mass index, CI: confidence intervals, CPRD: Clinical Practice Research Datalink, IMD: Index of Multiple Deprivation, OR: odds ratio, Ref: reference group, SAIL: The Secure Anonymized Information Linkage databank, SMR: Scottish Morbidity Records

Table 3.3: Top 20 most prevalent individual health conditions in pregnant women

CPRD (UK), n=37641					SAIL (Wales), n=27782				SMR (Scotland), n=6099			
No	**Health conditions**	**Percentage, % (95% CI)**			**Health conditions**	**Percentage, % (95% CI)**			**Health conditions**	**Percentage, % (95% CI)**		
1	Depression (diagnosis)	23.43	(23.01	-23.87)	Depression (diagnosis)	24.07	(23.57	-24.58)	Common mental health disorders (prescription)	22.66	(21.61	-23.71)
2	Anxiety (diagnosis)	18.98	(18.58	-19.38)	Anxiety (diagnosis)	23.05	(22.56	-23.55)	Asthma	9.94	(9.19	-10.69)
3	Allergic rhinoconjunctivitis	16.35	(15.98	-16.73)	Allergic rhinoconjunctivitis	18.53	(18.08	-19.00)	Allergic rhinoconjunctivitis	7.56	(6.90	-8.22)
4	Asthma	14.63	(14.27	-14.99)	Asthma	17.17	(16.73	-17.62)	Peptic ulcer disease/GORD	6.98	(6.35	-7.62)
5	Migraine	12.71	(12.38	-13.05)	Migraine	13.47	(13.07	-13.88)	Atopic eczema	6.35	(5.73	-6.96)
6	Other mental health conditions	8.85	(8.57	-9.14)	Other mental health conditions	9.43	(9.09	-9.78)	Other mental health conditions	4.84	(4.30	-5.38)
7	IBS	7.97	(7.70	-8.25)	IBS	7.83	(7.52	-8.15)	Migraine	3.69	(3.22	-4.16)
8	Other skin conditions	5.47	(5.25	-5.71)	Other chronic headaches	6.60	(6.31	-6.90)	IBS	3.16	(2.73	-3.60)
9	PCOS	4.66	(4.45	-4.88)	Other skin conditions	5.71	(5.44	-5.98)	Thyroid disorder	3.12	(2.68	-3.55)
10	Psoriasis	3.90	(3.70	-4.10)	Atopic eczema	3.97	(3.74	-4.20)	Severe mental illness	2.26	(1.89	-2.64)
11	Female infertility	3.81	(3.62	-4.01)	PCOS	3.96	(3.73	-4.20)	Cholelithiasis	2.15	(1.78	-2.51)
12	Other chronic headaches	3.53	(3.35	-3.72)	Psoriasis	3.62	(3.41	-3.85)	Depression (diagnosis)	1.71	(1.38	-2.03)
13	Thyroid disorder	3.34	(3.16	-3.52)	Thyroid disorder	2.45	(2.28	-2.64)	Epilepsy	1.57	(1.26	-1.89)
14	Atopic eczema	3.06	(2.89	-3.24)	Alcohol misuse	2.25	(2.08	-2.43)	Anxiety (diagnosis)	1.36	(1.07	-1.65)
15	Severe mental illness	2.42	(2.26	-2.58)	Substance misuse	2.20	(2.03	-2.38)	Substance misuse	1.23	(0.95	-1.51)
16	Cholelithiasis	2.02	(1.88	-2.17)	Cholelithiasis	2.11	(1.95	-2.29)	Female infertility	1.18	(0.91	-1.45)
17	Substance misuse	1.98	(1.84	-2.13)	Severe mental illness	2.07	(1.91	-2.24)	Endometriosis	1.05	(0.79	-1.31)
18	Eating disorder	1.88	(1.74	-2.02)	Eating disorder	1.80	(1.65	-1.97)	Hypertension	0.93	(0.69	-1.18)
19	Endometriosis	1.68	(1.55	-1.82)	Inflammatory arthritis	1.40	(1.27	-1.55)	Diabetes mellitus	0.79	(0.57	-1.01)
20	Inflammatory arthritis	1.46	(1.34	-1.59)	Endometriosis	1.31	(1.18	-1.45)	Psoriasis	0.71	(0.50	-0.92)

Common mental health disorders (CMHD): anxiety or depression by prescription (drug phenome using community prescription data) if the woman doesn't already have a ICD-10 diagnosis code; other chronic headaches: tension headaches, cluster headaches, chronic headaches; other mental health conditions: obsessive compulsive disorder, self-harm, personality disorder, dissociative disorder; other skin conditions: seborrheic dermatitis, rosacea, lichen planus, hidradenitis suppurativa; severe mental illness (SMI): bipolar disorder, schizophrenia, psychosis or meeting drug phenome for SMI; GORD: gastroesophageal reflux disease; IBS: Irritable bowel syndrome; PCOS: polycystic ovarian syndrome

Table 3.4: Top ten mutually exclusive combinations of multimorbidity in pregnant women

CPRD (UK), n=37641			SAIL (Wales), n=27782			SMR (Scotland), n=6099		
All health conditions	**n**	**%**	**All health conditions**	**n**	**%**	**All health conditions**	**n**	**%**
Anxiety, Depression	825	2.19%	Anxiety, Depression	748	2.69%	Common mental health disorders (CMHD), Asthma	195	3.20%
Asthma, Allergic rhinoconjunctivitis	370	0.98%	Asthma, Allergic rhinoconjunctivitis	319	1.15%	Peptic ulcer disease/GORD, CMHD	195	3.20%
Depression, Other mental health conditions	214	0.57%	Anxiety, Depression, Other mental health conditions	164	0.59%	Allergic rhinoconjunctivitis, CMHD	145	2.38%
Migraine, Allergic rhinoconjunctivitis	178	0.47%	Allergic rhinoconjunctivitis, Anxiety, Depression	140	0.50%	Allergic rhinoconjunctivitis, Asthma	132	2.16%
Anxiety, Depression, Other mental health conditions	175	0.46%	Asthma, Anxiety, Depression	138	0.50%	Atopic eczema, CMHD	125	2.05%
Asthma, Depression	172	0.46%	Migraine, Anxiety, Depression	128	0.46%	Migraine, CMHD	101	1.66%
Allergic rhinoconjunctivitis, Depression	171	0.45%	Allergic rhinoconjunctivitis, Depression	120	0.43%	Other mental health conditions, CMHD	96	1.57%
Migraine, Depression	161	0.43%	Migraine, Allergic rhinoconjunctivitis	117	0.42%	Asthma, atopic eczema	94	1.54%
Asthma, Anxiety, Depression	140	0.37%	Depression, Other mental health conditions	109	0.39%	Asthma, Peptic ulcer disease/GORD	91	1.49%
Asthma, Migraine*	136	0.36%	Asthma, Depression	105	0.38%	Irritable bowel syndrome, CMHD	90	1.48%
Physical health conditions	**n**	**%**	**Physical health conditions**	**n**	**%**	**Physical health conditions**	**n**	**%**
Asthma, Allergic rhinoconjunctivitis	626	1.66%	Asthma, Allergic rhinoconjunctivitis	594	2.14%	Asthma, Allergic rhinoconjunctivitis	132	2.16%
Migraine, Allergic rhinoconjunctivitis	318	0.84%	Migraine, Allergic rhinoconjunctivitis	239	0.86%	Asthma, Atopic eczema	94	1.54%
Asthma, Migraine*	273	0.73%	Asthma, Migraine	189	0.68%	Asthma, Peptic ulcer disease/GORD	91	1.49%
Allergic rhinoconjunctivitis, Irritable bowel syndrome	175	0.46%	Allergic rhinoconjunctivitis, Irritable bowel syndrome	143	0.51%	Irritable bowel syndrome, Peptic ulcer disease/GORD	79	1.30%
Migraine, Irritable bowel syndrome	175	0.46%	Migraine, Irritable bowel syndrome	136	0.49%	Allergic Rhinitis, Peptic ulcer disease/GORD	76	1.25%
Allergic rhinoconjunctivitis, Other skin conditions	140	0.37%	Asthma, Migraine, Allergic rhinoconjunctivitis	129	0.46%	Atopic eczema, Peptic ulcer disease/GORD	64	1.05%
Asthma, Migraine, Allergic rhinoconjunctivitis	133	0.35%	Migraine, Other chronic headaches	123	0.44%	Allergic rhinoconjunctivitis, Atopic eczema	62	1.02%

Asthma, Irritable bowel syndrome	117	0.31%	Allergic rhinoconjunctivitis, Other chronic headaches	115	0.41%	Migraine, Peptic ulcer disease/GORD	50	0.82%
Migraine, Other skin conditions	98	0.26%	Asthma, Irritable bowel syndrome	110	0.40%	Asthma, Irritable bowel syndrome	45	0.74%
Allergic rhinoconjunctivitis, Other chronic headaches	87	0.23%	Allergic rhinoconjunctivitis, Other skin conditions	98	0.35%	Cholelithiasis, Peptic ulcer disease/GORD	43	0.71%

These multimorbidity combinations are mutually exclusive. For instance, the count for '*anxiety and depression'* will include women with exactly these two conditions only, it does not include women with combinations of '*anxiety, depression'* and other condition/s.

* The percentage of asthma and migraine multimorbidity combination is higher when considering physical health conditions only as it would include combination of these conditions with mental health conditions which are no longer accounted for.

GORD: Gastroesophageal reflux disease

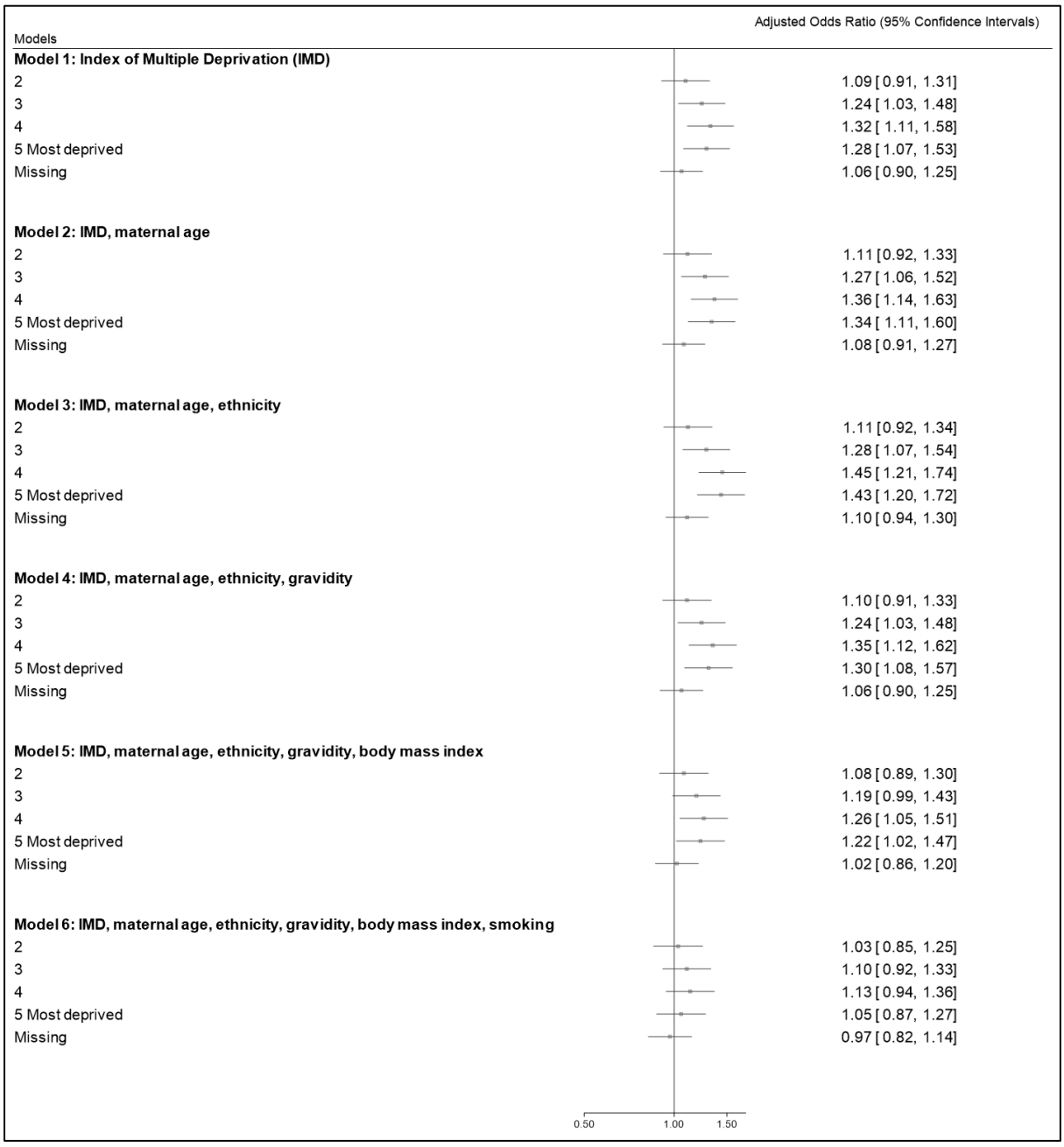
Table 3.5: Prevalence of selected health conditions in pregnant women by social deprivation and ethnicity

Health conditions	% by patient level IMD quintiles in CPRD (England), n=13075						P value for X^2 test
	1, least deprived n=2326	2 n=1835	3 n=1878	4 n=1853	5, most deprived n=1908	Missing n=3275	
Example of health conditions that increased with deprivation							
***Depression (diagnosis)	20.55	22.29	24.55	24.82	25.58	22.32	<0.001
*Asthma	12.85	14.22	14.70	15.00	14.83	12.61	0.049
***Other mental health conditions	5.33	6.21	8.31	9.01	10.01	6.93	<0.001
Psoriasis	3.31	4.31	3.09	4.16	3.41	3.82	0.258
Cardiovascular disease	2.06	2.07	1.70	1.89	2.67	2.29	0.378
***Severe mental illness	1.16	1.58	1.60	2.75	2.99	2.05	<0.001
**Epilepsy	0.90	1.20	1.65	2.00	2.04	1.04	0.002
Venous thromboembolism	0.77	0.65	0.59	0.49	1.26	0.98	0.073
**Substance misuse	0.52	1.36	1.33	1.46	2.10	1.37	0.001
Example of health conditions that decreased with deprivation							
**Anxiety (diagnosis)	20.77	20.05	21.35	18.78	17.82	17.77	0.005
Allergic rhinoconjunctivitis	18.14	16.13	16.03	16.68	15.57	16.15	0.254
*Migraine	14.32	13.35	15.44	12.14	13.16	12.76	0.034
**Irritable bowel syndrome	10.15	8.88	9.16	7.99	6.71	9.04	0.003
**Polycystic ovarian syndrome	8.34	5.78	7.03	6.26	5.29	6.41	0.001
Other skin conditions	6.58	6.70	6.02	6.80	4.98	6.44	0.179
Alcohol misuse	0.82	0.65	0.59	0.81	0.68	0.55	0.820

Health conditions	% by ethnicity in CPRD (England)						P value for X^2 test
	White n=8302	Black n=490	Mixed n=214	Others n=336	South Asians n=843	Missing n=2890	
Example of health conditions that were more prevalent in White ethnic group							
***Depression (diagnosis)	25.20	13.27	20.56	14.29	10.32	23.91	<0.001
***Anxiety (diagnosis)	21.27	9.80	20.09	10.42	10.08	18.86	<0.001
***Asthma	14.33	11.22	14.02	6.55	10.79	14.60	<0.001
***Migraine	14.30	10.20	11.21	8.63	9.85	13.46	<0.001
***Irritable bowel syndrome	10.07	9.80	6.07	2.68	3.91	7.06	<0.001
***Other mental health conditions	8.44	5.31	10.28	4.17	1.90	6.92	<0.001
Other skin conditions	6.75	3.88	5.61	5.06	5.93	5.64	0.050
***Psoriasis	4.05	1.22	3.27	1.49	1.66	3.91	<0.001
Serious mental illness	2.11	1.63	1.40	0.60	1.19	2.18	0.159
**Substance misuse	1.47	0.82	1.40	0.00	0.00	1.56	0.002
Epilepsy	1.46	0.41	2.80	0.60	1.07	1.52	0.099
Venous thromboembolism	0.93	0.41	1.40	0.60	0.47	0.62	0.309
***Alcohol misuse	0.90	0.00	1.40	0.30	0.00	0.31	<0.001
Example of health conditions that were more prevalent in ethnic minority groups							
***Allergic rhinoconjunctivitis	15.56	22.65	17.29	19.94	16.25	17.65	<0.001
***Polycystic ovarian syndrome	6.60	5.10	8.88	8.93	9.85	5.33	<0.001
Cardiovascular disease	2.18	3.88	1.40	1.79	2.14	1.80	0.090

The selected health conditions were the top ten most common conditions in this study or leading causes of maternal death. Other mental health conditions: obsessive compulsive disorder, self-harm, personality disorder, dissociative disorder. Severe mental illness (SMI): bipolar disorder, schizophrenia, psychosis or meeting drug phenome for SMI. Other skin conditions: seborrheic dermatitis, rosacea, lichen planus, hidradenitis suppurativa.

Figure 3.1: Forest plot of odds ratio for multimorbidity and social deprivation



Legend: Multimorbidity was defined using the 31 health conditions in Barnet et al's study, logistic regression was used to analyse the study cohort in CPRD England (n=13,075). The reference group was index of multiple deprivation (IMD) quintile 1 (least deprived).

Chapter end summary

This chapter addressed the evidence gap highlighted in Chapter 1 by describing how maternal multimorbidity is distributed in the United Kingdom. This was achieved with an observational study design using routine health records, following principles of measuring multimorbidity outlined in Chapter 1. The rationale for using routine health records was discussed in Chapter 2.

With the knowledge of how prevalent maternal multimorbidity is, the next step would be to quantify what this translates to for maternal and child outcomes. As discussed in Chapter 1, selection of what outcomes to measure should be guided by a core outcome set to ensure its relevance and to allow evidence synthesis. The next chapter presents a study protocol to develop a core outcome set for studies of pregnant women with multimorbidity.

Chapter 4: Protocol for the development of a core outcome set for studies of multimorbidity in pregnancy

Chapter overview

Chapter 1 discussed how a core outcome set can avoid poorly selected, collected, and reported outcomes. Chapter 2 gave a broad overview of and rationale for the key steps in developing a core outcome set. Following the core outcome set handbook,[142] this chapter meets *Objective 3:* to develop a study protocol for a core outcome set for studies of pregnant women with multimorbidity. The published manuscript is presented as follows.

Published manuscript

Lee SI, Eastwood K-A, Moss N, et al. Protocol for the development of a core outcome set for studies of pregnant women with pre-existing multimorbidity. *BMJ Open* 2021;11(10):e044919. doi: 10.1136/bmjopen-2020-044919

Personal contribution

- Designed the study following the COMET handbook
- Applied for ethics approval
- Prepared study documents
- Involved patient and public involvement co-investigator in designing Figure 4.2
- Drafted and submitted the manuscript for publication and responded to reviewers' comments

Title: Protocol for the development of a core outcome set for studies of pregnant women with pre-existing multimorbidity

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4.1 Abstract

Introduction

Increasingly more pregnant women are living with pre-existing multimorbidity (≥2 long-term physical or mental health conditions). This may adversely affect maternal and offspring outcomes. This study aims to develop a COS for maternal and offspring outcomes in pregnant women with pre-existing multimorbidity. It is intended for use in observational and interventional studies in all pregnancy settings.

Methods and analysis

We propose a four-stage study design: 1) systematic literature search, 2) focus groups, 3) Delphi surveys, and 4) consensus group meeting. The study will be conducted from June 2021 – August 2022.

First, an initial list of outcomes will be identified through a systematic literature search of reported outcomes in studies of pregnant women with multimorbidity. We will search the Cochrane library, Medline, Embase and CINAHL. This will be supplemented with relevant outcomes from published COS for pregnancies and childbirth in general, and multimorbidity. Second, focus groups will be conducted amongst 1) women with lived experience of managing pre-existing multimorbidity in pregnancy (and/or their partners), and 2) their health/social care professionals to identify outcomes important to them.

Third, these initial lists of outcomes will be prioritised through a three-round online Delphi survey using predefined score criteria for consensus. Participants will be invited to suggest additional outcomes that were not included in the initial list. Finally, a consensus meeting using the nominal group technique will be held to agree on the final COS. The stakeholders will include 1) women (and/or their partners) with lived experience of managing multimorbidity in

pregnancy, 2) health/social care professionals involved in their care, and 3) researchers in this field.

Ethics and dissemination

This study has been approved by the University of Birmingham's Ethical Review Committee. The final COS will be disseminated through peer-reviewed publication and conferences and to all stakeholders.

Strengths and limitations of this study

- Core outcome set (COS) development in accordance to the COS standards for development (COS-STAD)
- Extensive patient, public and stakeholder involvement at each stage
- Pragmatic design to make the COS development feasible in the context of multimorbidity
- The applicability of the COS may be limited to high income countries
- Responder bias may influence the types of outcomes included in the final COS

4.2 Background

Multimorbidity is a state of having two or more long-term physical or mental health conditions.[1] Despite an increase in multimorbidity within the general population,[171] there is sparse literature for pregnant women with multimorbidity. Studies in the USA have reported that between 0.8% to 13.9% of hospital births were from women with multiple chronic conditions.[43 47] Using a list of 79 chronic conditions, our preliminary study found that one in four pregnant women in the UK had active multimorbidity at conception.[172]

Studies have shown that multimorbidity is associated with increased risk of adverse obstetric outcomes (e.g. preterm birth) and severe maternal morbidities as a consequence of childbirth (e.g. hysterectomy, eclampsia).[43 47] The 2020 UK national maternal mortality review reported that 90% of women who died within a year of pregnancy had multiple health and social risk factors.[173] The leading direct cause of maternal death included thrombosis, thromboembolism and maternal suicide; leading indirect cause of death included cardiac diseases, epilepsy and stroke.[173] In addition to acute complications (e.g. eclampsia) and chronic complications (progression from gestational diabetes to type II diabetes) for the mother, evidence suggests that pre-existing maternal morbidities and medications taken for these morbidities can lead to offspring complications such as neurodevelopmental disorders and congenital anomalies.[43 174-177] Current observational evidence and interventions focus on single morbidities. There is an urgent need for further understanding of the consequence of pre-existing maternal multimorbidity and development of interventions to improve maternity care for these women.[178 179]

To facilitate future research studies, a core outcome set (COS) is required. This will standardise the outcomes being reported, allow for evidence synthesis, and ensure outcomes important to women, their families, carers and health and social care professionals are captured.[142] The importance of COS in women's health is endorsed by the Core Outcomes in Women's Health

(CROWN) initiative.[129] The Core Outcome Measures in Effectiveness Trial (COMET) initiative collates resources for COS development and maintains a COS database.[180]

A recent scoping review identified 26 COSs relevant to maternity service users, of which three were related to pre-existing maternal morbidities in pregnancy (diabetes, epilepsy, infertility).[181] A search for COS in pregnancy on the COMET database further identified two published COS (depression, rheumatological conditions) and three in progress (cardiac disease, venous thromboembolism and immune thrombocytopenia).[180] There is currently no COS for multimorbidity in pregnancy. We propose a pragmatic study design to develop a COS for observational and interventional studies, for pregnant women with pre-existing multimorbidity, covering obstetrics, maternal and offspring outcomes.

4.3 Methods

This study is designed in accordance with the COS standards for development (COS-STAD) recommendations and the protocol follows the COS-STAP statement (Supplementary Material 4.1); study findings will be reported following the COS standards for reporting (COS-STAR).[182-184] The planned start and end dates for the study are June 2021 and August 2022, respectively. The study is registered on the COMET database.[185]

The study will consist of four stages: 1) systematic literature search for reported outcomes for mother and child in studies of pregnant women with multimorbidity; 2) focus groups of women with lived experience of managing pre-existing multimorbidity in pregnancy and/or their partners, and their health/social care professionals; 3) Delphi surveys amongst stakeholders to prioritise the core outcomes; and 4) a consensus meeting to agree on the final COS (Figure 4.1).

Scope of the COS

The population is pregnant women; the exposure is pre-existing multimorbidity, defined as having two or more long-term physical or mental health conditions at conception.[1] This does not include pregnancy related morbidities (e.g. gestational diabetes) which will be considered as pregnancy outcomes. The morbidities do not have to be independent of each other. For instance, if a morbidity is a consequence of another morbidity (e.g., diabetic eye disease and diabetes), these will be classed as two separate morbidities. The COS will be applicable principally to observational studies but will also inform interventional studies for pregnancy in all settings.

Maternal outcomes will include the antenatal, intrapartum, and post-partum period. Offspring outcomes will include the neonatal (first one month), infant (first one year), pre-pubertal (two to 11 years old), pubertal period (12-18 years old) and adulthood.[186] We have included outcomes across the lifespan of the offspring to inform observational studies that take a life-course approach.[187] Evidence is emerging that pre-existing maternal morbidities can impact on offspring long-term health in early adulthood.[188] Pregnancy outcomes in the rest of this protocol will refer to both maternal and offspring outcomes.

Patient and public involvement (PPI)

This protocol has been shaped by extensive PPI. PPI for this study will be three-tiered: (1) patient representatives in the scientific advisory group (SAG), (2) PPI advisory group and (3) patient and public stakeholders as research participants.

The SAG consists of clinicians (specialists in maternal and fetal medicine, obstetrics, perinatal mental health, general practice and public health), researchers and women representatives collaborating on a larger project studying pregnant women with multimorbidity (MuM-

PreDiCT).[189] NM, a women representative from the SAG has advised on the study design, co-authored this protocol and created Figure 4.2 that illustrates the PPI in the COS development.[190]

Stage 1: Systematic literature search

A pragmatic approach to identifying a list of initial outcomes will be adopted given the wide range of potential multimorbidities. We will first identify outcomes from published COS for pregnancy and childbirth and published COS for multimorbidity from the COMET database.[132-134 191] We will then conduct a systematic literature search for reported outcomes in published studies of pregnant women with multimorbidity.

Search strategy

The following databases will be searched: Cochrane library, Medline, Embase and CINAHL. Relevant key search terms will include pregnancy (population and maternal outcomes), multimorbidity (exposure) and offspring (offspring outcomes) derived from previous literature.[191-193]

Study selection and data extraction

The inclusion criteria are: systematic reviews, interventional studies, observational studies, qualitative studies, and patient reported outcome measures (PROM) studies; studies reporting pregnancy, maternal and offspring outcomes; and studies of pregnant women with multimorbidity. The exclusion criteria are: ongoing studies with no published outcomes, editorials, commentaries, narrative reviews, case reports, case series, diagnostic accuracy studies, laboratory studies and animal studies. No time or language limits will be applied. Full text screening will be conducted by two independent reviewers.

Two reviewers will extract the following data from included studies: author, year of publication, study design, PROM domains, types of outcomes, definition of and measurement

tools for the outcomes. Any discrepancy between the two independent reviewers for study selection and data extraction will be resolved with a third reviewer.

Stage 2: Focus groups

Outcomes identified in the published literature may represent outcomes considered as important to researchers.[142] Therefore, focus groups will be conducted to ensure the capture of outcomes considered as important to women with lived experience of managing pre-existing multimorbidity in pregnancy and/or their carers/partners (two focus groups), and health/social care professionals involved in their care (one focus group). The synergistic discussion in focus groups will allow participants to consider outcomes which are important to others and stimulate in-depth discussions.[143]

We will aim to include 6-8 participants per focus group. Sampling will be purposive and guided by the sampling matrix to provide a broad representation of stakeholders and characteristics (Table 4.1). Recruitment channels are listed in Table 4.2. Involvement of the under-served population will be guided by our PPI advisory group and the MuM-PreDiCT group's strategy for diverse representation.[194]

Based on the advice of our PPI advisory group, the focus groups will be held virtually. Participants will be sent participant information sheets in advance of the meeting and consent will be taken 24 hours later either in electronic form or verbally. The focus group will last for 90 minutes or until no further new ideas are forthcoming. A topic guide will be developed based on previous literature, and with the guidance of qualitative experts and patient representatives in the SAG and our PPI advisory group.[195 196] The focus group will be facilitated by a researcher with qualitative methodology training. The focus group discussion will be recorded using the virtual meeting platform, the recordings will be transcribed and imported to

nVivo. Data analysis will be inductive, following a structured, multistage approach to thematic analysis.[197]

Initial list of outcomes

The initial list of outcomes generated from stages 1 and 2 will be reviewed and refined by the SAG and PPI advisory group to combine outcomes that are clinically and pathophysiologically similar to avoid redundancy.[142 198] Pregnancy outcomes will be categorised by: (1) maternal or offspring outcomes, and (2) by an established taxonomy of outcomes (mortality/survival, physiological/clinical, life impact/functioning, resource use and adverse events/effects).[199]

Stage 3: Delphi surveys

The Delphi technique collates stakeholder opinions using sequential surveys. The response is summarised and fed back to stakeholders anonymously in subsequent rounds. Stakeholders consider the collective views before re-rating the outcomes. This provides a mechanism to reconcile different opinions to reach a consensus.[142] This study will employ a three round Delphi survey which is generally sufficient to reach consensus (Figure 4.1).[200] Participants will have the opportunity to suggest additional outcomes that were not included in the initial list.

The surveys will be hosted on a secure platform online. The three groups of stakeholders that will be invited to participate and the recruitment channels are outlined in Table 4.2. There is no recommended sample size for Delphi surveys; instead of basing the sample size on statistical power, this is often a pragmatic choice.[142] Previous obstetric COS has achieved sample size of around 20-40 for patients and 50-100 for health care professionals.[198 201-203] To reach the target sample size, snowballing recruitment will be encouraged. To check for representation, the survey will ask for participant characteristics including types of long-term conditions constituting multimorbidity, age, ethnicity, education level and socioeconomic status (patient representatives, as outlined in Table 4.1), specialty and job roles (health care professionals and

researchers). Participant's name and email contact will be included to avoid duplicate entry, for sending up to two personalised reminders (one week apart) and following up on incomplete response. This information will be kept securely, confidentially and separate from the survey responses.

Care will be taken in explaining the concept of COS to lay participants, using supporting materials from the COMET website.[180] The wording of the survey will be developed using appropriate language commonly used by representatives in the focus groups. The SAG and PPI advisory group will also ensure plain language is used to describe the outcomes of interest. Outcomes will be presented in alphabetical order to avoid any response effects related to the order of survey items.[142 204]

Each outcome will be rated on a 9-point Likert scale: 1-3 (not important), 4-6 (important but not critical) and 7-9 (critically important). An '*unable to score'* option will be provided to allow for participants who may not have the expertise to score certain outcomes.[142] The 9-point Likert scale is commonly used in COS studies and recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[142 205]

Score criteria for consensus[206]

- *Consensus in* is when ≥70% of all participants rated 7-9 (critically important) for an outcome.
- *Consensus out* is when ≥70% of all participants rated 1-3 (not important) for an outcome.
- *No consensus* is for any other scores.
- *For further discussion* is when: (1) ≥70% of all participants rated 4-6 (important but not critical) for an outcome, or (2) when ≥70% of patient representatives have rated 7-9 for an outcome but *consensus in* is not reached.

Pilot study

The survey will be piloted before the Delphi rounds to check face validity. It will also inform the time frame required for completion of each Delphi round.

1st Delphi

Participants will be sent a participant information sheet explaining the objectives of the COS study. Completion of the online survey assumes implied consent. Participants will be informed that they can withdraw their response from the study within one week of submitting the survey. Once the name and contact details are separated from the survey response, it will not be possible to withdraw their survey response.

At the end of the survey, an open question will invite participants to suggest a maximum of two additional outcomes. If a new outcome is suggested by two or more participants, it will then be added to the 2nd Delphi round. Depending on how many new outcomes that will be presented, this criterion may be modified on a pragmatic basis.

2nd Delphi

Participants who responded to the 1st Delphi round will be invited to participate in the 2nd Delphi. A summary response from the 1st Delphi stratified by stakeholder groups will be presented for all outcomes.

3rd Delphi

Participants who responded to the 2nd Delphi round will be invited to participate in the 3rd Delphi. Outcomes that reached *no consensus* will be included as options in the 3rd Delphi survey. A summary response from the 2nd Delphi round, stratified by stakeholder groups will also be presented. Attrition rate will be calculated for each subsequent round.

Stage 4: Consensus meeting

At the time of writing, the UK is undergoing social distancing due to the COVID-19 pandemic. In addition, our SAG patient representative has advised that travelling to meetings may not be convenient for mothers with childcare needs. Therefore, the consensus meeting will be conducted through a virtual platform online.

The consensus meeting panel will be purposefully selected from the SAG, PPI advisory group and Delphi survey respondents to ensure representation of a range of backgrounds. In the 3rd Delphi survey, participants will be asked about their willingness to attend the consensus meeting. For meaningful engagement in the consensus meeting, we will aim for 10-15 participants.[142 190 204]

An experienced facilitator will be the non-voting chair. Summary scores stratified by stakeholder groups will be presented for outcomes that met the *'for further discussion'* criteria. Nominal group technique will be used to discuss these outcomes.[206 207] Participants will be asked to contemplate independently whether these outcomes should be included. Each participant will be invited to voice their reasoning in turn using a round-robin format to avoid domination of the discussion by selected few. This will be followed by an open discussion, after which a final anonymous binary vote of yes /no will be conducted for each of these outcomes. Outcomes that received ≥70% yes votes will be included in the final COS.

4.4 Discussion

The proposed COS will be applicable for observational and interventional studies for pregnant women with pre-existing multimorbidity. Further interventional studies are urgently needed to tackle multimorbidity in pregnancy and reduce the associated adverse outcomes. It is therefore

important to have a predefined COS to inform future research studies to enable valid comparisons between study findings.

Strength

There is currently no COS for studies of pregnant women with multimorbidity. As multimorbidity covers a wide range of diseases, this presents a unique methodological challenge to the COS development. This study aims to adopt a pragmatic approach to make the task manageable whilst still following the COS-STAD minimum standards. Inclusion of observational studies in generating the initial list of outcomes may detect rare but important clinical outcomes especially for offspring.[208]

The Delphi surveys, nominal group technique and anonymous final vote in the consensus meeting will encourage participation of all stakeholders and avoid dominance of selected figures. As outlined in Figure 4.2, PPI will have a meaningful role throughout the COS development to ensure accessibility and relevance to patient stakeholder groups and that patient perspectives are represented in the governance of the COS development.[190]

To widen its applicability, the proposed COS will include both maternal and offspring outcomes and will include outcomes that are common to all pregnant women with multimorbidity. Finally, by creating this COS, we hope to encourage and facilitate urgently needed research for pregnant women with multimorbidity.

Limitation

The focus groups, Delphi survey and consensus meeting will be conducted in English. Although efforts will be made to encourage international participation, this may limit the generalisability of the findings to high income countries. The use of online platforms may lead to under-representation of the digitally disadvantaged groups. Similarly, responder bias may influence the types of outcomes included in the final COS. To ensure representation of the

socially disadvantaged / marginalised group and health/social care professionals with busy work schedules, our approach will be flexible and where necessary / preferred by the participants, we will offer the option of one-to-one interviews instead of focus groups.

As further epidemiological knowledge is gained in identifying common morbidity clusters in pregnant women, the COS may need to be updated to incorporate outcomes specific to these clusters.

4.5 Dissemination

The final COS will be fed back to all stakeholders. Patient and public representatives will be encouraged and supported to share the difference they have made. With the guidance of the SAG and the PPI advisory group, a collaborative dissemination plan will be formulated. This will include submitting the findings for publication in a peer reviewed journal, dissemination at conferences and registering the study on the COMET database.

Authors' contributions: Our authors list includes PPI co-investigators NM and RP. SIL, KAE, NM, AAL, AS, AA, BT, CNP, CY, CM, DOR, HH, JIK, KMA, LL, PB, RP, SB, UA, ST, KN and MB conceived the study; SIL led the development of the protocol and drafted the initial manuscript with contribution and supervision from KN, ST, MB, KAE; SIL, KAE, NM, AAL, AS, AA, BT, CNP, CY, CM, DOR, HH, JIK, KMA, LL, PB, RP, SB, UA, ST, KN and MB contributed to the study design, critically reviewed and revised the protocol drafts. LL, BT, MB contributed to the qualitative element of the study design and, together with NM, RP, SB and KMA, advised on the recruitment channels; PPI co-investigator NM designed Figure 2. SIL, KAE, NM, AAL, AS, AA, BT, CNP, CY, CM, DOR, HH, JIK, KMA, LL, PB, RP, SB, UA, ST, KN and MB agreed on the final draft manuscript for submission and are accountable for all aspects of the work.

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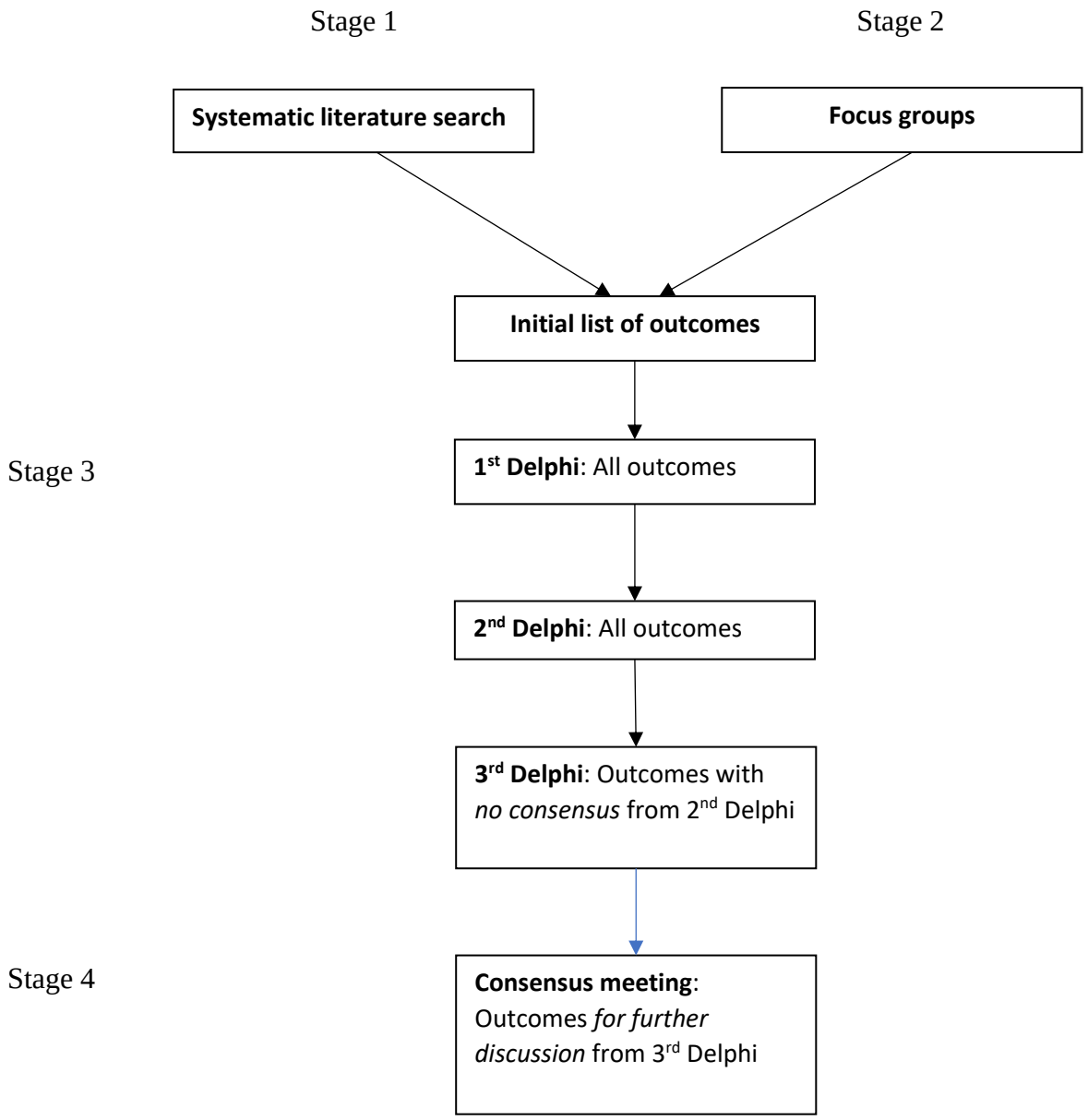
Competing interests: None declared.

Ethics: This project has been reviewed and approved by the Science, Technology, Engineering and Mathematics Ethical Review Committee at the University of Birmingham (reference: ERN_20-1264A). Health Research Authority (HRA) has advised that this project does not require HRA and HCRW approval or NHS/HSC R&D permissions as it is a service evaluation/improvement project.

Figure 4.1: Flowchart of COS development method



NB: For the 2nd, 3rd Delphi surveys and the consensus meeting, an aggregate score from the previous round, stratified by stakeholder groups, will be presented.

Figure 4.2: Description of patient and public involvement in the COS development

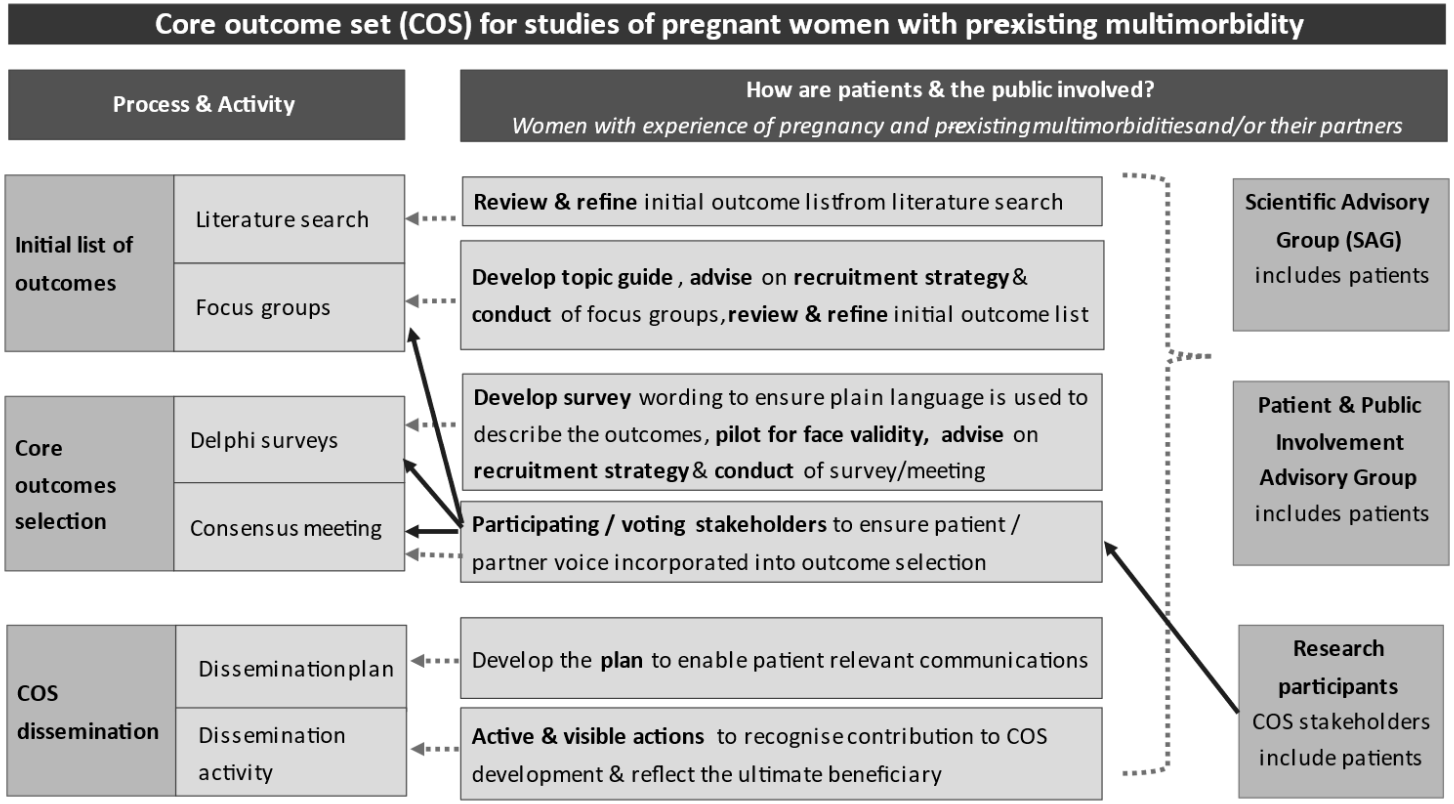


Table 4.1: Sampling matrix for the focus groups, Delphi surveys and consensus meeting

Characteristics	**Target / minimum numbers**		
	Focus groups	**Delphi surveys[209]**	**Consensus meeting**
1) Women with lived experience of managing pre-existing multimorbidity (2+ long-term conditions) in pregnancy	12-16	50	5
Physical health conditions	6	8-10	1
Mental health conditions	3-6	8-10	1
Ethnic minority	3-6	8-10	2
Socioeconomically disadvantaged/ marginalised groups (e.g., homeless, refugee, asylum seeker, drug, and alcohol service users, disabled, victims of domestic abuse)[6]	3-6	8-10	1
2) Health / social care professionals	6-8	50	5
Obstetric medicine / maternal medicine	1-2	8-10	1
Obstetric	1-2	8-10	1
Midwifery / antenatal practitioner	1-2	8-10	1
Perinatal mental health	1-2	8-10	1
Other: e.g., primary care, public health, neonatologist, paediatrician, health visitor, commissioner, maternity service provider, social worker, drug and alcohol service provider, maternity advocate /educator	2	8-10	1
3) Researchers Academics, triallist, journal editors (as future implementers)	-	5-10	2

NB: *Target/minimum numbers are estimates. Due to the overlap of characteristics between participants (e.g., physical, and mental health conditions, health/social care professionals and researchers) we will continuously review the characteristics of participants so that we can identify any under-represented groups and target recruitment efforts in these areas.

Table 4.2: Stakeholders and recruitment channels

Stakeholder group	Potential recruitment channels[23 210]
1) Patient representatives Women with lived experience of managing pre-existing multimorbidity (two or more long-term physical or mental health conditions) in pregnancy and/or their partners/carers	• Service user associations/groups: e.g., Maternity Voice Partnership • Parent support networks: e.g., National Childbirth Trust • Community groups: local maternity groups, baby/toddler groups, local authority baby class, nursery, health visitor society, faith group, baby groups by church • Social media: Facebook, Twitter, Instagram, LinkedIn • Parent oriented social media: home-schooling, weaning, budget family menu sites, breastfeeding, outdoor activities for family, local outdoor groups, Mumsnet, Gingerbread (single parents) • Patient support groups/charities for specific conditions: Tommy's, Epilepsy Action, Association of Medical Research UK member charities, National Council for Voluntary Organisations • Royal Colleges women's networks: Royal College of Obstetrics and Gynaecology Women's Voices Involvement Panel, Royal College of Midwifery Maternity Voices Network • Victim of domestic abuse: Refuge, Women's Aid, WE:ARE (Women's Empowerment and Recovery Educators) • Disabled: Disabled Parents Network, disabled parents Facebook groups • Drug and alcohol: Drug and Alcohol Abuse Support for Women • Refugee: Refugee Council, Refugee Survival Trust • LGBT: LGBT Mummies Tribe, Stonewall, Facebook groups for transgender men or lesbian women experiencing pregnancy
2) Health / social care professionals Any health/ social care professionals involved in providing multidisciplinary team care for pregnant women: e.g., obstetric physicians, obstetricians, physicians, paediatricians, neonatologists, psychiatrists, primary care clinicians, public health professionals, clinicians of established joint antenatal clinics, perinatal mental health team, drug and alcohol services, social services, midwives, health visitors, dieticians, policy makers, commissioners.	- Personal, professional, and clinical network of the researchers - Royal colleges - Societies (e.g., McDonald Obstetric Medicine Society, European Board and College of Obstetrics and Gynaecology) - Maternity charities (e.g., Ammalife, Elly) - Social media for professional groups (e.g., Twitter, Facebook).
3) Researchers Academics, triallist, journal editors (as future implementers)	The SAG's personal network, social media (Twitter), the COMET and Core Outcomes in Women's Health (CROWN) network, the Cochrane Pregnancy and Childbirth group, peer-reviewed journals of obstetric medicine and obstetrics

Chapter end summary

This chapter set out how a core outcome set for studies of pregnant women with multimorbidity will be developed using a four-step approach in Chapters 5-7. It prespecified the sampling matrix that will guide recruitment in Chapters 6 and 7 and the consensus threshold for Chapter 7. The next chapter will describe the first step, a systematic search of the literature to catalogue research outcomes that have been studied, which will inform the design of the Delphi surveys in Chapter 7.

Chapter 5: Systematic literature search for core outcome set development

Chapter overview

This chapter followed the first of four steps described in Chapter 4 to build a core outcome set. It described a systematic search of the literature to meet *Objective 4:* identify types of outcomes reported in existing literature for pregnant women with multimorbidity. The study selection criteria are guided by the concepts of multimorbidity and pre-existing maternal multimorbidity described in Chapter 1.

Personal contribution

- Developed the search strategy
- Conducted the literature search in the electronic databases
- Screened title and abstracts and full texts and compared findings with second reviewer
- Extracted data and compared findings with second reviewer
- Written the manuscript

5.1 Abstract

Background: Variation in outcome reporting precludes pooling of results for evidence synthesis. A core outcome set is needed to standardise outcome reporting in observational and interventional studies of pregnant women multimorbidity. This study aims to catalogue outcomes reported in previous studies of pregnant women with multimorbidity to inform the development of a core outcome set.

Methods: A systematic literature search was conducted in two stages. Stage one searched the COMET and CROWN database for published core outcome sets for pregnancy and childbirth and for multimorbidity. Stage two searched Medline, Embase, CINAHL and Cochrane Library for studies reporting outcomes for pregnant women with multimorbidity; two reviewers conducted full text screening and data extraction from 2017 to 2021 until outcome saturation was reached. Maternal and child outcomes were categorised by survival, clinical (further subdivided by pregnancy period of antenatal, peripartum, postnatal and long-term for mothers; fetal, neonatal, infant, and longer term for children), life impact/functioning, and resource use outcomes.

Results: Stage one's search identified three core outcome sets and five systematic reviews; stage two identified 26 studies. An initial list of 185 outcomes (115 maternal and 70 child outcomes) were extracted. For maternal outcomes, there were one survival outcome, 79 clinical outcomes (13 antenatal, 64 peripartum, two postnatal/longer-term outcomes), 18 life impact/functioning outcomes and 17 resource use outcomes. For child outcomes, there were four survival outcomes, 62 clinical outcomes (seven fetal outcomes, 52 neonatal outcomes, one infant outcome, two long-term outcomes) and four resource use outcomes. Eighteen out of the 26 included studies reported the composite outcome of severe maternal morbidity/end organ injury.

Conclusion:

This systematic literature search identified a wide range of maternal and child outcomes for studies of pregnant women with multimorbidity. The list of outcomes will inform the design of a Delphi survey for a core outcome set.

5.2 Background

Multimorbidity in pregnancy is increasingly an important health issue to consider in preconception and pregnancy care.[66 178] Evidence is emerging that maternal pre-existing multimorbidity is associated with adverse outcomes for pregnant women and their offsprings.[66] For research in this field to progress further, a core outcome set is needed to standardise the types of outcomes that are being reported in studies. It is a set of outcomes that should be reported as a minimum in all studies of a health condition or intervention and is developed with stakeholders.[142] Without a core outcome set, heterogeneity in study outcomes precludes pooling of results for evidence synthesis and outcomes that are being measured may not be relevant to pregnant women with multimorbidity and their family.[120]

The first step in developing a core outcome set is to catalogue a long list of outcomes that have been reported in previous research.[142] It reflects what outcomes were considered important to measure by researchers in the field.[142] Complemented by outcomes identified through qualitative studies, this initial list of outcomes will then be prioritised through consensus methods such as Delphi surveys to reach a final set of core outcomes.[142] This study aims to identify the types of outcomes that have been previously reported in studies of pregnant women with multimorbidity through a systematic literature search. It is part of a core outcome set development study, the study protocol has been published.[211]

5.3 Methods

In Chapter 3's epidemiological study, maternal multimorbidity was defined using 79 health conditions.[172] A literature search for studies reporting pregnancy outcomes associated with each of these 79 individual health conditions would be resource intensive. Therefore, a two-stage approach was taken instead. In stage one, core outcome set repositories were searched for published core outcome sets for (i) pregnancy and childbirth, and (ii) multimorbidity. In stage two, a systematic literature search was conducted for studies reporting outcomes for pregnant women with multimorbidity. The systematic literature search was reported following the PRISMA checklist.[212]

The findings from this study will support the next stage of a core outcome set development. The extracted types of outcomes will inform the design of Delphi surveys. The quality of the included studies was not appraised, and the effect sizes were not extracted and synthesised. Therefore, this study does not constitute a systematic review.

Search strategy

For stage one, the Core Outcome Measures in Effectiveness Trials (COMET) and Core Outcomes in Women's and Newborn Health (CROWN) databases were searched for published core outcome sets in pregnancy and childbirth and multimorbidity. For stage two, Medline, Embase, Cumulated Index to Nursing and Allied Health Literature (CINAHL) and Cochrane Library were searched from inception to 11th August 2021 for studies of pregnant women with multimorbidity. Medical Subject Headings and free text terms for the concept 'multimorbidity' and 'pregnancy' were used in the search strategy (Table 5.1), informed by previous systematic reviews.[55 213]

In Chapter 4's protocol, we proposed to use the concepts of 'pregnancy' (population, outcome), 'multimorbidity' (exposure) and 'offspring' (outcome) for the search terms. However, in the

scoping search, the search term ‘offspring’ resulted in studies that were conducted in children or adolescents with multimorbidity. The search strategy was modified to include the concepts for the target population (pregnancy) and exposure (multimorbidity), with the rationale that any outcomes for the target population would be captured in this broader search strategy.

Study selection

Studies that reported maternal or offspring outcomes for pregnancy with pre-existing maternal multimorbidity were included. The study population should include pregnant women with two or more long-term physical or mental health conditions that pre-existed before pregnancy and are not pregnancy complications; or children born to mothers with multimorbidity. Co-morbidity studies that recruited pregnant women based on an index conditions or specific combinations of health conditions were excluded as they would not be representative of pregnant women with multimorbidity.

Study designs included systematic reviews, interventional, observational, qualitative, patient reported outcomes and model validation studies. Published conference abstracts identified in the four bibliographic databases were included if there were sufficient details to assess the inclusion and exclusion criteria and if types of outcomes could be extracted. The following types of publications were excluded: ongoing studies with no reported outcomes, editorials, commentaries, narrative reviews, guidelines, case reports, case series, diagnostic accuracy studies, laboratory studies and animal studies. No language limitation was applied. The full inclusion and exclusion criteria are listed in Table 5.2. The reference lists of included studies were screened for additional studies.

Title and abstract screening was conducted using Rayyan.[214] Full text screening was conducted by two researchers (SL and MS) independently, using EndNote. The list of included and excluded studies were compared. Any discrepancies or queries were discussed and if not resolved, were discussed further with the study supervisors.

From inception to 11th August 2021, the systematic literature search identified 18962 titles for studies reporting outcomes for pregnant women with multimorbidity. Overly large reviews are resource intensive and may not result in additional outcomes.[142] The COMET handbook suggested conducting the literature search in stages until outcome saturation is reached in such circumstances.[142] We therefore first screened and extracted outcomes for recent years (2019-2021), and extended the process on a yearly basis (i.e. 2018, then 2017). Saturation was reached when no additional new outcomes were identified.

Data extraction

Data were extracted for the following: study title, author, year of publication, country, study population, methods of measuring maternal multimorbidity, types of outcomes and definition of the outcomes as reported in the study. Two reviewers (SIL and MS) extracted the data independently. The extracted data were compared, and discrepancies discussed, any remaining queries were resolved with the study supervisors.

The extracted outcomes were categorised by: (i) maternal or child outcomes, and (ii) an established taxonomy of outcomes:[199] mortality/survival, physiological/clinical (further subdivided by pregnancy period of antenatal, peripartum, postnatal and long-term for mothers; fetal, neonatal, infant and longer term for children), life impact/functioning, and resource use.

The outcomes were extracted verbatim.[142] The same outcomes that were labelled with different wordings were grouped together. For example, maternal death, maternal mortality, in hospital maternal mortality, and mortality were all grouped together. As the findings from this study will be incorporated into a Delphi survey, efforts were made to group outcomes with similar construct together to reduce survey burden. For example, breastfeeding initiation at different time points, success in breastfeeding, confidence with breastfeeding, baby receives breast milk were grouped under ‘breastfeeding’.

5.4 Results

Search results

Stage one's search of the COMET and CROWN core outcome set repository identified one core outcome set for multimorbidity,[132] two core outcome sets for maternity care, pregnancy and childbirth,[133 134] and five systematic reviews conducted for core outcome sets (Figure 5.1).[130 181 191 215 216]

Stage two's search of studies reporting outcomes for pregnant women with multimorbidity initially identified 18962 articles from inception till 11th August 2021. Outcomes saturation was reached after screening 7534 articles from 2017 to 2021. Thirty-two full texts were assessed for eligibility, three additional articles were included from screening the reference list of the included articles. A total of 28 articles were included from 26 studies (Figure 5.2).[43 44 46-48 63 64 173 217-236]

Examples of study selection that required discussion

As many of the outcome studies for maternal multimorbidity were conducted in the United States, Bateman et al's Obstetric Comorbidity Index was commonly used to measure the exposure (maternal multimorbidity).[64] As discussed in Chapter 1, this index included both pre-pregnancy long-term conditions and pregnancy complications such as pre-eclampsia.[64] After discussion, studies using this index was included as it still captured maternal multimorbidity. Despite the term 'comorbidity', this index does not focus on an index condition.[64]

Another key challenge in study selection was ascertaining whether maternal multimorbidity, or commonly termed as 'obstetric comorbidity', was studied as the exposure or a covariate. For example, the study by Little and Varner et al aimed to characterise emergency department use by pregnant women in Ontario.[83 237] The number of pre-pregnancy comorbidities was one of

many covariates / risk factors assessed in the regression analysis, therefore these studies were excluded. In contrast, Clapp et al aimed to compare the outcomes for low and high risk patients (measured with comorbidity index) between low and high acuity hospital (proportion of high risk births at the hospital).[233] The study examined the impact of pregnant women's comorbidities on severe maternal morbidity, stratified by low and high acuity hospitals.[233] After discussion with study supervisors, this study was included.

Characteristics of included studies

Tables 5.3 and 5.4 list the included studies from stage one and stage two searches respectively. Supplementary Material 5.1 lists the studies excluded from stage two searches and the reasons for exclusion.

For stage one, the number of core outcomes in the existing three core outcome sets ranged from 17 to 48.[132-134] For stage two, the included studies were predominantly from the United States (n=21),[43 46-48 64 217 219 220 222-231 233-235] followed by Canada (n=2),[63 236] United Kingdom (n=2),[44 173] and Denmark (n=1).[221] Most included studies were observational studies (n=18),[43 44 46-48 173 219 220 222-224 227-230 233-235] followed by model validation studies (n=7)[64 217 221 225 226 231 236] and one systematic review on the measurement properties of comorbidity indices in maternal health research.[63] The data source or study settings were predominantly in hospitals (n=20),[43 44 46-48 63 64 217 220 222 225 226 228-231 233-236] followed by population based birth or pregnancy records (n=5),[219 221 223 224 227] and population based maternity mortality records (n=1).[173]

Seventeen studies defined maternal multimorbidity using an obstetric comorbidity index or risk score.[63 64 217 219-221 225-231 233-236] The number of reported outcomes ranged from one to 20. Eighteen studies reported the composite outcome of severe maternal morbidity / end organ injury and were predominantly based in the United States (n=15).[43 47 48 63 64 217 220 221 225 227-231 233-236]

List of outcomes

Table 5.5 presents the list of outcomes extracted from the included studies from both stages of searches. Outcome definitions from The National Maternal and Perinatal Audit (England, Scotland and Wales) were also included to aid future studies.[238] The component conditions for the composite outcomes severe maternal morbidity and end organ injury are listed in Tables 5.6 and 5.7.

Overall, there were 185 outcomes: 115 maternal outcomes and 70 child outcomes. When categorised by the taxonomy of outcomes, for maternal outcomes, there were one survival outcome, 79 clinical outcomes (13 antenatal, 64 peripartum, two postnatal / longer-term outcomes, the latter were both perinatal mental health outcomes), 18 life impact / functioning outcomes and 17 resource use / service outcomes. For child outcomes, there were four survival outcomes (intrauterine fetal demise, stillbirth, perinatal death and neonatal death), 62 clinical outcomes (seven fetal outcomes, 52 neonatal outcomes, one infant outcome related to infant feeding, two long-term outcomes [neurodevelopmental outcomes and cerebral palsy]) and four resource use / service outcomes.

5.5 Discussion

Main findings

The systematic search of core outcome set databases identified three core outcome sets and five systematic reviews. The systematic search of medical literature databases identified 26 studies that reported outcomes for pregnant women with multimorbidity. Together, an initial list of 185 outcomes (115 maternal and 70 child outcomes) were extracted, most of the reported outcomes were clinical outcomes. Severe maternal morbidity was a composite outcome measure commonly reported in the included studies.

Comparison with existing literature

This systematic literature search identified 185 outcomes, similar to other systematic reviews conducted for the development of core outcome sets, which generally identified large number of outcomes (>100).[202 239 240] For example, a systematic review of randomised trials for interventions to prevent pre-eclampsia extracted 119 different outcomes (72 maternal outcomes, 47 offspring outcomes);[239] a systematic review of reviews on interventions to prevent stillbirth extracted 237 outcomes (150 maternal outcomes, 87 offspring outcomes).[240] This is in line with the observation that there is variation in outcomes reporting in the respective fields, necessitating the development of core outcome sets to standardise outcomes reporting.[239 240]

Strengths

Existing literature for multimorbidity in pregnancy is sparse.[66] The associated maternal and offspring outcomes are potentially broad, depending on the specific combinations of health conditions the pregnant woman has. This systematic literature search has been adapted to address these challenges. The key strength of this study is the robust and pragmatic systematic search methods employed. Four bibliographic databases and two core outcome set databases were searched. Keyword and Medical Subject Headings for multimorbidity and pregnancy

were used in the search strategy, guided by previous systematic reviews. Two researchers independently conducted the full text screen and data extraction. For transparency, the outcomes and outcome definitions were extracted verbatim.

Limitations in the context of current literature

Limitations of the study included not searching the entirety of the literature from inception. The study also did not search for grey literature such as thesis repository, Open Grey, conference proceedings (e.g., Royal College of Midwives conference), and therefore may have missed some outcomes.

The search of the core outcome set databases has yielded most of the outcomes extracted in this study. Although this strategy ensures comprehensive coverage of maternal and offspring outcomes in general, it has resulted in a long list of outcomes that may not be specific for pregnancy with multimorbidity. When presented in the subsequent Delphi survey, the long list of outcomes may result in survey fatigue.

Although data extraction was completed by two researchers, the grouping of similar outcomes was conducted by only one researcher and may have resulted in misclassification errors. However, the inventory of outcomes was reviewed by the multidisciplinary research group prior to being presented in the Delphi surveys.

Pragmatic search strategy by stages until outcome saturation

The current study conducted the systematic literature search in stages until outcome saturation was reached in 2017. This method was suggested by the COMET handbook when a search is overly large.[142] It was also employed by Egan et al in their development of a core outcome set for studies of gestational diabetes prevention and treatment.[202]

Multimorbidity in pregnancy is a relatively new area of research, with its emerging importance first discussed by Beeson et al in 2018.[178] Brown et al's recent systematic review of adverse

maternal outcomes associated with pre-pregnancy multimorbidity identified seven studies.[66] Even then, three of the seven included studies were limited to specific combinations of health conditions (comorbidities with index health conditions); the earliest study was published in 2018.[66] Brown et al's systematic review identified five types of outcomes: any pregnancy complication, severe maternal morbidity and mortality, pre-eclampsia and related conditions, hospital transfers, and perinatal emergency department visits;[66] all, except the non-specific first outcome, were included in this current study. These findings suggest that the current study's pragmatic search strategy (2017 to 2021) is unlikely to have missed any important types of outcomes.

Inclusion of existing core outcome sets

Outcomes that are applicable to pregnancy and childbirth in general would also be applicable to pregnant women with long-term conditions and multimorbidity. In the core outcome set for epilepsy in pregnancy, generic obstetric outcomes such as maternal mortality, stillbirth, preterm birth were included, alongside disease specific outcomes such as seizure control in pregnancy and sudden unexpected death in epilepsy.[198] In contrast, multimorbidity in pregnancy is much more heterogenous, it would not be possible to include disease specific outcomes for every single long-term conditions. However, there are general outcomes that are applicable to all types of multimorbidity, related to the challenges of living with multiple health conditions. Examples included shared care decision makings and treatment burden.[132] Therefore the current study also included existing core outcome set for multimorbidity.

Defining unique outcomes

Young et al proposed that a unique outcome is "one that has original meaning and context; outcomes with different words, phrasing, or spelling addressing the same concept and context should be categorized as one outcome."[241] The review highlighted the inconsistencies in how authors define, group and count outcomes in the core outcome set literature.[241] The

inconsistency arises as the granularity at which the outcomes are grouped may differ and there is a lack of standard guidance.[241]

For example, in the current study, 'vaginal birth', 'instrumental birth' and 'caesarean birth' (which may be further subdivided into 'elective caesarean' and 'emergency caesarean') could potentially be grouped with the broader outcome 'mode of birth'. 'Small for gestational age', 'low birth weight' and 'large for gestational age' could potentially be grouped with the broader outcome 'birth weight'. For some health conditions such as maternal diabetes mellitus, 'large for gestational age' and macrosomia may be of particular importance; for others, 'small for gestational age' may be more relevant. For the purpose of minimising survey burden, ultimately the broader outcome categories may be chosen and decisions are made on a pragmatic basis.

With this in mind, in some instances, different constructs of an outcome were grouped together, for instance: breastfeeding at different time points, success with breastfeeding, confidence with breastfeeding, and baby receiving breast milk. This reflects the main aim of the current study, which was to inform the development of the Delphi survey. However, the less stringent application of the definition of a unique outcome limits this study's ability to quantify outcome reporting heterogeneity in studies of pregnancy with multimorbidity.

Young et al also proposed that outcomes that differ only by the timing of outcome measurement should not be considered as a unique outcome.[241] The current study has therefore grouped such outcomes together, for example: obstetric haemorrhage (intrapartum haemorrhage, postpartum haemorrhage), hypertensive disorder of pregnancy (intrapartum, postpartum), and maternal satisfaction (antenatal, intrapartum and postpartum).

Research implications

This initial list of outcomes reflects the types of outcomes that researchers felt were important and have reported in previous studies.[142] As observed from simple counts, clinical outcomes

were most represented in the initial inventory of outcomes, covering different stages of pregnancy (antenatal, peripartum, postnatal) and early childhood (fetal, neonatal, infant).

Although present in small numbers, other non-physiological outcomes were also identified: experience-based outcomes (e.g., satisfaction with care, birth experience, confidence in role as a mother), resource outcomes (e.g., health care cost, readmissions) and life impact / functioning outcomes (e.g., quality of life, treatment burden and physical functioning). Such outcomes often may have more relevance to people living with the health conditions. The importance of experiential outcomes is discussed further in Chapter 8. Some of these are salutogenically focused, measuring positive maternal and neonatal health and well-being outcomes. Smith et al argued that intrapartum intervention studies tend to focus on adverting adverse outcomes instead of measuring factors contributing to positive outcomes.[216] Future studies should consider positive framing of outcomes.

To ensure outcomes that matter to all key stakeholders will subsequently inform the Delphi survey, the next step in the core outcome set development is to explore what outcomes are important to women with multimorbidity and experience of pregnancy or planning a pregnancy, their partners and health care professionals.

Conclusion

The systematic literature search identified a wide range of maternal and child outcomes. This reflects the broad scope of maternal and child outcomes that can be studied for pregnant women with multimorbidity. The long list of outcomes will inform the design of a Delphi survey, through which a core outcome set will be prioritised.

Table 5.1: Search strategy

Database	Search details	Search terms
Stage 1: Published core outcome sets for pregnancy and childbirth and for multimorbidity in core outcome set databases		
COMET	Conducted on 15th September 2021	Disease category: Pregnancy & childbirth Disease name: Multimorbidity
CROWN	Conducted on 7th October 2021	Hand searched
Stage 2: Studies reporting outcomes for pregnant women with multimorbidity or their children		
Medline	Conducted on 11th August 2021 Ovid Medline (R) and In-Process, In-Data Review & Other Non-indexed Citations, 1946 to 10th August 2021	**Multimorbidity** 1. (multimorbidity* or multi-morbidit* or comorbidit* or co-morbidit* or polymorbidit* or poly-morbidit* or multicondition* or multi-condition* or 'multiple chronic condition*' or 'morbidity burden' or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) adj2 (disease* or illness* or condition* or diagnos* or morbid*))).ti,ab. or exp Multimorbidity/ or exp Comorbidity/ (n=298,023) **Pregnancy** 2. exp Pregnancy/ or exp Pregnant women/ or exp Gravidity/ or exp Mothers/ or exp Obstetrics/ or exp Delivery, obstetric/ or exp Parturition/ or exp Maternal Health/ or exp Maternal health services/ or (pregnan* or gravid* or gestation* or 'pregnant wom#n' or matern* or mother* or obstetric* or (child adj3 bearing) or childbearing or parturition or childbirth or child-birth or child birth).ti,ab. (n=1,343,221) 3. 1 and 2 (n=9297) 4. Limit 3 to human (n=8130)
Embase	Conducted on 11th Aug 2021 Embase (Ovid) 1974 to 10th Aug 2021	**Multimorbidity** 1. (multimorbidity* or multi-morbidit* or comorbidit* or co-morbidit* or polymorbidit* or poly-morbidit* or multicondition* or multi-condition* or 'multiple chronic condition*' or 'morbidity burden' or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) adj2 (disease* or illness* or condition* or diagnos* or morbid*))).ti,ab. or exp Multiple Chronic Conditions/ or exp Comorbidity/ (n=525,241) **Pregnancy** 2. exp Pregnancy/ or exp Pregnant Woman/ or Mother/ or exp Obstetrics/ or exp Obstetric Delivery/ or Birth/ or exp Childbirth/ or Maternal Care/ or (pregnan* or gravid* or gestation* or

		'pregnant wom#n' or matern* or mother* or obstetric* or (child adj3 bearing) or childbearing or parturition or childbirth or child-birth).ti, ab. (n=1,455,813) 3. 1 and 2 (n=16,553) 4. Limit 3 to human (n=15,641)
CINAHL	Conducted on 11th August 2021	ID Search Hits S1 (MH "Pregnancy+") 228,070 S2 (MH "Mothers+") 46,291 S3 (MH "Obstetrics") 6,412 S4 (MH "Delivery, Obstetric+") 15,558 S5 (MH "Maternal Health Services+") 33,349 S6 pregnan* OR gravid* OR gestation* OR "pregnant wom?n" OR matern* OR mother* OR obstetric* OR (child N3 bearing) OR childbearing OR parturition OR childbirth OR child-birth OR "child birth" 403,834 S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6 407,310 S8 (MH "Comorbidity") OR "multimorbidit* or multi-morbidit* or comorbidit* or co-morbidit* or polymorbidit* or poly-morbidit* or multicondition* or multi-condition* or "multiple chronic condition*" or "morbidity burden" or ((multiple or coexisting or co-existing or concurrent or con-current or comorbid or co-morbid) N2 (disease* or illness* or condition* or diagnos* or morbid*))" 65,877 S9 S7 AND S8 1,945
Cochrane Library	Conducted on 11th August 2021	ID Search Hits #1 MeSH descriptor: [Multimorbidity] explode all trees 56 #2 MeSH descriptor: [Comorbidity] explode all trees 3665 #3 (multimorbidity* OR multi-morbidit* OR comorbidit* OR co-morbidit* OR polymorbidit* OR poly-morbidit* OR multicondition* OR multi-condition* OR "multiple chronic conditions" OR "morbidity burden" OR ((multiple OR coexisting OR co-existing OR concurrent OR con-current OR comorbid OR co-morbid) NEAR/2 (disease* OR illness* OR condition* OR diagnos* OR morbid*))):ti,ab 22058 #4 #1 OR #2 OR #3 24721 #5 MeSH descriptor: [Pregnancy] explode all trees 23021 #6 MeSH descriptor: [Pregnant Women] explode all trees 357

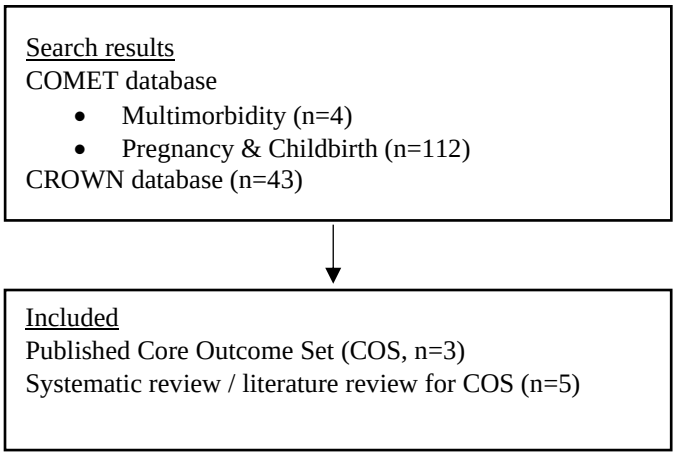
		#7 MeSH descriptor: [Gravidity] explode all trees 62 #8 MeSH descriptor: [Mothers] explode all trees 1936 #9 MeSH descriptor: [Obstetrics] explode all trees 198 #10 MeSH descriptor: [Delivery, Obstetric] explode all trees 5420 #11 MeSH descriptor: [Parturition] explode all trees 468 #12 MeSH descriptor: [Maternal Health] explode all trees 69 #13 MeSH descriptor: [Maternal Health Services] explode all trees 2378 #14 (pregnan* OR gravid* OR gestation* OR (pregnant NEXT wom?n) OR matern* OR mother* OR obstetric* OR (child NEAR/3 bearing) OR childbearing OR parturition OR childbirth OR child-birth OR (child NEXT birth)):ti,ab 91692 #15 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 96928 #16 #4 AND #15 1088

Table 5.2: Inclusion and exclusion criteria

No	Concept	Question
1	**Population**	**Include** Study identified or recruited the following population to study their outcomes: - pregnant women with multimorbidity, OR - children born to mothers with multimorbidity, OR - general population of pregnant women and compared the outcomes of those with multimorbidity versus those with no multimorbidity **Exclude** - Participants who were identified or recruited based on the presence of an index condition (co-morbidity studies) - Participants who were identified or recruited based on specific combination of diseases, which would limit their representation of pregnant women with multimorbidity - Participants who were identified or recruited based on the presence of an outcome
2	**Exposure / intervention**	**Exposure:** Maternal multimorbidity that pre-existed prior to pregnancy **Definition of multimorbidity** - 2 or more long-term physical or mental health conditions - Pre-existing long-term conditions at conception, prior to pregnancy - Does not include pregnancy related conditions or complications related to pregnancy such as gestational diabetes, pre-eclampsia - *Severe maternal morbidity* refers to pregnancy complications and not pre-existing long-term conditions; it is the outcome of interest not exposure of interest **Intervention**: Any intervention with the target population being pregnant women with multimorbidity **Exclude** - 'Comorbidities' adjusted as a covariate, confounder, effect modifier, mediator - 'Comorbidities' refer to one disease or listed as individual diseases and not analysed as a combination of diseases or when it is not clear whether 'comorbidities' refers to multimorbidity
3	**Outcome**	**Include** - any types of pregnancy / maternal / offspring outcomes (i.e., not limited to health outcomes) NB. risk factors/ predictors/ factors associated with multimorbidity in pregnant women are <u>not outcomes</u> **Exclude** - Studies that have not collected / reported any outcomes **Example outcomes based on the taxonomy of outcomes:** i. *death* – mortality, survival ii. *clinical/physiological* – e.g., cardiac outcome, psychiatric outcome

		iii. *life impact* – physical/social/role/emotional/cognitive functioning, quality of life, adherence, satisfaction iv. *resource use* – economic / hospital/ further intervention/carer burden v. *adverse events*
4	**Study design / publication types**	**Include:** - systematic reviews - interventional studies / trials (randomised / non-randomised controlled studies / quasi-experimental) - observational (cohort / cross sectional) - qualitative studies - patient reported outcome measures (PROM) studies - model validation study (if outcomes that the model of multimorbidity is trying to predict is reported) **Exclude:** - ongoing studies with no reported outcomes - editorials / commentaries - narrative reviews - guidelines - case reports / case series - diagnostic accuracy studies – except tools to assess multimorbidity risk / status - laboratory studies - animal studies NB. - no language limitation - abstracts / conference proceedings are also included if able to extract the types of outcomes the authors have collected / measured

Figure 5.1: Stage one: COMET and CROWN database search results



COMET: Core Outcome Measures in Effectiveness Trials; CROWN: Core Outcomes in Women's and Newborn Health

Figure 5.2: Stage two: PRISMA flow chart of the search results for studies reporting outcomes for pregnant women with multimorbidity or their children

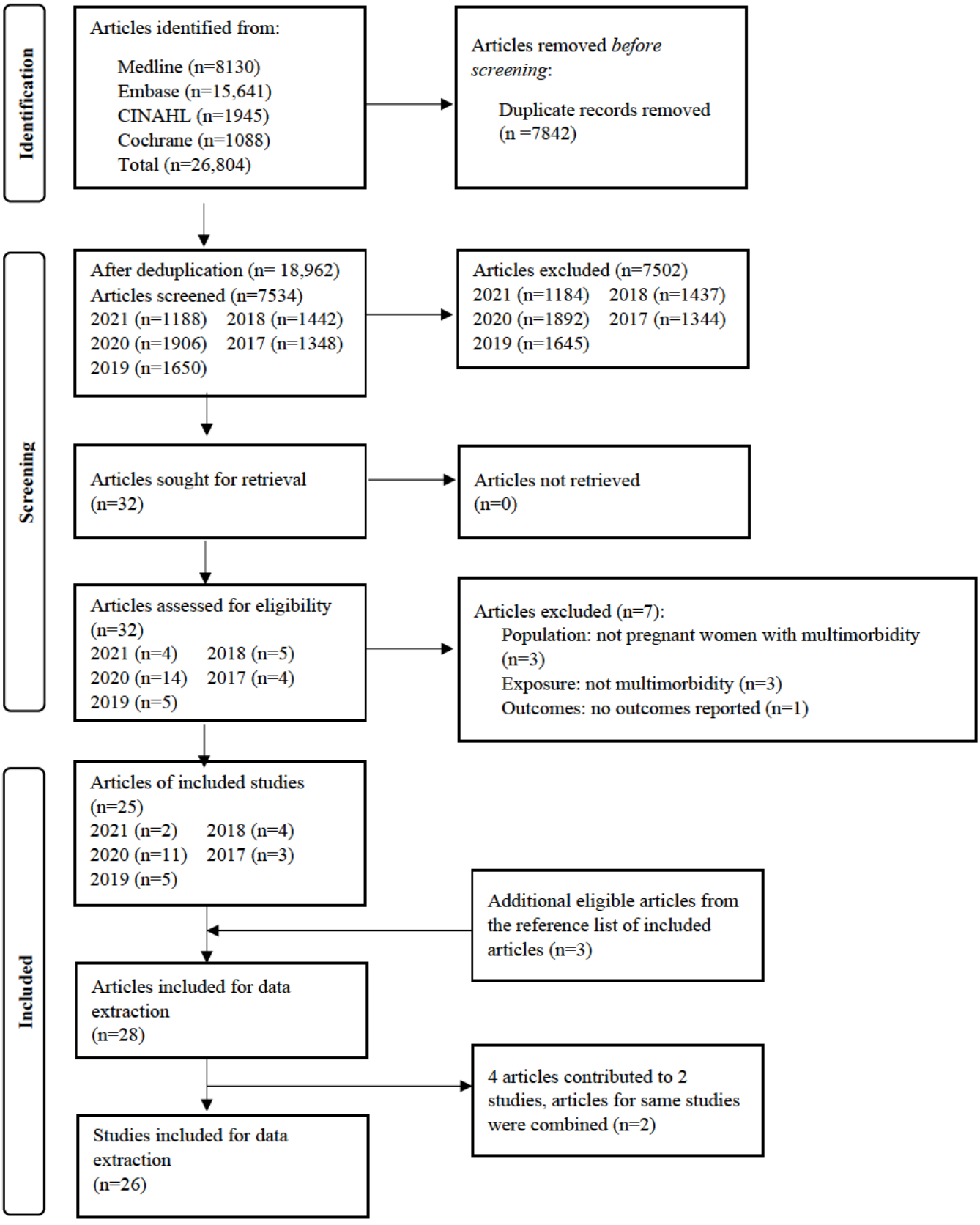


Table 5.3: Stage one: Search of the COMET and CROWN database for published core outcome sets

Existing, published core outcome sets for multimorbidity		
No	**References**	**Comments**
1	Smith SM, Wallace E, Salisbury C, Sasseville M, Bayliss E, Fortin M. A Core Outcome Set for Multimorbidity Research (COSmm). Annals of family medicine. 2018;16(2):132-8.	17 core outcomes
Existing, published core outcome sets for pregnancy		
2	Devane D, Begley CM, Clarke M, Horey D, C OB. Evaluating maternity care: a core set of outcome measures. Birth (Berkeley, Calif). 2007;34(2):164-72	48 core outcomes
3	Nijagal MA, Wissig S, Stowell C, Olson E, Amer-Wahlin I, Bonsel G, et al. Standardized outcome measures for pregnancy and childbirth, an ICHOM proposal. BMC Health Services Research. 2018;18(1):953.	24 core outcomes
Systematic reviews / literature reviews for core outcome sets		
1	Herman D, Lor KY, Qadree A, Horn D, D'Souza R. Composite adverse outcomes in obstetric studies: a systematic review. BMC pregnancy and childbirth. 2021;21(1):107.	31 components in maternal morbidity/mortality composite outcomes, 45 components in perinatal morbidity/mortality composite outcomes, 34 components in combined maternal-perinatal morbidity/mortality composite outcomes.
2	Slavin V, Creedy DK, Gamble J. Core Outcome Sets Relevant to Maternity Service Users: A Scoping Review. Journal of Midwifery & Women's Health. 2021;66(2):185-202.	The review included 26 COS but only 1 COS was for pregnancy in general (the others were condition specific), which is already included (Devane 2007).
3	SBU Policy Support. Core outcome sets for research within the area of maternity care. Overview of completed and ongoing studies2020. Available from: https://www.sbu.se/en/publications/sbu-bereder/core-outcome-sets-for-research-within-the-area-of-maternity-care/	The review included 19 studies, 3 were for pregnancy in general, of which 2 were already included (Devane 2007, Nijagal 2018). One additional study prioritised maternity care quality indicators using the COS methodology was identified: Bunch KJ, Allin B, Jolly M, Hardie T, Knight M. Developing a set of consensus indicators to support maternity service quality improvement: using Core

		Outcome Set methodology including a Delphi process. BJOG. 2018;125(12):1612-8. (14 core metrics)
4	Duffy J, Rolph R, Gale C, Hirsch M, Khan KS, Ziebland S, et al. Core outcome sets in women's and newborn health: a systematic review. BJOG. 2017;124(10):1481-9.	The review identified 20 systematic reviews and 4 published COS, of which 1 systematic review (Smith 2014) and 1 COS (Devane 2007) for pregnancy in general are already included.
5	Smith V, Daly D, Lundgren I, Eri T, Benstoem C, Devane D. Salutogenically focused outcomes in systematic reviews of intrapartum interventions: a systematic review of systematic reviews. Midwifery. 2014;30(4):e151-6.	16 salutogenically focused reported outcomes, 49 non-salutogenically focused reported outcomes.

COS: core outcome set

Table 5.4: Stage two: Studies reporting outcomes for pregnant women with multimorbidity or their children

No	Full Reference	Study design	Country	Population	Exposure (maternal multimorbidity)	Number of reported outcomes	Reported outcomes
1	D'Arcy R, Knight M, Mackillop L. A retrospective audit of the socio-demographic characteristics and pregnancy outcomes for all women with multiple medical problems giving birth at a tertiary hospital in the UK in 2016. BJOG: An International Journal of Obstetrics and Gynaecology. 2019;126:128.	Observational, conference abstract	UK	All women giving birth at a tertiary hospital in 2016	2 or more medical conditions	6	1. Pre-eclampsia 2. Obstetric Cholestasis 3. Thromboembolism 4. Emergency caesarean section 5. Preterm delivery 6. Low birth weight
2	Easter SR, Bateman BT, Sweeney VH, Manganaro K, Lassey SC, Gagne JJ, et al. A comorbidity-based screening tool to predict severe maternal morbidity at the time of delivery. American Journal of Obstetrics & Gynecology. 2019;221(3):271.e1-.e10.	Validation	USA	All patients with pregnancies ≥23 weeks gestation presenting for labour and delivery at a single tertiary-care centre from February through July 2018	Obstetric comorbidity index	2	1. Maternal death 2. Severe maternal morbidity
	Easter SR, Sweeney V, Manganaro K, Lassey SC, Bateman BT, Robinson JN. 278: Prospective clinical validation of the obstetric comorbidity index for maternal risk assessment. American Journal of Obstetrics and Gynecology. 2019;220:S198-S9.	Validation, conference abstract	USA	All patients with pregnancies at or beyond 23 weeks gestation presenting for labour and delivery from February to June 2018	Obstetric comorbidity index	1	1. Severe maternal morbidity
3	Salahuddin M, Mandell DJ, Lakey DL, Eppes CS, Patel DA. Maternal risk	Observational	USA	Nulliparous, term, singleton, vertex	Maternal risk factor index (0-4)	1	1. Delivery route

	factor index and cesarean delivery among women with nulliparous, term, singleton, vertex deliveries, Texas, 2015. Birth. 2019;46(1):182-92.			deliveries to women aged 15-49 years in Texas			
4	Somerville NJ, Nielsen TC, Harvey E, Easter SR, Bateman B, Diop H, et al. Obstetric Comorbidity and Severe Maternal Morbidity Among Massachusetts Delivery Hospitalizations, 1998-2013. Maternal & Child Health Journal. 2019;23(9):1152-8.	Observational	USA	All delivery hospitalizations during 1998–2013 in Massachusetts	Obstetric comorbidity index	1	1. Severe maternal morbidity
5	Bliddal M, Moller S, Vinter CA, Rubin KH, Gagne JJ, Pottegard A. Validation of a comorbidity index for use in obstetric patients: A nationwide cohort study. Acta Obstetricia et Gynecologica Scandinavica. 2020;99(3):399-405.	Validation	Denmark	All completed pregnancies (both live- and stillborn infants) in Denmark from 1 July 2000 to 1 December 2014	Obstetric comorbidity index	2	1. Maternal death 2. End organ injury
6	Brown CC, Adams CE, George KE, Moore JE. Associations Between Comorbidities and Severe Maternal Morbidity. Obstetrics & Gynecology. 2020;136(5):892-901.	Observational	USA	All delivery hospitalisation in year 2016-2017 from the National Inpatient Sample	Number of comorbidities	2	1. Severe maternal morbidity 2. Non transfusion severe maternal morbidity
7	Cao S, Dong F, Okekpe CC, Dombrovsky I, Valenzuela GJ, Roloff K. Prevalence of the number of pre-gestational diagnoses and trends in the United States in 2006 and 2016. Journal of Maternal Fetal and Neonatal Medicine. 2020.	Observational	USA	All pregnant patients admitted for delivery	Number of pregestational diagnosis	20	1. Number of pregnancy complications 2. Chorioamnionitis 3. Gestational diabetes 4. Haemorrhage 5. Infection 6. Intrauterine fetal demise 7. Intrauterine growth restriction

							8. Laceration (cervical, vaginal, perineal) 9. Large for gestational age 10. Malpresentation 11. Meconium 12. Non-reassuring fetal heart tones 13. Oligohydramnios 14. Placental abruption 15. Placental insufficiency 16. Placenta previa 17. Polyhydramnios 18. Pregnancy induced hypertension 19. Preterm delivery 20. Preterm premature rupture of membranes
8	Field CP, Stuebe AM, Verbiest S, Tucker C, Ferrari R, Jonsson-Funk M. 917: Early identification of women likely to be high utilizers of perinatal acute care services. American Journal of Obstetrics and Gynecology. 2020;222:S567-S8.	Observational, conference abstract	USA	Women who received prenatal care and delivered at the North Carolina Women's Hospital between July 1, 2014, and June 30, 2016, who had at least one prenatal outpatient encounter before 20 weeks' gestation	Number of non-obstetric diagnosis documented in the first 20 weeks of pregnancy	5	1. Severe maternal morbidity 2. Infant admitted to Newborn Critical Care Unit 3. High utilisation of perinatal acute care services 4. Emergency department visit 90 days following birth 5. Readmission 90 days following birth
9	Fresch R, Stephens KK, DeFranco E. 1193: The combined influence of multiple maternal medical conditions on incidence of primary cesarean	Observational, conference abstract	USA	Ohio live birth records from 2006-2015	Multiple medical comorbidities	1	1. Caesarean delivery

	section. American Journal of Obstetrics and Gynecology. 2020;222:S734-S5.						
10	Fresch RJ, DeFranco E, Stephen K. The combined influence of maternal medical conditions on the risk of fetal growth restriction. Obstetrics and Gynecology. 2020;135:154S-5S.	Observational, conference abstract	USA	Ohio live birth records from 2006–2015	Multiple medical comorbidities	2	1. Fetal growth restriction 2. Severe fetal growth restriction
11	Leonard SA, Kennedy CJ, Carmichael SL, Lyell DJ, Main EK. An Expanded Obstetric Comorbidity Scoring System for Predicting Severe Maternal Morbidity. Obstetrics & Gynecology. 2020;136(3):440-9.	Validation	USA	All live births occurring in California-licensed hospitals during 2016 and 2017	Obstetric comorbidity score	2	1. Severe maternal morbidity 2. Non transfusion severe maternal morbidity
12	Liu V, Hedderson M, Greenberg M, Kipnis P, Escobar GJ, Ruppel H. Development of an obstetrics comorbidity risk score for clinical and operational use. Journal of Women's Health. 2020;29:A14.	Validation, conference abstract	USA	Pregnancies from Kaiser Permanente Northern California between 2010 and 2017	Obstetric comorbidity risk score	4	1. Severe pre-eclampsia 2. Eclampsia 3. Haemorrhage 4. Death
13	Main EK, Leonard SA, Menard MK. Association of Maternal Comorbidity With Severe Maternal Morbidity: A Cohort Study of California Mothers Delivering Between 1997 and 2014. Annals of Internal Medicine. 2020;173(11):S11-S8.	Observational	USA	All mothers delivering in California during 1997 to 2014.	Maternal comorbid conditions individually and as a maternal comorbidity index score (Bateman 2013, Easter 2019)	1	1. Severe maternal morbidity
14	Ranjit A, Olufajo O, Zogg C, Robinson JN, Luo G. To determine if maternal adverse outcomes predicted by obstetric comorbidity index (OBCMI) varies according to race. Obstetrics and Gynecology. 2020;135:37S-8S.	Observational, conference abstract	USA	All admissions for deliveries in the National Inpatient Database (2010–2014)	Obstetric comorbidity index	1	1. Severe maternal morbidity / mortality

15	Salahuddin M, Mandell DJ, Lakey DL, Ramsey PS, Eppes CS, Davidson CM, et al. Maternal comorbidity index and severe maternal morbidity during delivery hospitalizations in Texas, 2011-2014. Birth. 2020;47(1):89-97.	Observational	USA	Delivery-related hospitalizations among Texan women aged 15-49 years	Medical (chronic and behavioural) and obstetric (pregnancy-induced) conditions as measured by the maternal comorbidity index developed by Bateman 2013	1	1. Severe maternal morbidity
16	Sutton D, Oberhardt M, Oxford-Horrey CM, Prabhu M, Aubey J, Riley LE, et al. 711 Obstetric comorbidity index corresponds with racial disparity in maternal morbidity providing insight for risk reduction. American Journal of Obstetrics and Gynecology. 2021;224:S445-S6.	Observational, conference abstract	USA	All deliveries in a four-hospital system from January 2016 through January 2020	Obstetric comorbidity index (Leonard 2020)	1	1. Non transfusion severe maternal morbidity
17	Oberhardt M, Sutton D, Oxford-Horrey C, Prabhu M, Sheen JJ, Riley L, et al. 8 Augmenting or Replacing Obstetric Comorbidity Index with Labor & Delivery Features Improves Prediction of Non-Transfusion Severe Maternal Morbidity. American Journal of Obstetrics and Gynecology. 2021;224:S5.	Validation, conference abstract	USA	All women delivering in a four-hospital system from January 2016 through January 2020	Obstetric comorbidity index (Leonard 2020)	1	1. Non transfusion severe maternal morbidity
18	Admon LK, Winkelman TNA, Heisler M, Dalton VK. Obstetric Outcomes and Delivery-Related Health Care Utilization and Costs Among Pregnant Women With Multiple Chronic	Observational	USA	Deliveries in 2013–2014 from the National Inpatient Sample, a nationally representative sample of hospital	Multiple chronic conditions	6	1. Preterm delivery 2. Caesarean delivery 3. Severe maternal morbidity and mortality 4. Need for hospital transfer (heath care utilisation)

	Conditions. Preventing Chronic Disease. 2018;15:E21.			discharges in the United State			5. Hospital length of stay (health care utilisation) 6. Health care cost
19	Clapp MA, James KE, Kaimal AJ. The effect of hospital acuity on severe maternal morbidity in high-risk patients. American Journal of Obstetrics & Gynecology. 2018;219(1):111.e1-.e7.	Observational	USA	Hospital deliveries in the 2013 Nationwide Readmission Database	Comorbidity index (Bateman 2013)	1	1. Severe maternal morbidity
	Clapp MA, James KE, Kaimal AJ. The association between hospital acuity and severe maternal morbidity in a nationwide sample. American Journal of Obstetrics and Gynecology. 2018;218:S41-S2.	Observational, conference abstract	USA	Hospital deliveries in the 2013 Nationwide Readmission Database	Comorbidity index (Bateman 2013)	1	1. Severe maternal morbidity
20	Metcalfe A, Wick J, Ronksley P. Racial disparities in comorbidity and severe maternal morbidity/mortality in the United States: an analysis of temporal trends. Acta Obstetricia et Gynecologica Scandinavica. 2018;97(1):89-96.	Observational	USA	All delivery hospitalizations among women aged 10–55 between 1993 and 2012 recorded in the Nationwide Inpatient Sample data	Comorbidities, individually and as Obstetric comorbidity index score	2	1. Severe maternal morbidity 2. In hospital maternal mortality
21	Aoyama K, D'Souza R, Inada E, Lapinsky SE, Fowler RA. Measurement properties of comorbidity indices in maternal health research: a systematic review. BMC Pregnancy & Childbirth. 2017;17(1):372.	Systematic review	Canada	Pregnant and postpartum women in general wards and intensive care units at acute care hospitals	Comorbidity indices	2	1. End organ injury 2. Mortality
22	Cunningham SD, Herrera C, Udo IE, Kozhimannil KB, Barrette E, Magriples U, et al. Maternal Medical	Observational	USA	Women aged 18 to 44 who gave birth in 2011 observed in	Maternal medical complexity	1	1. Health care expenditure during pregnancy

	Complexity: Impact on Prenatal Health Care Spending among Women at Low Risk for Cesarean Section. Womens Health Issues. 2017;27(5):551-8.			the inpatient claims data	including numbers of comorbidities		
23	Hehir MP, Ananth CV, Wright JD, Siddiq Z, D'Alton ME, Friedman AM. Severe maternal morbidity and comorbid risk in hospitals performing <1000 deliveries per year. American Journal of Obstetrics & Gynecology. 2017;216(2):179.e1-.e12.	Observational	USA	Births from 1998 through 2011, from the Nationwide Inpatient Sample	Comorbidity index (Bateman 2013)	1	1. Severe maternal morbidity
	Additional papers from reference list						
24	Bateman BT, Mhyre JM, Hernandez-Diaz S, Huybrechts KF, Fischer MA, Creanga AA, et al. Development of a comorbidity index for use in obstetric patients. Obstetrics and Gynecology. 2013;122(5):957-65.	Validation	USA	Women who delivered in-hospital and were eligible for Medicaid	Maternal comorbidity index	3	1. End organ injury 2. Death 3. Maternal intensive care unit admission
25	Metcalfe A, Lix L, Johnson J-A, Currie G, Lyon A, Bernier F, et al. Validation of an obstetric comorbidity index in an external population. BJOG: An International Journal of Obstetrics & Gynaecology. 2015;122(13):1748-55.	Validation	Canada	All women who delivered a live or stillborn infant in a hospital in the Calgary Zone of Alberta Health Services and conceived between 4 November 2007 and 23 February 2008	Obstetric comorbidity index	2	1. Maternal end organ damage 2. Extended length of stay for delivery
26	Knight M, Bunch K, Tuffnell D, Shakespeare J, Kotnis R, Kenyon S, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care - Lessons	Observational	UK	Women who died during or up to a year after pregnancy in the UK in 2016-18,	Multiple disadvantage (main elements: mental health, substance	1	1. Maternal mortality

	learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2016-18. Oxford: National Perinatal Epidemiology Unit, University of Oxford 2020.			with pregnant women who had multiple problem as a subgroup	use, domestic abuse)		

UK: United Kingdom; USA: United States of America

Table 5.5: List of initial outcomes from the systematic literature search

No	Outcomes	Definition of outcomes	References
	MATERNAL OUTCOMES		
	Maternal: Mortality / survival		
1	• Maternal death[47 133 134 173 191 221 226] • Maternal mortality[216] • In hospital maternal mortality[236] • Mortality[132]	• From the start of delivery admission to the hospital through 30 days postpartum.[221] • Combined with severe maternal morbidity as "severe maternal morbidity and mortality".[47] • Combined with serious morbidity as "maternal mortality or serious morbidity".[216] • Combined with end organ injury as a composite outcome of maternal end organ injury or death, during the delivery admission through 30 days postpartum.[64] • Died during or up to six weeks after the end of pregnancy.[133 173] • Died between six weeks and one year after the end of pregnancy.[173] • Death of a female from any cause related to or aggravated by pregnancy or its management (excluding accidental or incidental causes) during pregnancy and childbirth or within 42 days of pregnancy termination, irrespective of site or duration of the pregnancy.[134] • From core outcome set for multimorbidity[132]	Devane 2007[133] Bateman 2013[64] Smith 2014[216] Aoyama 2017[63] Admon 2018[47] Metcalfe 2018[236] Nijagal 2018[134] Smith 2018[132] Easter 2019[217] Bliddal 2020[221] Knight 2020[173] Liu 2020[226] Ranjit 2020[228] Herman 2021[191]

	Maternal: Physiological / clinical		
	Antenatal		
2	• Pregnancy induced hypertension[222] • Pre-eclampsia[44] • Severe pre-eclampsia[226] • Eclampsia[226] • Intrapartum hypertensive disorders of pregnancy[133] • Hypertensive disorders of/in pregnancy[133] [191] • Postnatal hypertensive disorders of pregnancy[133]	A group of diseases characterized by high blood pressure with or without proteinuria; this group includes pre-eclampsia, eclampsia, and the syndrome of HELLP.[133]	Devane 2007[133] D'Arcy 2019[44] Cao 2020[222] Liu 2020[226] Herman 2021[191]
3	Obstetric cholestasis		D'Arcy 2019[44]
4	Gestational diabetes mellitus		Cao 2020[222] Herman 2021[191]
5	Chorioamnionitis		Cao 2020[222]
6	Fluid abnormalities on ultrasound (oligohydramnios or polyhydramnios)		Herman 2021[191]
7	Oligohydramnios		Cao 2020[222]
8	Polyhydramnios		Cao 2020[222]
9	Placental abruption		Cao 2020[222] Herman 2021[191]
10	Placental insufficiency		Cao 2020[222]
11	Placenta previa		Cao 2020[222]
12	Smoking rate at booking		Bunch 2018[242]
13	Nausea / vomiting / dehydration		Smith 2014[216]
14	Headache		Smith 2014[216]
	Peripartum		
15	Types of labour onset	Manner in which labour started, i.e., induced, spontaneous, planned caesarean section.	Devane 2007[133]
16	Spontaneous rupture of membranes		Smith 2014[216]
17	Preterm premature rupture of membranes		Cao 2020[222]

18	• Delivery route[219] • Mode of birth[133,216]	• Vaginal/spontaneous, vaginal/forceps, vaginal/vacuum, and caesarean. Caesarean included those with and without attempted trial of labour.[219] • E.g., spontaneous vaginal, forceps, vaginal breech, caesarean section, vacuum extraction.[133]	Devane 2007[133] Smith 2014[216] Salahuddin 2019[219]
19	• Caesarean delivery[47 223] • Caesarean birth[216 238] • Caesarean section[191] • Caesarean section delivery rate in Robson group 1 women[242] • Caesarean section delivery rate in Robson group 2 women[242] • Caesarean section delivery rate in Robson group 5 women[242]	• Robson group 1: Nulliparous, single cephalic, ≥ 37 weeks, spontaneous labour[242 243] • Robson group 2: Nulliparous, single cephalic, ≥ 37 weeks, induced or caesarean before labour[242 243] • Robson group 5: Multiparous, previous caesarean, single cephalic ≥ 37 weeks[242 243]	Smith 2014[216] Admon 2018[47] Bunch 2018[242] NMPA 2018[238] Fresch 2020[223] Herman 2021[191]
20	Emergency caesarean section		D'Arcy 2019[44]
21	• Vaginal birth after previous caesarean section (VBAC)[133] • Trial of labour after previous caesarean delivery[133] • Rate of successful vaginal birth after a single previous caesarean section[242] • Vaginal birth after caesarean section[238]	**NMPA**[238] **Overall VBAC 2nd birth**: of women having their second baby after having had a caesarean section for their first baby,* the proportion who give birth to their second baby vaginally. **Attempted VBAC 2nd birth**: of women having their second baby after having had a caesarean section for their first baby, the proportion who attempt to have a vaginal birth for their second baby. **VBAC 2nd birth in attempted**: of women having their second baby after having had a caesarean section for their first baby and who attempted to have a vaginal birth for their second baby, the proportion who give birth to their second baby vaginally. * The measure is limited to this group of women because of the limitations of historical records and because this is	Devane 2007[133] Bunch 2018[242] NMPA 2018[238]

		the largest group of women considering VBAC. The rates reported do therefore not include women who also had a previous vaginal birth.	
22	• Any instrumental/assisted vaginal birth[216] • Operative vaginal delivery[191] • Instrumental birth[238]	Birth is assisted by the use of an instrument (either ventouse or forceps).[238]	Smith 2014[216] NMPA 2018[238] Herman 2021[191]
23	• Normal (i.e., physiological) birth without intervention[133] • Rate of birth without intervention[242] • Birth without intervention[238] • Spontaneous vaginal birth (or 'normal vaginal birth') [238,216]	• Vaginal birth without induction, episiotomy, or epidural.[133] • The NMPA *birth without intervention* measure refers to spontaneous birth which starts and progresses spontaneously (i.e. without induction, augmentation with drugs, instrumental or caesarean birth), and without epidural/spinal/general anaesthesia or episiotomy.[238] • The NMPA *spontaneous vaginal birth* measure refers to all vaginal births without the use of instruments. This includes women who have their labour induced, who have augmentation (a 'drip' to increase contractions) or an episiotomy.[238]	Devane 2007[133] Smith 2014[216] Bunch 2018[242] NMPA 2018[238]
24	Place of birth		Devane 2007[133]
25	Anaesthesia with gastric reference (Mendelson's syndrome, etc.)	Mendelson's syndrome is a chemical pneumonitis due to aspiration of gastric content.[244]	Smith 2014[216]
26	• Use of pharmacological analgesia/anesthesia[133] • Analgesia[216]	• E.g., Entonox, epidural, pethidine.[133] • Request for/any type, epidural, narcotics, general anaesthesia, etc.[216]	Devane 2007[133] Smith 2014[216]
27	'Drugs' other than analgesics	Administration/ side effects, etc.	Smith 2014[216]
28	Postnatal administration of drugs		Herman 2021[191]
29	• Induction and/or labour augmentation (artificial rupture of membrane/ oxytocin)[216]	A process by which labour is started artificially, either by giving medications to soften the cervix and start	Smith 2014[216] NMPA 2018[238]

	• Induction of labour[238]	contractions, by a doctor or midwife breaking the waters, or both.[238]	
30	Oxytocin augmentation of labour	Drug used to assist progress of labour.	Devane 2007[133]
31	Number (count) of pregnancy complications		Cao 2020[222]
32	Adverse event / outcome, serious complication		Smith 2014[216]
33	Maternal near miss		Herman 2021[191]
34	Procedural or anaesthesia complication		Herman 2021[191]
35	Medication-related serious adverse events	Includes serious allergic reaction and any serious event as a result of medication for e.g., cardiac events, pulmonary embolism, and intensive care unit admission.	Herman 2021[191]
36	• Intrapartum haemorrhage[133] • Postpartum haemorrhage[133 191] • Haemorrhage[222 226] • Rate of postpartum haemorrhage of ≥1500 ml[242] • Bleeding / blood loss[216] • Obstetric haemorrhage[238]	• Excessive blood loss from the birth canal during labour. [133] • Excess blood loss from the birth canal after childbirth.[133] • Of any type and variously defined.[216] • Of women who give birth to a singleton baby between 37+0 and 42+6 weeks of gestation, the proportion who sustained an obstetric haemorrhage of 1500ml or more. Also reported obstetric haemorrhage of 500ml or more.[238]	Devane 2007[133] Smith 2014[216] Bunch 2018[242] NMPA 2018[238] Cao 2020[222] Liu 2020[226] Herman 2021[191]
37	• Infection[222] • Maternal infection[191 216] • Infectious morbidity[191]	Fever/temperature/sepsis, etc.[216]	Smith 2014[216] Cao 2020[222] Herman 2021[191]
38	Placenta	Retained, manual removal, etc.	Smith 2014[216]
39	Caesarean section wound infection		Devane 2007[133]
40	• Wound[216] • Wound complications[191]	Haematoma, wound healing, fistula of any type, etc.[216]	Smith 2014[216] Herman 2021[191]
41	• Ruptured uterus[133] • Uterine rupture of dehiscence[191]		Devane 2007[133] Herman 2021[191]
42	Uterine inversion		Herman 2021[191]

43	Uterine	Expulsive effort, hyperstimulation, rupture, etc.	Smith 2014[216]
44	• Laceration (cervical, vaginal, perineal) • Cervical laceration		Cao 2020[222] Herman 2021[191]
45	• Perineal/vaginal trauma[216] • Perineal trauma[191]	Of any type including episiotomy.	Smith 2014[216] Herman 2021[191]
46	Episiotomy		NMPA 2018[238]
47	Intact perineum		Smith 2014[216]
48	• Anal sphincter damage[133] • Third- and fourth-degree tear rate among women delivering vaginally[242] • Third and fourth degree tear[238]	"Third degree" (extending into the anal sphincter) and "fourth degree" (anal mucosa) tears. Of women who give birth vaginally to a singleton baby in the cephalic position between 37+0 and 42+6 weeks of gestation, the proportion who sustained a third or fourth degree tear.[238]	Devane 2007[133] Bunch 2018[242] NMPA 2018[238]
49	• Pulmonary embolism[133] • Thromboembolic event (deep vein thrombosis, pulmonary embolism)[216] • Venous thromboembolism[191] • Thromboembolism[44]	Also listed under severe maternal morbidity and end organ injury see Tables 5.6 and 5.7.	Devane 2007[133] Smith 2014[216] D'Arcy 2019[44] Herman 2021[191]
50	• Transfusion[134] • Blood transfusion[216]	• Any transfusion of red blood cells within the first 42 days postpartum[134] • Also listed under severe maternal morbidity and end organ injury see Tables 5.6 and 5.7	Smith 2014[216] Nijagal 2018[134]
51	Anaemia	Or any reference to Haemoglobin levels/iron administration.[216]	Smith 2014[216] Herman 2021[191]
52	• Smoking rate at delivery[242] • Smoking cessation in pregnancy[238]	Of those women who are recorded as being current smokers at their booking visit, the proportion who are no longer smokers by the time of birth.[238]	Bunch 2018[242] NMPA 2018[238]
53	Mobility during labour		Smith 2014[216]
54	Pregnancy prolongation		Smith 2014[216]
55	Labour length/duration	Length of any stage, prolonged labour, etc.	Smith 2014[216]
56	Comfort		Smith 2014[216]
57	Maternal perception of pain experienced	'Pain' of any type including assessment.[216]	Smith 2014[216]
58	Relaxation		Smith 2014[216]

59	Resuscitation measures, arrest, or loss of consciousness		Smith 2014[216]
60	Miscellaneous / other	Fetal-maternal haemorrhage, zavanelli procedure, pulmonary oedema, additional tests, cord prolapse, etc.	Smith 2014[216]
61	Blood pressure		Smith 2014[216]
62	• Surgical reference[216] • Additional operations[191]	Type of surgery, duration of surgery, etc. [216]	Smith 2014[216] Herman 2021[191]
63	Dilation and curettage for retained products of conception		Herman 2021[191]
64	Extension of uterine incision		Herman 2021[191]
65	Symphysiotomy		Smith 2014[216]
66	Hysterectomy	Also defined in severe maternal morbidity, see Table 5.6.	Herman 2021[191]
67	Respiratory morbidity	Also defined in severe maternal morbidity and end organ injury, see Tables 5.6 and 5.7.	Herman 2021[191]
68	Renal impairment	Also defined in severe maternal morbidity and end organ injury, see Tables 5.6 and 5.7.	Herman 2021[191]
69	Tissue injury (bladder and/or bowel injury)	Also defined in severe maternal morbidity, see Table 5.6.	Herman 2021[191]
70	• Coagulation abnormalities • Coagulopathy	Also defined in severe maternal morbidity and end organ injury, see Tables 5.6 and 5.7.	Herman 2021[191]
71	Hepatic complications	Also defined in end organ injury, see Table 5.7.	Herman 2021[191]
72	Cardiac complications	Also defined in severe maternal morbidity, see Table 5.6.	Herman 2021[191]
73	Bowel obstruction		Herman 2021[191]
74	Pulmonary oedema	Also defined in severe maternal morbidity and end organ injury, see Tables 5.6 and 5.7.	Herman 2021[191]
75	Abnormal maternal biomarkers		Herman 2021[191]
76	Severe maternal morbidity	See Tables 5.6 and 5.7.	Smith 2014[216] Hehir 2017[235] Admon 2018[47] Clapp 2018[233] Metcalfe 2018[236] Easter 2019[217] Sommerville 2019[220] Brown 2020[43] Field 2020[48]

			Leonard 2020[225] Main 2020[227] Ranjit 2020[228] Salahuddin 2020[229]
77	Non transfusion severe maternal morbidity	Severe maternal morbidity excluding deliveries that had an indicator of blood transfusion but no other severe maternal morbidity indicator.[43]	Brown 2020[43] Leonard 2020[225] Sutton 2020[230] Oberhardt 2021[231]
78	• End organ injury[64 221] • End organ damage[236]	See Table 5.7.	Bateman 2013[64] Metcalfe 2015[236] Aoyama 2017[63] Bliddal 2020[221]
	Postnatal and long-term (beyond birth episode)		
79	• Postnatal depression[133] • Postpartum depression[134]	Assessed via the Patient Health Questionnaire-2 with optional follow-up with the Edinburgh Postnatal Depression Scale.[134 245-247]	Devane 2007[133] Nijagal 2018[134]
80	Puerperal psychosis		Devane 2007[133]
	Maternal: Life impact / functioning		
81	Maternal fecal incontinence[133] Incontinence[134 216]	Tracked via either the International Consultation on Incontinence Questionnaire-Short Form or Wexner.[134] Any type.[216]	Devane 2007[133] Smith 2014[216] Nijagal 2018[134]
82	Pain with intercourse	Tracked via Patient Reported Outcomes Measurement Information System Sexual Function and Satisfaction (PROMIS SFFAC102 PR).	Nijagal 2018[134]
83	Health-related quality of life[132 134]	• From core outcome set for multimorbidity.[132] • Tracked via the Patient-Reported Outcomes Measurement Information System Global10.[134]	Nijagal 2018[134] Smith 2018[132]
84	Well-being[216]	Mother/father, psychological/emotional.[216]	Smith 2014[216]
85	• Mental health[132] • Maternal negative related expression[216]	• From core outcome set for multimorbidity[132] • Anxiety, dissatisfaction, fatigue, depression, low self-esteem, post-traumatic stress disorder, etc.[216]	Smith 2014[216] Smith 2018[132]

86	Treatment burden	From core outcome set for multimorbidity	Smith 2018[132]
87	Self-rated health	From core outcome set for multimorbidity	Smith 2018[132]
88	Self-management behaviour	From core outcome set for multimorbidity	Smith 2018[132]
89	Self-efficacy	From core outcome set for multimorbidity	Smith 2018[132]
90	Perceived/personal control		Smith 2014[216]
91	Adherence	From core outcome set for multimorbidity	Smith 2018[132]
92	Activities of daily living	From core outcome set for multimorbidity	Smith 2018[132]
93	Physical function	From core outcome set for multimorbidity	Smith 2018[132]
94	Physical activity	From core outcome set for multimorbidity	Smith 2018[132]
95	• Mother-infant attachment[134] • Positive relationship with infant/bonding[216] • Negative expression of mother–infant interaction (detachment, difficulty with infant, prolonged crying, etc.)[216]	Tracked via the Mother-Infant Bonding Scale.[134]	Smith 2014[216] Nijagal 2018[134]
96	• Confidence with role as a mother[134] • Maternal parenting confidence[216]	How confident will you feel when your baby is born/do you feel about looking after your baby? Not at all confident/Not very confident/Somewhat confident/ Confident/Very confident.[134]	Smith 2014[216] Nijagal 2018[134]
97	Care giver experience/satisfaction		Smith 2014[216]
98	Views (mother's and/or father's)		Smith 2014[216]
	Maternal: Resource use		
99	Health care use	From core outcome set for multimorbidity.[132]	Smith 2018[132]
100	Late maternal complication	Admission or re-admission within the first 42 days postpartum for childbirth related complications	Nijagal 2018[134]
101	High utilisation of perinatal acute care services	Three or more obstetric triage, emergency department or inpatient admissions during pregnancy.	Field 2020[48]
102	Unscheduled visit to the emergency department or clinic		Herman 2021[191]
103	• Hospitalisation[216] • Need for hospital admission[191]	Length of stay, admission, readmission, etc.[216]	Smith 2014[216] Herman 2021[191]
104	Emergency department visit	90 days following birth.	Field 2020[48]
105	• Readmission[48] • Maternal postnatal readmission to hospital[133]	• 90 days following birth.[48]	Devane 2007[133] NMPA 2018[238] Field 2020[48]

	• Unplanned maternal readmission[238]	• Of women giving birth to a singleton baby between 37+0 and 42+6 weeks of gestation, those who have an unplanned, overnight readmission to hospital within 42 days of giving birth, excluding those accompanying an unwell baby.[238]	
106	High dependency unit/postnatal stay		Herman 2021[191]
107	• Maternal intensive care unit (ICU) admission[64 191 216] • Mother requires admission to intensive care[133] • Maternal need for intensive care[134]	• During the delivery hospitalization through 30 days postpartum.[64] • Admission to an intensive care unit or a unit that provides 24-h medical supervision and is able to provide mechanical ventilation or continuous vasoactive drug support at any point during pregnancy through 42 days postpartum for pregnancy or childbirth related complications.[134]	Devane 2007[133] Bateman 2013[64] Smith 2014[216] Nijagal 2018[134] Herman 2021[191]
108	Need for hospital transfer	Health care utilisation.	Admon 2018[47]
109	• Hospital length of stay[47] • Maternal length of stay[134] • Extended length of stay for delivery[236]	• Health care utilisation.[47] • Number of consecutive days in the hospital from delivery to discharge.[134] • A length of stay ≥3 days following a vaginal delivery or ≥5 days following a caesarean delivery.[236]	Metcalfe 2015[236] Admon 2018[47] Nijagal 2018[134]
110	• Health care cost[47 132] • Health care expenditure during pregnancy[46] • Cost / economic outcomes[216]	• Delivery-associated hospital charges. Mean charges and cost per delivery hospitalisation.[47] • Health care expenditure for the entire pregnancy, prenatal and childbirth periods. The prenatal observation period for each patient was defined as date of admission for childbirth minus 300 days.[46] • From core outcome set for multimorbidity, so not limited to pregnancy period only.[132]	Smith 2014[216] Cunningham 2017[46] Admon 2018[47] Smith 2018[132]

111	Communication	Consultation related, from core outcome set for multimorbidity.	Smith 2018[132]
112	• Shared decision making[132] • Confidence as an active participant in healthcare decisions[134]	• Consultation related, from core outcome set for multimorbidity.[132] • Thinking about your care during your pregnancy/your labour and birth/the months after your baby was born, were you given information about your choices for maternity care? Were you given enough information to help you decide about your care? Were you given information at the right time to help you decide about your care? No/To some extent/Yes.[134]	Nijagal 2018[134] Smith 2018[132]
113	Prioritization	Consultation related, from core outcome set for multimorbidity.	Smith 2018[132]
114	• Quality health care (patient-rated)[132] • Maternal satisfaction (antenatal)[133] • Maternal satisfaction (intrapartum)[133] • Maternal satisfaction (postnatal)[133] • Satisfaction with the results of care[134] • Maternal satisfaction with care experience[216] • Confidence in healthcare providers[134]	• From core outcome set for multimorbidity.[132] • How satisfied are you with the results of your care during your pregnancy/your labour and birth/the months after your baby was born? Very unsatisfied/Unsatisfied/Neither satisfied nor dissatisfied/Satisfied/Very satisfied.[134] • Do you have confidence and trust in the staff caring for you? No/To some extent/Yes.[134]	Devane 2007[133] Smith 2014[216] Nijagal 2018[134] Smith 2018[132]
115	Birth experience	Assessed via The Birth Satisfaction Scale–- Revised.[134 248]	Nijagal 2018[134]
	OUTCOMES FOR CHILDREN		
	Children: Mortality / survival		
116	• Intrauterine fetal demise[222] • Fetal death[216]		Smith 2014[216] Cao 2020[222]
117	Stillbirth	• A fetal death in late pregnancy.[133]	Devane 2007[133] Smith 2014[216] Nijagal 2018[134]

		• Pregnancy loss at or after 28 + 0 weeks gestation of a birth weight of greater or equal to 1000 g.[134]	
118	• Neonatal death[133 134] • Neonatal loss[216]	• Death before the age of 28 completed days after live birth.[133] • Death of a live born neonate up to 28 days of life.[134]	Devane 2007[133] Smith 2014[216] Nijagal 2018[134]
119	Perinatal death		Herman 2021[191]
	Children: Physiological / clinical		
	Fetal		
120	• Intrauterine growth restriction[133 222] • Fetal growth restriction (FGR)[224] • Severe fetal growth restriction (SFGR)[224]	• Commonly used when the birthweight is at or below the 10th percentile for gestational age and sex.[133] • FGR: birthweight 10th percentile for gestational age[224] • SFGR: birthweight 5th percentile for gestational age[224]	Devane 2007[133] Cao 2020[222] Fresch 2020[224]
121	• Non-reassuring fetal heart tones[222] • Fetal heart rate changes necessitating delivery[191]		Cao 2020[222] Herman 2021[191]
122	Fetal heart rate monitoring		Smith 2014[216]
123	Fetal blood sampling	Umbilical cord blood, fetal blood sampling, lactate.	Smith 2014[216]
124	• Fetal position (malpresentation, change, etc.)[216] • Malpresentation[191 222]		Smith 2014[216] Cao 2020[222] Herman 2021[191]
125	Ultrasound sign		Herman 2021[191]
126	Abnormal doppler findings on ultrasound		Herman 2021[191]
	Neonatal (first 28 days)		
127	• Preterm delivery[44 47 222] • Preterm labour[133] • Spontaneous preterm birth[134] • Iatrogenic preterm birth[134] • Preterm[216] • Preterm birth[191]	• < 37 weeks[47] • Onset of labour before 37 completed weeks of pregnancy.[133] • Live birth at < 37 +0 weeks gestation occurring after spontaneous labour or rupture of membranes.[134]	Devane 2007[133] Smith 2014[216] Admon 2018[47] Nijagal 2018[134] D'Arcy 2019[44] Cao 2020[222] Herman 2021[191]

		• Caesarean or labour induction before < 37 weeks + 0 gestation excluding those occurring after spontaneous labour or rupture of membranes.[134] • Birth, retinopathy of prematurity, gestational age at birth.[216]	
128	Prematurity		Herman 2021[191]
129	• Apgar score[216] • Apgar score at 5 min[133 238] • Proportion of babies born at term with an Apgar score <7 at 5 minutes[242] • Low Apgar score[191]	• At 1, 5 or 10 minutes or <7 or 'low' at ≤5 minutes.[216] • Of liveborn, singleton babies born between 37+0 and 42+6 weeks of gestation, the proportion who are assigned an Apgar score of less than 7 at five minutes of age.[238]	Devane 2007[133] Smith 2014[216] Bunch 2018[242] NMPA 2018[238] Herman 2021[191]
130	Gestational age at birth[133]		Devane 2007[133]
131	• Infant birthweight[133] • Birthweight[216] • Birth weight abnormalities (including small and large for gestational age)[191]		Devane 2007[133] Smith 2014[216] Herman 2021[191]
132	Small for gestational age[238]	Term babies with a birth weight below the 10th centile, and below the 2nd centile using United Kingdom 1990 charts.[238]	NMPA 2018[238]
133	Low birth weight		D'Arcy 2019[44]
134	Large for gestational age		Cao 2020[222]
135	• Meconium[222] • Meconium aspiration[133] • Meconium-stained liquor / meconium aspiration syndrome[216]	The newborn inhales a mixture of meconium and amniotic fluid, either in the uterus or just after delivery.[133]	Devane 2007[133] Smith 2014[216] Cao 2020[222]
136	• Neonatal resuscitation required[133] • Resuscitation measures, arrest, or loss of consciousness[216]		Devane 2007[133] Smith 2014[216]
137	Oxygen dependence	Administration of oxygen by any route for greater than 24 hours at any point during the first 28 days of life.	Nijagal 2018[134]
138	Neonatal respiratory morbidity		Herman 2021[191]

139	• Birth asphyxia[133] • Asphyxia or acidaemia[191]	Occurs when a baby does not receive enough oxygen before, during, or just after birth.[133]	Devane 2007[133] Herman 2021[191]
140	Any pH levels <7.20 and BD >12.0		Smith 2014[216]
141	Hypoxic ischemic encephalopathy	A condition of injury to the brain.[133]	Devane 2007[133] Herman 2021[191]
142	Babies with encephalopathy[238]	The proportion of singleton babies born at 35+0 to 42+6 weeks of gestation with encephalopathy in the first 72 hours of life, defined as showing two or more of the following neurological signs in the same day within the first 72 hours of life: - abnormal tone - reduced consciousness (lethargic or comatose) - convulsions (seizures).[238]	NMPA 2018[238]
143	Intraventricular haemorrhage		Herman 2021[191]
144	Periventricular leukomalacia		Herman 2021[191]
145	Retinopathy of prematurity		Herman 2021[191]
146	• Neonatal fitting/seizures[133] • Seizures[191]		Devane 2007[133] Herman 2021[191]
147	Congenital anomaly	Chromosomal, genetic, and/or structural.[133]	Devane 2007[133] Herman 2021[191]
148	Patent ductus arteriosus		Herman 2021[191]
149	• Neonatal infection[133 216] • Neonatal sepsis[191] • Infectious morbidity[191]	Fever/sepsis including specific types of infections.[216]	Devane 2007[133] Smith 2014[216] Herman 2021[191]
150	Shoulder dystocia		Devane 2007[133]
151	• Jaundice[216] • Hyperbilirubinaemia[191]		Smith 2014[216] Herman 2021[191]
152	Transition to extra-uterine life		Smith 2014[216]
153	Necrotizing enterocolitis / bowel perforation		Herman 2021[191]
154	• Infant requiring intubation[133] • Intubation /ventilation[191] • Babies receiving mechanical ventilation[238]	Mechanical ventilation refers to invasive ventilation with an endotracheal tube and ventilator. Therefore, babies requiring non-invasive breathing support, such as continuous positive airway pressure, are not included in this measure. The time frame for this measure is limited to	Devane 2007[133] NMPA 2018[238] Herman 2021[191]

		the first 72 hours of life in order to reflect morbidity that is more likely to be attributed to events around the time of birth. Of liveborn, singleton babies born between 37+0 and 42+6 weeks of gestation, the proportion who receive mechanical ventilation in the first 72 hours of life.[238]	
155	Hypoglycaemia		Herman 2021[191]
156	Fetal or neonatal anaemia		Herman 2021[191]
157	Inotropic support / hypotension		Herman 2021[191]
158	• Birth injury to infant[133] • Birth injury[134] • Neonatal birth trauma[191] • Labour and/or birth trauma[216]	Subdural and cerebral haemorrhage, massive epicranial subaponeurotic haemorrhage, other injuries to skeleton due to birth trauma, injury to spine and spinal cord due to birth trauma, injury to brachial plexus due to birth trauma, other cranial and peripheral nerve injuries due to birth trauma in single live-born neonates.[134]	Devane 2007[133] Smith 2014[216] Nijagal 2018[134] Herman 2021[191]
159	Peripheral nerve injury (at discharge from hospital)		Herman 2021[191]
160	Basal skull fracture		Herman 2021[191]
161	Spinal cord injury		Herman 2021[191]
162	Hypothermia		Herman 2021[191]
163	Decreased response to pain		Herman 2021[191]
164	Stupor		Herman 2021[191]
165	Clinically significant genital injury		Herman 2021[191]
166	Hypotonia		Herman 2021[191]
167	Coma		Herman 2021[191]
168	Tube feeding		Herman 2021[191]
169	Loss to follow-up		Herman 2021[191]
170	Ischemic injury		Herman 2021[191]
171	Amniotic band syndrome		Herman 2021[191]
172	Twin anaemia-polycythaemia sequence		Herman 2021[191]
173	Twin-to-twin transfusion syndrome reoccurrence		Herman 2021[191]
174	Systemic inflammatory response syndrome		Herman 2021[191]
175	Allergic reaction		Herman 2021[191]

176	Postnatal administration of drugs		Herman 2021[191]
177	Composite of infant morbidity outcomes	Short-/long-term; including any disability, hypoxic ischemic encephalopathy, asphyxia, seizures, respiratory distress syndrome, Periventricular leukomalacia, cerebral palsy, etc.	Smith 2014[216]
178	Skin to skin contact[238]	Of liveborn babies born between 34+0 and 42+6 weeks of gestation, the proportion who received skin to skin contact within one hour of birth.[238]	NMPA 2018[238]
	Infant (first 1 year)		
179	• Method of infant feeding[133] • Breastfeeding at discharge[133] • Breastfeeding initiation rate[242] • Breastfeeding rate at 6–8 weeks[242] • Breastfeeding at 3 months[133] • Success with breastfeeding[134] • Confidence with breastfeeding[134] • Breastfeeding[216] • Negative expression of breastfeeding (failure, not established, etc.)[216] • Babies receiving breast milk[238]	• (Success) Please indicate how you are feeding your baby. My baby has received only breast milk in the past 7 days. This may include breast milk in a bottle/My baby has received a combination of breast milk, formula, or water in the past 7 days/My baby has received only formula, water, or other liquids but not breast milk in the past 7 days.[134] • (Confidence) How confident do you feel about breastfeeding? Not at all confident/Not very confident/ Somewhat confident/Confident/Very confident. Option to track via the Breastfeeding Self-Efficacy Scale – Short Form.[134] • E.g., initiation, duration, success[216] • Of liveborn babies born between 34+0 and 42+6 weeks of gestation, the proportion who received any breast milk for their first feed, and the proportion receiving any breast milk at the time of discharge from the maternity unit.[238]	Devane 2007[133] Smith 2014[216] Bunch 2018[242] Nijagal 2018[134] NMPA 2018[238]
	Longer term (prepubertal 2-11 years old, pubertal 12-18 years old, adulthood)		
180	Abnormal neurodevelopmental outcome at age 2 years		Herman 2021[191]

181	Severe cerebral palsy at 2 years corrected age for prematurity		Herman 2021[191]
	Children: Resource use		
182	• Admission to newborn critical care unit[48] • Neonatal admission to special care and/or intensive care unit[133] • Neonatal admission to NICU/SCBU[216] • Neonatal intensive care unit admission[191] • Proportion of babies born at term admitted to the neonatal intensive care unit[242] • Babies admitted to a neonatal unit[238]	**NMPA**[238] Term: of liveborn, singleton babies born between 37+0 and 42+6 weeks of gestation, the proportion who are admitted to a neonatal unit. Late preterm: of liveborn, singleton babies born between 34+0 and 36+6 weeks of gestation, the proportion who are admitted to a neonatal unit.	Devane 2007[133] Smith 2014[216] Bunch 2018[242] NMPA 2018[238] Field 2020[48] Herman 2021[191]
183	Neonate length of stay	Number of consecutive days in hospital from birth through 28 days of life.	Nijagal 2018[134]
184	• Neonatal readmission to hospital[133] • Proportion of babies readmitted to hospital at <30 days of age[242]		Devane 2007[133] Bunch 2018[242]
185	Transfer to long-term care facility		Herman 2021[191]

HELLP: haemolysis, elevated liver enzyme and low platelets; FGR: fetal growth restriction; PROMIS SFFAC102 PR: Patient Reported Outcomes Measurement Information System Sexual Function and Satisfaction; NICU: neonatal intensive care unit; NMPA: National Maternal and Perinatal Audit; SCBU: special care baby unit; SFGR: severe fetal growth restriction; VBAC: vaginal birth after previous caesarean secti

Table 5.6: Severe maternal morbidity

No	List of morbidities under severe maternal morbidity	Definition of severe maternal morbidity	Paper that the severe maternal morbidity was extracted from
1	1. Haemorrhage 2. Hypertension / neurologic 3. Renal 4. Sepsis 5. Pulmonary 6. Cardiac 7. Intensive care unit/invasive monitoring 8. Surgical/bladder/bowel complications 9. Anaesthesia complications	Based on the American College of Obstetrician Gynaecologists and Society for Maternal-Fetal Medicine consensus definition. These guidelines define SMM as **unintended outcomes** of the process of labour and delivery that **result in significant short-term or long-term consequences** to a woman's health. The consensus statement specifically avoids providing a comprehensive list of outcomes to define SMM but propose potential scenarios that constitute this outcome and classify SMM into 9 different causes.[217]	Easter 2019[217]
2	1. Acute myocardial infarction 2. Acute renal failure 3. Adult respiratory distress syndrome 4. Amniotic fluid embolism 5. Aneurysm 6. Blood transfusion[236] 7. Cardiac arrest/ventricular fibrillation 8. Disseminated intravascular coagulation 9. Eclampsia 10. Heart failure during procedure or surgery 11. Internal injuries of thorax, abdomen, and pelvis 12. Intracranial injuries 13. Puerperal cerebrovascular disorders 14. Pulmonary oedema / acute heart failure 15. Severe anaesthesia complications 16. Sepsis 17. Shock 18. Sickle cell anaemia with crisis	Lifesaving procedures or life-threatening events from delivery hospitalization administrative data.[220]	Metcalfe 2018[234] Sommerville 2019[220]

	19. Thrombotic embolism[220] / air and thrombotic embolsim[234] 20. Cardiac monitoring 21. Conversion of cardiac rhythm 22. Hysterectomy 23. Operations of the heart and pericardium 24. Temporary tracheostomy 25. Ventilation		
3	**Diagnosis-based indicators** 1. Acute myocardial infarction 2. Aneurysm 3. Acute Renal Failure 4. Adult respiratory distress syndrome 5. Amniotic fluid embolism 6. Cardiac arrest or ventricular fibrillation 7. Disseminated intravascular coagulation 8. Eclampsia 9. Heart failure or arrest during surgery or procedure 10. Puerperal cerebrovascular disorders 11. Pulmonary oedema or Acute heart failure 12. Severe anaesthesia complications 13. Sepsis 14. Shock 15. Sickle cell disease with crisis 16. Air and thrombotic embolism **Procedure-based indicators** 17. Conversion of cardiac rhythm 18. Blood products transfusion 19. Hysterectomy 20. Temporary tracheostomy 21. Ventilation	Identified using the Centres for Disease Control and Prevention (CDC) SMM indicator list.[43 225] SMM defined as 1) had at least one of the five procedure-based indicators or 2) had at least one of the 16 diagnosis-based indicators and additionally had: a) in hospital death, b) a caesarean delivery with a length of stay 5 days or longer, or c) a vaginal delivery with a length of stay 3 days or longer.[43] The Alliance for Innovation on Maternal Health classification scheme was followed for defining SMM, where delivery hospitalizations with any of the 21 conditions were defined as delivery hospitalizations with SMM.[229] Combined with severe maternal morbidity as "severe maternal morbidity and mortality".[47]	Admon 2018[47] Brown 2020[43] Field 2020[48] Leonard 2020[225] Main 2020[227] Salahuddin 2020[229]

CDC: Centres for Disease Control and Prevention; SMM: Severe maternal morbidity

Table 5.7: End organ injury

No	List of end organ injury	Definition	Paper that the end organ injury was extracted from
1	1. Acute Heart Failure 2. Acute Liver Disease 3. Acute Myocardial Infarction 4. Acute Renal Failure 5. Acute Respiratory Distress Syndrome/Respiratory Failure 6. Coma 7. Delirium 8. Disseminated Intravascular Coagulation/Coagulopathy 9. Puerperal Cerebrovascular Disorders 10. Pulmonary Oedema 11. Pulmonary Embolism 12. Sepsis 13. Shock 14. Status Asthmaticus 15. Status Epilepticus	End organ injury from the start of delivery admission to the hospital through 30 days postpartum, from Bateman 2013.[64 221] Outcome was named as "Severe Maternal Morbidity" in the study.[233 235] The presence of any 1 of 15 diagnoses representative of acute organ injury and critical illness.[235] Combined with death as a composite outcome of maternal end organ injury or death, during the delivery admission through 30 days postpartum.[64]	Bateman 2013[64] Metcalfe 2015[236] Hehir 2017[235] Clapp 2018[233] Bliddal 2020[221]

Chapter end summary

This chapter compiled an initial list of research outcomes relevant to studies of pregnant women with multimorbidity that will inform the Delphi survey in Chapter 7. As discussed in Chapter 2, outcomes reported in the literature may be more reflective of researcher's priorities. Therefore, the next chapter will use qualitative methods to explore what outcomes are important to service users and service providers.

Chapter 6: Focus groups for core outcome set development

Chapter overview

This chapter followed the second of four steps and the sampling matrix outlined in Chapter 4 to develop a core outcome set. Using qualitative methods, it addressed *Objective 5:* to explore outcomes that are important to women with multimorbidity who have been pregnant or planning to be pregnant, their partners and health care professionals. The manuscript that has been accepted for publication is presented as follows.

Manuscript accepted for publication in BMC Pregnancy and Childbirth

Personal contribution

- Study design working with the study team and the patient and public involvement (PPI) advisory group
- Applied for ethical approval
- Prepared study documents
- Liaised with charities and organisations for recruitment
- Organised and conducted the focus group
- Transcribed the audio recording
- Analysed the focus group transcript with a second reviewer and involved PPI members in the interpretation of the themes
- Drafted the manuscript

Title: Key outcomes for reporting in studies of pregnant women with multiple long-term conditions: a qualitative study

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6.1 Abstract

Background: Maternal multiple long-term conditions are associated with adverse outcomes for mother and child. We conducted a qualitative study to inform a core outcome set for studies of pregnant women with multiple long-term conditions.

Methods: Women with two or more pre-existing long-term physical or mental health conditions, who had been pregnant in the last five years or planning a pregnancy, their partners and health care professionals were eligible. Recruitment was through social media, patients and health care professionals' organisations and personal contacts. Participants who contacted the study team were purposively sampled for maximum variation.

Three virtual focus groups were conducted from December 2021 to March 2022 in the United Kingdom: (i) health care professionals (n=8), (ii) women with multiple long-term conditions (n=6), and (iii) women with multiple long-term conditions (n=6) and partners (n=2). There was representation from women with 20 different physical health conditions and four mental health conditions; health care professionals from obstetrics, obstetric/maternal medicine, midwifery, neonatology, perinatal psychiatry, and general practice. Participants were asked what outcomes should be reported in all studies of pregnant women with multiple long-term conditions. Inductive thematic analysis was conducted. Outcomes identified in the focus groups were mapped to those identified in a systematic literature search in the core outcome set development.

Results: The focus groups identified 63 outcomes, including maternal (n=43), children's (n=16) and health care utilisation (n=4) outcomes. Twenty-eight outcomes were new when mapped to the systematic literature search.

Outcomes considered important were generally similar across stakeholder groups. Women emphasised outcomes related to care processes, such as information sharing when transitioning between health care teams and stages of pregnancy (continuity of care). Both women and partners wanted to be involved in care decisions and to feel informed of the risks to the pregnancy and baby. Health care professionals additionally prioritised non-physiological outcomes, including quality of life and financial implications for the women; and longer-term outcomes, such as children's developmental outcomes.

Conclusion: The findings will inform the design of a core outcome set. Participants' experiences provided useful insights of how maternity care for pregnant women with multiple long-term conditions can be improved.

6.2 Background

Women with long-term conditions are at higher risk of adverse pregnancy outcomes.[34 74] Pregnancy can also impact on women's underlying long-term conditions. [71] These challenges are likely to be multiplied in women who have two or more long-term conditions, also known as multimorbidity or multiple long-term conditions.[1] They may have to take multiple medications[249] or attend appointments with different health care teams to manage their multiple long-term conditions.[118] Recent studies suggest that maternal multiple long-term conditions are associated with higher risk of adverse outcomes such as preterm birth.[44 47] This is significant as one in five pregnant women has multiple long-term conditions in the United Kingdom (UK).[172] Current health care systems and guidelines are configured for single health conditions.[115] Therefore maternal multiple long-term conditions present a unique challenge to pregnancy and is a priority for maternity research.[178]

An outcome is a measurement or observation used to assess the effect of an intervention or an exposure (in this case maternal multiple long-term conditions) to the health and well-being of the population of interest.[119 142]The MuM-PreDiCT consortium is developing a core outcome set for studies of pregnant women with multiple long-term conditions.[211] This minimum set of outcomes is recommended to be reported in all studies in this field to enable comparison between studies and combining of information in systematic reviews and meta-analyses.[180] To ensure its relevance, the core outcome set is being developed with multiple stakeholders, including pregnant women with multiple long-term conditions and health care professionals.

The study protocol for the core outcome set has been reported elsewhere,[211] but briefly it involves a four stage process: systematic literature search and focus groups to generate an initial list of outcomes, followed by prioritisation through Delphi surveys and a consensus setting meeting.[211]

Systematic reviews of outcomes reported in previous literature may not represent the views of key stakeholders, especially service users.[142] Our systematic literature search did not identify qualitative studies of pregnant women with multiple long-term conditions. The Core Outcome Measures for Effectiveness Trials (COMET) Handbook recommends supplementing the initial list of outcomes with qualitative studies involving key stakeholders.[142] The words participants used to describe their views and experiences can subsequently be used to label and explain outcome items in the Delphi surveys.[142 143]

This focus group study aims to explore outcomes that women, partners, and health care professionals feel should be reported in all studies of pregnant women with multiple long-term conditions. The findings will inform the design of a Delphi survey for a core outcome set for studies or pregnant women with multiple long-term conditions.

6.3 Methods

Study design

Interviews and focus groups have been used as qualitative methods to inform core outcome sets.[143] As the experience and outcomes of pregnancy may vary depending on the women's unique combination of health conditions, we chose to conduct focus groups for synergistic discussions.[143]

Inclusivity statement

Where the words 'women', 'maternal', or 'mother' are used, these also include people who do not identify as women but have been pregnant, planning to be pregnant or have given birth.

Inclusion criteria

Participants were eligible for the focus groups if they were women with two or more pre-existing long-term physical or mental health conditions, who have been pregnant in the last 5 years or are planning a pregnancy; their partners; and health care professionals who look after pregnant women with multiple long-term conditions and their children. Participants had to be able to converse in English and based in the UK.

Recruitment

We planned to conduct three focus groups, one for health care professionals, one for women, and one for women with or without their partners. After discussion with our patient and public involvement (PPI) advisory group, we aimed to recruit eight participants per focus group to facilitate optimal discussion and to account for dropouts. The PPI advisory group also recommended inviting partners to attend alongside their pregnant partner, instead of a focus group for partners only. This would help focus the discussion on outcomes relevant to studies of pregnant women with multiple long-term conditions.

Recruitment and sampling was guided by a sampling matrix prespecified in the core outcome set protocol, based on physical or mental health conditions, ethnicity, under-served populations and specialties of health care professionals.[211] We additionally aimed for representation from all four devolved nations in the United Kingdom and partners.

Study adverts were shared through social media platforms (Facebook, Twitter, Instagram, and websites) of charities and organisations for patients, pregnancy, mothers, and health care professionals, and with personal contacts of the multidisciplinary research team. The recruitment campaign took place in October 2021 for health care professionals and January 2022 for women and partners, and lasted for two to three months. Potential participants contacted the research team directly and were provided with the participant information sheets. They completed a sampling questionnaire which iteratively informed the recruitment strategy. We then undertook maximum variation purposive sampling from the pool of eligible potential participants.[143]

Data collection

The initial topic guide was developed based on the study aim and previous qualitative studies for core outcome set development in obstetrics.[143 196 250] This was then reviewed by and pilot tested (test run of a group discussion) with our PPI advisory group. The discussion in the pilot test focused on maternity care experiences and proposed solution. In order to efficiently draw out discussions on outcomes, the PPI advisory group advised that the topic guide was simplified to an open question of what outcomes are important to stakeholders, and included a case vignette to illustrate what is an outcome. The topic guide was then revised based on their feedback (Supplementary Material 6.1).

Three focus groups were conducted from December 2021 to March 2022, one for each of the following groups:

(1) health care professionals,

(2) women with multiple long-term conditions, and

(3) women with multiple long-term conditions with or without their partners.

Due to difficulties with face-to-face meetings during the COVID-19 pandemic, the focus groups were conducted virtually using Zoom and audio recorded.

The lead facilitator (SIL) is a female doctoral student, public health specialist trainee and qualified as a general practitioner. She has previously undertaken qualitative data analysis and training in qualitative research. The supporting team included researchers with expertise in qualitative research in health service, public health, and maternity.

The health care professionals' focus group was planned for one hour to increase participation rate, based on feedback from potential participants. There were two facilitators: one led the

discussion whilst one monitored the chat function. To build rapport with the participants, the lead facilitator shared her clinical background.

The two women and partners' focus groups each lasted two hours. There were three facilitators, the additional clinical facilitator was designated to provide support should participants become distressed. Women and partners were emailed with a £25 e-voucher each for reimbursement. The lead facilitator shared her medical history (long-term condition) and characteristics of under-served populations (physical disability and ethnic minority) with the participants. To encourage participants to speak freely, the facilitators did not share their clinical background. After each focus group, the facilitators debriefed and reflected on their initial impressions.

Analysis

Thematic analysis was conducted with an inductive approach.[251] The analysis focused on research outcomes discussed or inferred by participants. The stages of pregnancy were used as a prompt to facilitate the focus group discussions. Therefore, we pre-specified that themes (outcomes) will be provisionally categorised by the different stages of pregnancy (before, during and after pregnancy) and by maternal and children's outcomes.

The audio recordings of the focus groups were transcribed verbatim by SIL. This allowed for familiarisation with the data. Two researchers coded the transcripts independently, the initial codes were collated into potential themes using nVivo 12 and Microsoft Word. The codes and themes / outcomes were then compared and discussed. Themes identified from the focus groups of health care professionals and women/partners were compared and contrasted in tabular form.

Further checking was conducted by a multidisciplinary team, including MB (obstetrician), ZV (midwife) and RP (woman's representative) who read the transcripts and reviewed the developed themes. The key themes with extracted quotes were presented to our PPI advisory

group, with their opinions sought on key queries, especially on the labelling of themes. This approach helped maintain researcher reflexivity[252] and enriched the analysis. The outcomes identified in the focus groups were then compared with the list of outcomes identified in a systematic literature search.

Patient and public involvement

The PPI advisory group advised on the study design and recruitment strategy, design of the recruitment materials (e.g., participant information sheets and study poster) and shared the study advert through their networks. They pilot tested the topic guide and was involved in interpreting the data analysis. A PPI co-investigator (RP) reviewed the anonymised transcripts against the key themes identified. The final manuscript was reviewed by PPI co-investigators (RP and NM).

6.4 Results

Characteristics of study participants

Supplementary Material 6.2 presents the participant flow chart. Nineteen health care professionals expressed interest and were eligible, 10 were available on the scheduled focus group date and were invited to participate. Three health care professionals who expressed interest thereafter were kept on the waiting list and all were eventually invited to participate as five original participants could not attend. Twenty-five women expressed interest and were available on the focus group dates, 18 were invited to participate based on the sampling frame, subsequently six could not attend. Overall, eight health care professionals, 12 women and two partners participated in one of the three focus groups. Table 6.1 presents the characteristics of study participants for each focus group. There was representation from health care

professionals from obstetrics, obstetric/maternal medicine, midwifery, neonatology, perinatal psychiatry, and general practice; and women with 20 different physical health conditions and four mental health conditions.

Thematic categories

Table 6.2 presents the coding tree consisting of thematic categories, themes / outcomes, and subthemes. Five thematic categories were identified: (i) Care Outcomes, (ii) Clinical Outcomes, (iii) Role as mothers or parents, (iv) Other outcomes, and (v) Consideration for future studies. An overview of the thematic categories is presented here with selected quotes, with supplementary quotes in Supplementary Material 6.3.

(i) Care outcomes

Participants highlighted stages of pregnancy where input from health and social care professionals were important. Preconception counselling was important to plan whether women have to change or stop medications they take for their long-term conditions. Women and health care professionals felt that postnatal support should be longer than the conventional six weeks given the complexity of women's multiple long-term conditions. Women may need support looking after their newborn baby, whilst managing their multiple long-term conditions that may have been adversely impacted by the pregnancy. Key care outcomes were whether the relevant components of care were provided and of good quality.

Specific components of care were discussed at length. Examples relevant to women with multiple long-term conditions included: multidisciplinary coordination of care, holistic care, and continuity of care. Health care professionals said that women want to know whether they or their baby will need to have more appointments or tests than routine care. Women described the burden of having to attend multiple appointments with different specialties and want more

coordinated care. Continuity of care included transfer of information as women and their baby transitioned through different teams (e.g., specialist team to general team) and different stages of pregnancy. They valued seeing the same health care professionals throughout pregnancy:

> *"I had a fantastic consultant…he was there throughout ...an advocate who knew all my health conditions, he led on one of them, but he knew the others and linked up with my other doctors." (FG2, women [W]4)*

Feeling informed of their care and conditions was an outcome that was frequently discussed. Women and partners valued honest communication of potential risk to their pregnancy and baby. They want to be informed of: what is happening during birth, the side effects of medication in pregnancy, actions they can take for self-care, and support or services available for their specific needs. Being sufficiently informed was crucial in helping them mentally prepare to face adverse outcomes.

> *"…I needed to prepare myself, psychologically for the possibility that the baby might not be able to stay with me [after birth]…having that information before…made it easier for me to manage ..." (FG3, W4)*

Women shared accounts of when they experienced discrimination due to health care professional's attitudes, to illustrate respectful care as an important outcome.

> *"…they said…how are you going to manage to look after your child…because disabled women are seen as…not basically being suitable for having children that we just get completely bypassed." (FG2, W2)*

Having maternity services that were accessible was an important structural measure of care. One participant shared experiences of encountering physical (e.g., lack of wheelchair access),

social (e.g., domestic violence) and communication barriers (e.g., lack of sign language interpreters).

Health care professionals and women spoke about women's desire to have minimal intervention during pregnancy and to their baby. However, the care needs arising from pregnant women's multiple long-term conditions may limit their birthing and care options. Women described the devastation of being separated from their newborn who required additional support after birth. These are outcomes that health care professionals would like to see being studied so they can counsel women. Despite the limitations of options, feeling involved in their care decision is an important outcome, as one participant shared her experience when this did not happen:

> *"…the consultant…goes, we just had a meeting and we decided that you cannot have a [type of birth]…I go…all…of you should be in here now, because you made decisions without me." (FG2, W1)*

Women spoke about the importance of measuring their experience of care, throughout the pregnancy and specifically during birth, and whether there were any birth injuries. Despite being involved in their birth plans, non-adherence by the care team can lead to women having negative birth experience. One disabled participant spoke about how difficult births may not relate to the obstetric factors but stemmed from the women not being listened to.

> *"…the main outcomes that need to be looked at are satisfaction with experience…birth satisfaction…I know a lot of people who've been through some very difficult births, and it's not related to the difficulties. It's related to…not being listened to, not being allowed adequate pain relief…not having their physical or mental health concerns taken into account." (FG2, W2)*

(ii) Clinical outcomes

Participants spoke about clinical outcomes such as maternal death, stillbirth, infant mortality, and preterm birth. Clinical outcomes that were specific to pregnant women with multiple long-term conditions included the impact of pregnancy on the women's long-term conditions (e.g., improvement in or worsening pain in inflammatory arthritis), the development of new health conditions (e.g., type 2 diabetes), and whether children inherited their mothers' long-term conditions.

One area of particular interest was the impact of medication in pregnancy. Availability of information on medication safety in pregnancy was important to women. Health care professionals felt it was important to measure the extent of non-adherence to medications as some women may stop their regular medications when pregnant or breastfeeding because of concerns about how the medications may affect their baby. Women struggled to articulate specific outcomes they were concerned about, but mentioned miscarriage, birth defects and baby's condition at birth. Health care professionals emphasised the importance of balanced discussion with women:

> *"…it's helpful to know the effects of…untreated…disease on the outcomes of the children so that you can weigh up the benefits and the risks of taking medication..." (FG1, health care professionals [HCP]1)*

Perinatal mental illness, emotional and mental wellbeing, and satisfaction with perinatal mental health support were identified as important outcomes. Health care professionals and women discussed how mental and physical health conditions are interlinked and can influence each other. They spoke about the emotional stress that women experienced long after the birthing event and hence the importance of receiving good perinatal mental health support. One participant highlighted that mental illness is a taboo in some ethnic minority groups, which

may impede access to diagnoses and support. Women shared their experience of not having satisfactory perinatal mental health support:

> *"I've had serious and complicated mental health issues, since our…[child] was born and I still have never been referred to community psychiatry. I got a very reluctant acceptance through [the] perinatal mental health [team]…" (FG3, W2)*

(iii) Role as mothers or parents

Both health care professionals and women participants spoke about the pressure women felt to be the perfect mother and to breastfeed. Where there were adverse child outcomes, health care professionals and women participants spoke of the guilt some pregnant women experienced, as they attributed the adverse child outcomes to their own long-term conditions or the medications they have to take. Women spoke about how circumstances around birth may disrupt parent (including the father) and infant bonding. Health care professionals discussed that mother and infant bonding and the ability to engage with parental roles could be outcomes to measure when evaluating an intervention. For example, in perinatal psychiatry:

> "*destabilization of [the women's] mental health [can lead to] potential disruption to mum, to baby, to the bond…[disruption to] establishing feeding…" (FG1, HCP8).*

(iv) **Other outcomes**

One of the key themes in this category was how the pregnancies of women with multiple long-term conditions impacted on their partner. Women described the carer role that their partner take on, to help them with their activities of daily living or managing their long-term conditions. Partners want to be informed of actions they can take to look after mother and baby. Women spoke of the emotional stress their partner experienced during the childbirth process, as they

were fearful of what might happen to the women. Partners shared contrasting experience of their involvement in the care of the pregnant women.

> *"…We're just the people who drive them there… we're constantly left where we may have to pick up the pieces of whatever has happened…I've just been ignored by doctors." (FG3, Partner [P]1)*

> *"…the nurses were keeping me well assured about what was going on…Even though you were freaking out… you're always well informed…" (FG3, P2)*

Consequently, whether partners felt they were involved and supported, in addition to their emotional and mental wellbeing were identified as important outcomes.

(v) Considerations for future studies

Health care professionals raised some considerations for future studies of pregnant women with multiple long-term conditions. This included assessing how outcomes may differ by ethnicity.

One health care professional spoke about framing outcomes in a positive way:

> *"…the impacts that we're considering for multiple morbidities are always negative…I wonder if we could have positive impacts. Having had a baby, people feel so much happier and better. They didn't think it was going to go well, but actually it did…" (FG1, HCP3)*

Health care professionals discussed that maternal and children's outcomes will vary greatly, depending on the women's long-term conditions. Sometimes women's outcome expectations may not be achievable. Therefore, core outcomes for studies of pregnant women with multiple long-term conditions should reflect experiences and not just binary outcomes:

"…I may recommend you not to get pregnant, because your risk…is so high, you may choose to get pregnant, but the satisfaction should be… you felt supported… whether your expectation has been met or not." (FG1, HCP4)

Outcomes by stakeholder groups

Table 6.3 tabulates the 63 outcomes by stakeholder groups. These were presented by maternal (43 outcomes) and children's outcomes (16 outcomes), health care utilisation (4 outcomes) and by the stages of pregnancy.

Comparison with outcomes reported in the literature

For the core outcome set development, our systematic literature search included two core outcome sets for maternity care, pregnancy and childbirth,[133 134] one core outcome set for multiple long-term conditions[132] and 26 studies of pregnant women with multiple long-term conditions,[43 44 46-48 63 64 173 217 219-231 233-236] which reported 185 outcomes. When mapped to these outcomes reported in the literature, this focus group study identified an additional 28 outcomes (Table 6.4).

6.5 Discussion

Main findings

We explored research outcomes that are important to women with multiple long-term conditions who have been pregnant or who are planning a pregnancy, partners, and health care professionals. In comparison to outcomes identified from a systematic literature search, our focus groups identified an additional 28 outcomes. Outcomes considered important were generally similar across stakeholder groups. Women emphasised on outcomes related to care

processes and wanted to feel informed of the risks to their pregnancy, their health conditions, and their baby. Partners said it was important to be informed of risks to the pregnant women and what they can do to look after mother and baby, and to feel involved in their care. Health care professionals additionally prioritised non-physiological outcomes, such as quality of life and financial implications for the women; and longer-term outcomes, especially for children, such as developmental outcomes.

Comparison with the literature

Medication in pregnancy

Medication in pregnancy may be a particular challenge for pregnant women with multiple long-term conditions as they may have to take many different medications.[253] In the focus groups, women specifically wanted information on medication safety in pregnancy and were concerned about the general risks on their babies. This is consistent with findings from studies of pregnant women with single long-term conditions.[254-259] However, within the focus groups, it was difficult to elicit specific outcomes that women were worried about for their children in relation to medication use. Other qualitative studies about medication in pregnancy have reported that women are concerned specifically about the effect of medication on fetal development, congenital anomalies and developmental disability.[256 258-260] Our health care professional participants expressed concerns about attributing observed adverse outcomes to fetal exposures in utero; or to suboptimal management of maternal health conditions.

Aspects of care

Previous literature on single long-term conditions in pregnant women reveal several aspects of care that were also important to our participants. Women with inflammatory arthritis spoke

about needing to time their conception and to adjust their medications,[256] highlighting the importance of preconception planning.

Earlier work on women with long-term conditions described their feeling of abandonment by health care professionals after giving birth.[118] They felt that their long-term conditions affected their ability to look after their babies.[256-258] The need for longer postnatal support was discussed both by women and health care professionals.

Studies suggest that women with long-term conditions may be more likely to develop perinatal mental illness.[43 261] Here, health care professionals discussed the importance of providing perinatal mental health support because of their understanding of the link between maternal mental illness and maternal bonding with the baby.

Women with long-term conditions described their experience of fragmented clinical care, meaning they took on the role of relaying information between different health care professionals.[118] Women also shared experiences of feeling discriminated against by health care professionals through the language used and how they were treated. In Rebić et al's systematic review on key challenges of pregnancy with inflammatory arthritis, women described facing 'judgement' from the community and health care professionals for their pregnancy intention and ability to fulfil parental responsibility.[256]

Single versus multiple long-term conditions

Our focus group did not include pregnant women with no or single long-term conditions for comparison with pregnant women with multiple long-term conditions. However, the findings in this study are likely to be common to all women who have been pregnant or given birth, with or without multiple long-term conditions. This is reflected by the overlap of findings with existing core outcome sets for all pregnancies in general [133 134] and with studies of pregnant

women with single condition. [254-259] A few of our findings are specific to pregnant women with multiple long-term conditions, such as quality of life, number of appointments and hospital admission (treatment burden), and development of new long-term conditions, as observed in the core outcome set for multimorbidity.[132]

There is currently no qualitative study specific to pregnant women with multiple long-term conditions. Hansen et al interviewed pregnant women with one or more long-term conditions in Denmark.[118] Although just under half of the study participants had two or more long-term conditions, it was not possible to disentangle the findings for those with (two or more conditions) and without (single conditions) multiple long-term conditions. Their experience is likely to be similar as even pregnant women with single condition still have to see multiple health care professionals (e.g., obstetrics, anaesthetist, and specialist for their long-term conditions) and balance the risk to their long-term conditions, pregnancy, and unborn child. However, the complexity and treatment burden are likely to be heighten when there are more than one long-term conditions to account for in the pregnancy care plan.

Strength and limitations

Representation of stakeholders

This focus group study involved a wide range of stakeholders, including health care professionals from different specialties, women with different long-term conditions, both who have had experience of pregnancy, childbirth and those who are planning a pregnancy, and their partners. In line with other qualitative studies in core outcome set development, we have included more service users than health care professionals to identify outcomes.[262] This is to ensure outcomes preferred by service users are included in subsequent prioritisation methods.[262]

This study included the perspective of partners, who may be a family member or take on the role of a carer. Previous studies have also included the perspectives of carers as 'involved witnesses'.[143] The presence of partners may enhance or inhibit the disclosure by women participants and vice versa. To partially account for this, one focus group was dedicated to women participants only. We did not conduct a focus group for partners only, and therefore may not have fully captured their views. However, in the focus group where two partners participated, there were discussions specifically around the impact of pregnancies of women with multiple long-term conditions, on partners and the family unit.

A key limitation of this study is the small sample size. As this study is part of a mixed-method core outcome set development and wider work of the MuM-PreDiCT consortium, within the available resources and project timeline, we only conducted three focus groups. The number of focus groups was not guided by data saturation. Despite using a maximum variation sampling strategy, it was not possible to have representation from all health conditions. It was also challenging to recruit partners. Therefore, it is possible that we have not captured all outcomes that are important to key stakeholders.

However, the literature search has already identified a long comprehensive list of reported outcomes. It included core outcome sets of pregnancy, childbirth, and maternity care in general, [133] [134] which were developed with service users and overlapped with many outcomes identified in this focus group. In addition, there will be opportunities for participants to suggest missing outcomes in the Delphi survey.

Participants were limited to those that could converse in English and in the UK. This limits the transferability of the study findings to non-English speaking pregnant women within the UK and other countries with different health care system, especially low-middle income countries.

Data collection

Qualitative methods used to inform core outcome set development included interviews, focus groups and secondary analysis of archived qualitative studies.[143 250] In this focus group study, we observed that participants were empowered to share their feelings and experiences after listening to other participant's stories, especially those with under-served characteristics or negative care experiences. However, some participants may find focus groups to be intimidating and inhibitive.[143] To overcome this, we harnessed the advantages of an online platform. Two participants chose to communicate using the chat function and had their camera turned off. A distress protocol was in place and a designated facilitator checked in on participants when required.

The online platform also helped overcome the logistic challenges of convening a group from different geographical location, people with clinical duties or childcare responsibilities. However, this together with the social media focused advertisement, may have led to digital exclusion.

A short video designed by the COMET group, explaining what a core outcome set is,[180] was shared with study participants before the focus groups. Based on pilot testing with our PPI advisory group, we used a case scenario to illustrate the concept of outcome. Nevertheless, the focus group discussions still focused on care experiences and processes. This issue was also encountered in other studies.[143] Through reflections after each focus group, the lead facilitator reframed participant's views or experiences into follow up questions about outcomes.

Data analysis

The lead facilitator, who also analysed the data, is medically trained. This may have biased her views in favour of health care professional's position, when interpreting themes relating to

participant's perceived quality of care. She also conducted the systematic literature search compiling outcomes reported in the literature. This exposure to the literature may have influenced how she labelled the outcomes identified in this study. However, these potential biases are counterbalanced by her dual role of having lived experience of a long-term condition, the input of a second facilitator and data analyst with no medical training and no prior exposure to the literature search, and extensive involvement of the PPI advisory group in interpreting the data.

Previous qualitative studies in core outcome set development have used different analyses approaches, including thematic analysis, framework approach and approach informed by grounded theory.[262-266] Recent studies used interpretive evidence synthesis methods to transform participants' experiences and views into measurable outcomes.[267 268] We undertook thematic analysis using a data driven approach but also ensured we addressed the research question. The term 'outcomes' was used in a broad way to capture some aspects of experience that were important to stakeholders, even if they are not easily measurable with existing measurement tools, or do not fit with traditional medical understandings of 'outcomes'.

When designing the Delphi survey, there was further deliberations with the multidisciplinary research team on combining outcome categories and labelling outcomes. Where possible, when preparing the plain English summary of the Delphi survey, we used the subthemes and words used by participants in this focus group study.

Implications for future research

The outcomes identified in this focus group will inform the design of a Delphi survey to develop a core outcome set for future studies of pregnant women with multiple long-term conditions.

Future studies should explore ethnic inequality in pregnancy outcomes as suggested by one participant. Another participant suggested considering positive outcomes. This concept was previously discussed by Smith et al who examined salutogenically focused outcomes of intrapartum interventions in systematic reviews.[216] The authors suggested shifting towards optimum or positive outcomes (health and wellbeing) instead of focusing on averting adverse outcomes.[216]

Although we focused on research outcomes, the rich description of women's experience of maternity care provided pointers of good clinical practice for health care professionals providing care to pregnant women with multiple long-term conditions and their children. This will be explored further in MuM-PreDiCT's upcoming interview study on the experience of maternity care of pregnant women with multiple long-term conditions.

Conclusion

Women with multiple long-term conditions emphasised outcomes related to the maternity care they received. Both women and their partners prioritised how better involvement in their care through enhanced communication and information sharing would help their experiences at different stages of pregnancy. These findings will inform the design of a standardised core outcome set for studies of pregnant women with multiple long-term conditions. However, women's experiences also provide useful insights into broader ways in which maternity care for pregnant women with multiple long-term conditions can be improved without additional costs.

DECLARATIONS

Ethics approval and consent to participate

This study has received ethical approval from the University of Birmingham Science, Technology, Engineering and Mathematics Ethical Review Committee (ERN_20-1264) and was conducted in accordance with the Declaration of Helsinki. An electronic copy of the consent form was emailed to participants, a signed copy was emailed back to the research team. Informed written and verbal consent was obtained from all participants.

Consent for publication

Not applicable as no identifying information is included in this manuscript.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary materials.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

SIL: Conceptualisation, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review and editing, Project administration.

SH: Methodology, Formal analysis, Investigation, Writing - review and editing.

ZV: Methodology, Formal analysis, Investigation, Resources, Writing - review and editing, Funding acquisition.

RP: Conceptualisation, Methodology, Resources, Formal analysis, Writing - review and editing, Funding acquisition.

AAL, CNP, CM, DOR, KMA, KAE, NM, SB: Conceptualisation, Resources, Writing - review and editing, Funding acquisition.

BT, LL, HH: Conceptualisation, Methodology, Writing - review and editing, Funding acquisition.

MS: Project administration, Writing - review and editing.

KN: Conceptualisation, Resources, Writing - review and editing, Supervision, Funding acquisition.

ST: Conceptualisation, Methodology, Resources, Writing - review and editing, Supervision, Funding acquisition.

MB: Conceptualisation, Methodology, Resources, Formal analysis, Investigation, Writing - review and editing, Supervision, Funding acquisition.

All authors read and approved the manuscript.

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Table 6.1: Characteristics of study participants

Characteristics	Focus group 1	Focus group 2	Focus group 3
Stakeholder groups	Health care professionals	Women with multiple long-term conditions and experience of pregnancy in the last 5 years / planning a pregnancy	Women with multiple long-term conditions and experience of pregnancy in the last 5 years / planning a pregnancy, and their partner
Time period	December 2021	February 2022	March 2022
Total number of participants, n	8	6	8 (4 women attended solo, 2 women attended with their partners)
Specialty / job role, n			
General practitioner	1	-	-
Maternal medicine subspecialist	1	-	-
Midwife	2	-	-
Neonatologist	1	-	-
Obstetrician	1		
Obstetric medicine specialist (general physician)	1	-	-
Perinatal psychiatrist	1	-	-
Pregnancy, n			
Pregnant in the last 5 years	-	4	3
Planning a pregnancy	-	1	2
Pregnant in the last 5 years and planning a pregnancy	-	1	1
Total number of self-reported long-term conditions			
Range	-	2 to 6	2 to 8
Median (IQR)	-	3 (2 to 3)	4 (2 to 4)
Physical health conditions			
Arrhythmia	-	-	1
Asthma	-	-	1
Cardiomyopathy	-	-	1
Coeliac disease	-	1	-
Degenerative disc disease	-	1	-
Diabetes mellitus	-	2	1
Factor V Leiden	-	1	-
Fibromyalgia	-	-	1

Functional neurological disorder	-	1	-
Gastroesophageal reflux disease, sphincter of Oddi dysfunction, gastritis	-	-	1
Hypermobile Ehlers-Danlos syndrome	-	1	-
Human immunodeficiency virus infection	-	1	1
Hypertension	-	1	1
Inflammatory bowel disease, ulcerative proctitis	-	1	1
Irritable bowel syndrome	-	-	1
Myofascial pain syndrome	-	1	-
Orthostatic hypotension	-	1	-
Polycystic ovarian syndrome	-	1	-
Psoriasis	-	-	2
Psoriatic arthritis	-	-	2
Mental health conditions			
Anxiety	-	2	3
Bipolar affective disorder	-	-	1
Complex post-traumatic stress disorder	-	1	1
Depression	-	3	2
Under-served population	-	Carer, disabled/deaf/blind, LGBTQ+, migrant, victims of domestic abuse.	LGBTQ+, refugee
Rural, n	-	1	5
Education level, n	-		
GCSE	-	-	1
A levels	-	1	1
Diploma		-	2
College	-	1	-
University	-	4	4
Ethnicity, n			
Asian	3	1	-
Black, Caribbean, or African	1	2	2
White	2	3	6
Mixed / multiple ethnic groups	1	-	-
Other	1	-	-

Age in years			
Range	32 to 64	28 to 44	22 to 49
Median (IQR)	54 (47 to 55)	33 (31 to 41)	38 (28 to 40)
Country, n			
England	7	3	6
Northern Ireland	-	-	2
Scotland	1	3	-

GCSE: general certificate of secondary education, IQR: interquartile range, LGBTQ+: lesbian, gay, bisexual, transgender, queer and others. NB: Maternal medicine specialists are obstetricians who subspecialise in maternal medicine; obstetric medicine specialists are internal medicine physicians who subspecialise in care of the pregnant women.

Table 6.2: Coding tree: Thematic categories, themes /outcomes, and subthemes

Thematic categories	Themes /outcomes	Subthemes
Care outcomes	Preconception support	Uptake of preconception support
		Quality of preconception counselling
		Preconception counselling on medications
	Interventions in pregnancy	Limited options
		Analgesia
	Postnatal and long-term care	Quality of postnatal support
		Length of postnatal support
		Postnatal support for raising a child
		Emotional support
		Support for family
	Breastfeeding support	
	Skin-to-skin	
	Quality and experience of care	
	Holistic care / multidisciplinary coordination of care	
	Shared care decision	
	Continuity of care	Information being passed on
		Seeing the same health care professionals
	Social and peer support	
	Information provision for preparedness	Informed of care
		Informed of potential risks
		Informed of support / services available
		Informed for self-care
	Birth experience	
	Accessibility of services	Physical barriers
		Social barriers
		Communication barriers
		Travel distances
	Health care professional (HCP)s' skills and knowledge	
	HCPs' knowledge of the woman	
	HCPs' attitude towards the woman	
	Hospitals' facilities and services	
	Personalised care	
	Consistency of care	
	Expectation of care and outcomes	
	Separation of mother from newborn baby	
	Admission to neonatal unit	

	Number of appointments	
	Length of hospitalisation	
	Number of admissions during pregnancy	
Clinical outcomes		
	Fertility	
	Maternal death	
	Impact on long-term conditions	
	Types of birth	
	Miscarriage	
	Birth injuries	
	Haemorrhage	
	Blood pressure	
	Perinatal mental health	Postnatal depression
		Impact on pre-existing mental illness
		Impact of mental health on physical health
		Impact of physical health on mental health
		Emotional and mental well-being
		Experience of perinatal mental health support
	Recovery time	
	Development of new health conditions	
	Long-term cardiovascular outcomes	
	Engagement with health behaviours	
	Change in medications	
	Compliance with medications	
	Quality of life	
	Timing of birth (preterm)	
	Baby's lung development (respiratory distress syndrome)	
	Infant mental health	
	Child's death	Neonatal mortality
		Infant mortality
	Baby's condition at birth	
	Birth defect	
	Birth weight	
	Impact of medication in pregnancy on child	
	Neonatal intervention	
	Inheritance of mother's conditions	
	Baby's growth	
	Developmental outcomes (child)	
	Metabolic syndrome (child)	

	Neonatal morbidity	Neonatal cardiovascular function Neonatal metabolic control Neonatal jaundice Baby's physiology
Role as mothers / parents	Ability to breastfeed	
	Establishing feeding Maternal guilt Pressure in maternal role Parent and infant bonding	
Other outcomes	Impact on partner	Partner's caring role Support for partner Involvement of partner Partner's mental well being
	Financial implications Participation in society (child)	
Considerations for future studies	Impact of ethnicity	
	Framing outcomes positively Focus on experiential outcomes	

Table 6.3: Identified outcomes presented by stakeholder groups

Stages of pregnancy		Women / partner and health care professionals	Women / partners only	Health care professionals only
Maternal outcomes, n=43	**Before pregnancy n=2**	Fertility Preconception care	-	-
	During pregnancy n=8	Maternal death Impact on long-term conditions Types of birth	Miscarriage Birth injuries	Interventions in pregnancy Haemorrhage Blood pressure
	After pregnancy n=13	Postnatal and long-term care Perinatal mental health Ability to breastfeed Pressure in maternal role Maternal guilt Parent and infant bonding	Breastfeeding support Skin-to-skin Recovery time Development of new health conditions	Long-term cardiovascular outcomes Engaging with healthy behaviour Establishing feeding
	All stages of pregnancy n=20	Quality and experience of care Change in medication Holistic care / multidisciplinary coordination of care Shared care decision Continuity of care Social and peer support Information provision for preparedness	Birth experience Accessibility of services Health care professionals': - Knowledge and skills - Knowledge of the woman - Attitude towards the woman Hospitals' facilities / services Personalised care Consistency of care Impact on partner	Financial implications Expectation of care and outcomes Compliance with medication Quality of life
Children's outcome n=16		Timing of birth (preterm birth)	Neonatal intervention Inheritance of mother's condition	Baby's growth Developmental outcomes

	Separation of mother from newborn baby Baby's lung development (respiratory distress syndrome) Infant mental health Child's death Baby's condition at birth Birth defect Birth weight / macrosomia Impact of medication in pregnancy		Metabolic syndrome Neonatal morbidity Participation in society
Health care utilisation n=4	Admission to neonatal unit Number of appointments	-	Length of hospitalisation Number of hospital admission during pregnancy

Table 6.4: Additional outcomes identified in the focus groups

Maternal outcomes

Before pregnancy

1. Fertility
2. Preconception care

During pregnancy

3. Impact on long-term conditions
4. Miscarriage

After pregnancy

5. Development of new health conditions
6. Long-term cardiovascular outcomes
7. Maternal guilt
8. Parent and infant bonding
9. Postnatal and long-term care
10. Pressure in maternal role
11. Recovery time

All stages of pregnancy

12. Accessibility of services
13. Change in medication
14. Consistency of care
15. Continuity of care
16. Expectation of care and outcomes
17. Holistic care / multidisciplinary coordination of care
18. Hospital's facilities / services
19. Impact on partner
20. Personalised care
21. Social and peer support

Children's outcome

22. Baby's growth
23. Impact of medication in pregnancy on child
24. Infant mental health
25. Inheritance of mother's condition
26. Metabolic syndrome
27. Participation in society
28. Separation from newborn baby

Chapter end summary

Together with outcomes identified in the systematic literature search in Chapter 5, findings in this chapter comprised the initial list of outcomes. This list of outcomes will then be prioritised through Delphi surveys and consensus meetings in Chapter 7 to achieve a final core outcome set.

Chapter 7: Core outcome set development for studies of multimorbidity in pregnancy

Chapter overview

An initial list of candidate outcomes was identified through a systematic search of the literature and focus groups with stakeholders in Chapters 5 and 6 respectively. This chapter used methods prespecified in Chapter 4 to meet *Objective 6:* to develop a core outcome set for studies of pregnant women with multimorbidity using consensus methods. The manuscript submitted for publication is presented as follows.

Manuscript under review by BMC Medicine

Personal contribution

- Study design working with the study team and the patient and public involvement (PPI) advisory group
- Applied for ethical approval
- Prepared study documents, designed and piloted the Delphi survey
- Conducted workshops to design the Delphi survey
- Liaised with charities and organisations for recruitment
- Liaised with study participants for the follow up survey and consensus meetings
- Organised the consensus meetings and chaired the first consensus meeting
- Analysed the data
- Drafted the manuscript

Title: The development of a core outcome set for studies of pregnant women with multimorbidity

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7.1 Abstract

Background: Heterogeneity in reported outcomes can limit the synthesis of research evidence. A core outcome set informs what outcomes are important and should be measured as minimum in all future studies. We report the development of a core outcome set applicable to observational and interventional studies of pregnant women with multimorbidity.

Methods: We developed the core outcome set in four stages: (i) a systematic literature search, (ii) three focus groups with UK stakeholders, (iii) two rounds of Delphi surveys with international stakeholders, and (iv) two international virtual consensus meetings. Stakeholders included women with multimorbidity and experience of pregnancy in the last five years, or are planning a pregnancy, their partners, health or social care professionals and researchers. Study adverts were shared through stakeholder charities and organisations.

Results: Twenty-six studies were included in the systematic literature search (2017 to 2021) reporting 185 outcomes. Thematic analysis of the focus groups added a further 28 outcomes. Two hundred and nine stakeholders completed the first Delphi survey. One hundred and sixteen stakeholders completed the second Delphi survey where 45 outcomes reached *Consensus In* (≥70% of all participants rating an outcome as *Critically Important*). Thirteen stakeholders reviewed 15 *Borderline* outcomes in the first consensus meeting and included seven additional outcomes. Seventeen stakeholders reviewed these 52 outcomes in a second consensus meeting, the threshold was ≥80% of all participants voting for inclusion. The final core outcome set included 11 outcomes. The five maternal outcomes were: maternal death, severe maternal morbidity, change in existing long-term conditions (physical and mental), quality and experience of care, and development of new mental health conditions. The six child outcomes were: survival of baby, gestational age at birth, neurodevelopmental conditions/impairment, quality of life, birth weight, and separation of baby from mother for health care needs.

Conclusion: Multimorbidity in pregnancy is a new and complex clinical research area. Following a rigorous process this complexity was meaningfully reduced to a core outcome set that balances the views of a diverse stakeholder group.

328 words

Keywords: multimorbidity, multiple chronic conditions, multiple long-term conditions, pregnancy, maternity, outcome, core outcome set

7.2 Background

One in five pregnant women in the United Kingdom (UK) has multiple, pre-existing long-term physical or mental health conditions (termed 'multimorbidity' hereafter).[172] Polypharmacy is prevalent in pregnant women with multimorbidity as they may have to manage their health conditions with multiple medications.[253] Recent studies have demonstrated that maternal multimorbidity is associated with adverse outcomes such as hypertensive disorders of pregnancy, utilisation of acute health services during the perinatal period, preterm birth, severe maternal morbidity and maternal mortality.[44 47 66] However, this evidence is sparse and the population is under-researched.[66] The impact of polypharmacy on the pregnancy, the women and her child is also unclear.

Research priorities for multimorbidity in pregnancy include understanding the long-term consequences for mother and child, and developing new interventions and models of care.[178] Both observational and interventional studies are needed to provide information that can help women with multimorbidity make informed decisions with their clinicians, and to develop interventions that will improve outcomes for mother and child. For instance, longitudinal observational studies are crucial to providing evidence on children's long-term outcomes.

As research in this field gains momentum globally,[42 59 66] a core outcome set is needed to avoid heterogeneity of reported outcomes, which can limit the synthesis of research and its usability.[129] A core outcome set informs what outcomes are important and should be reported as a minimum in all future studies for a particular health condition.[142] To ensure its relevance, core outcome sets are developed through consensus-setting methods with stakeholders including people living with the health conditions, health and social care professionals, and researchers.[142]

There are currently limited core outcome sets available for long-term conditions in pregnancy; examples include core outcome sets for epilepsy,[198] diabetes,[269] heart conditions[270] and rheumatological conditions in pregnancy.[271] Core outcome sets for pregnancies in general[133] [134] and for medication safety in pregnancy[272] do not have outcomes reflecting challenges specific to women with multimorbidity, such as the impact of pregnancy on their long-term conditions. Conversely, the core outcome set for multimorbidity[132] does not have pregnancy outcomes. To address this gap, and to guide future studies in this field, a core outcome set specific for pregnant women with multimorbidity is needed. This paper reports the development of a core outcome set for studies of pregnant women with multimorbidity.

7.3 Methods

Inclusivity statement

Where the words 'women', 'maternal', or 'mother' are used, these also refer to people who do not identify as women but have been pregnant or may be pregnant in the future.

Scope

We defined multimorbidity in pregnancy as having two or more long-term physical or mental health conditions that pre-existed before pregnancy.[172] This core outcome set was developed to be applicable to research involving pregnant women with multimorbidity. It is not limited to specific long-term conditions, specific interventions, or health care settings. The core outcome set would be applicable to observational and interventional studies.

Study design

The core outcome set development protocol has been published[211] and registered in the Core Outcome Measures in Effectiveness Trials (COMET) database.[185] It follows the guidance of the COMET handbook [142] and involves four stages: (i) systematic literature search and (ii) focus groups to generate the initial list of outcomes; (iii) Delphi surveys and (iv) consensus meetings to prioritise the core outcomes. This report is prepared in accordance with the Core Outcome Set Standards for Reporting (COS-STAR, Supplementary Material 7.1).[183]

Participants

We recruited participants from the following stakeholder groups:

(i) women with self-reported two or more long-term pre-existing conditions, who have been pregnant in the last five years or planning a pregnancy, and their partners;

(ii) health or social care professionals who provide care to pregnant women with multimorbidity or their children; and

(iii) researchers interested in this field.

Following the advice of our Patient and Public Involvement Advisory Group, we also recruited for partners, family, and carers as they can provide a different perspective.

We contacted charities and organisations for health conditions, pregnancy, parenthood, health or social care professionals and researchers. We approached health conditions-based charities guided by a list of 79 long-term conditions from our prior work.[172] We asked if they would share the study adverts with their members and through their social media platforms. We also recruited participants through professional contacts and networks.

Systematic literature search

The systematic literature search was conducted in two stages. We first searched for published core outcome sets for multimorbidity, pregnancy and childbirth in the COMET and Core Outcomes in Women's and Newborn's Health (CROWN) databases. We then searched for studies of pregnant women with multimorbidity in Medline, Embase, Cumulated Index to Nursing and Allied Health Literature (CINAHL) and Cochrane Library from inception to 11th August 2021. We used the concepts 'pregnancy' (population) and 'multimorbidity' (exposure) to inform the search strategy using Medical Subject Headings and free text terms. Studies that reported outcomes for pregnant women with multimorbidity or their children were included. Two reviewers (SIL and MS) independently screened the full texts and extracted the types of outcomes reported in the studies. Details of the literature search strategy and study selection are provided in Chapter 5. As no evidence synthesis was undertaken, the quality of included studies was not assessed.

Focus groups

As outcomes identified in the literature may be more representative of outcomes that are of interest to researchers rather than women or other stakeholders, we supplemented the initial list of outcomes with qualitative studies (focus groups) involving stakeholders.[142] The findings from the focus groups will be reported in more detail in a separate publication. Briefly, three focus groups were conducted in the UK from December 2021 to March 2022: one for women, one for women and their partners and one for health professionals. Participants were recruited through study adverts disseminated through social media platforms of patient charities and professional organisations. We undertook maximum variation purposive sampling to ensure representation from different health conditions, ethnic groups, under-served populations, UK regions, availability of partners, and specialties of health care professionals.[211] The focus

groups explored outcomes that stakeholders felt should be reported in all studies of pregnant women with multimorbidity. Thematic analysis was conducted with an inductive approach,[251] focusing on research outcomes discussed or inferred by participants. Outcomes from the focus groups were then compared to outcomes extracted from the systematic literature search to identify new outcomes.

Delphi surveys

Prior to designing the Delphi surveys, two workshops were convened with the multidisciplinary research team and Patient and Public Advisory Involvement Group: one for maternal outcomes and one for child outcomes. The aim of the workshops was to review and refine the initial list of outcomes from the systematic literature search and focus groups. To reduce survey burden, we prioritised outcomes that clinicians and patient representatives felt are of higher risk in women with multimorbidity than women with no or single health condition. Outcomes that were clinically and pathophysiologically similar were combined. Important outcomes that were missing were added. The refined list of outcomes was then further prioritised by stakeholders through two rounds of Delphi surveys.

The Delphi surveys were piloted by the research team and Patient and Public Involvement Advisory Group and amended for clarity. A plain English explanation of medical terminology was provided in the survey, reflecting terminology used by participants in the focus groups where possible. For each outcome, participants were asked to rate on a nine-point scale (1-3 *Not important*; 4-6 *Important but not critical*, 7-9 *Critically important)*. There was an *Unable to comment* option. Participants' demographics were collected to iteratively inform the recruitment strategy.

The Delphi survey was in English and was hosted on https://www.onlinesurveys.ac.uk/. The study advert with a direct link to the survey was shared through patient charities and

professional organisations' social media network internationally. The targeted sample size was 50 women and 50 health or social care professionals based on previous studies.[198 202 211 269] The first survey was opened from 28th April 2022 to 19th June 2022. Participants were invited to suggest up to two additional outcomes. New outcomes that were suggested by two or more participants were included in the second survey.

The second survey was opened from 24th June 2022 to 1st August 2022. Participants who took part in the first survey were sent personalised emails to take part in the second survey. All outcomes from the first survey were presented again. Participants were asked to reflect on the findings from the first survey before rescoring the outcomes.[142] They were given their individual scores and the aggregate scores across stakeholder groups (all participants, women/partners, and health professionals/researchers). These were presented as median scores and percentages of participants rating the outcomes as *Critically important*. As predefined in the study protocol,[211] *Consensus in* was considered when outcomes were rated as *Critically important* by ≥70% of all participants (combining all stakeholder groups). Participants were also asked to indicate their interest in joining the consensus meetings.

Attrition analysis was conducted to assess the impact of attrition from the second Delphi survey. For each outcome in the first Delphi survey, Mann-Whitney test was performed to compare the average scores,[142] Chi squared test was performed to compare the proportion of participants who rated an outcome as *Critically important.* Comparisons were made between participants who completed the first survey only and participants who completed both rounds of the survey.[142]

Consensus meetings

For both meetings, we sampled participants from the second survey, focus groups, the research team and Patient and Public Involvement Advisory Group. Participants that were available

were sampled with maximum variation to ensure representation from different stakeholder groups, specialty and geographical regions.[211] Similar to previous studies, and to facilitate discussion, we aimed to recruit 10 to 15 participants.[198 273 274]

First consensus meeting

The first consensus meeting discussed outcomes that were considered *Borderline.* Outcomes were considered *Borderline* if in the second survey: (i) ≥70% of all participants rated the outcome as *Important but not critical,* or (ii) when ≥70% of participants in one stakeholder group (women/partner or health professionals/researchers) rated an outcome as *Critically important* but *Consensus in* was not reached. Participants were asked to review the list of *Borderline* outcomes before the meeting.

The virtual meeting took place in September 2022 and was facilitated by a non-voting chair (SIL, public health). It was conducted following principles of a nominal group technique.[142] Participants voiced their opinions in turn without being interrupted in the *Round robin* session. This was followed by a *Group discussion* where participants could ask for clarifications from fellow participants. After hearing everyone's views, the meeting ended with a final binary vote, *Prioritisation*. *Borderline* outcomes that were voted in by ≥70% of all participants were included.

Second consensus meeting

The second consensus meeting reviewed all the outcomes that were included from the second Delphi survey and the first consensus meeting. Pre-meetings were arranged with all participants to brief on the aim of achieving a concise core outcome set. Participants were asked to review the list of outcomes before the meeting.

The meeting was conducted virtually in February 2023, the non-voting co-chairs were MB (obstetrician) and CG (neonatologist). The group discussion focused on which outcomes had overlapping concepts and could be combined. Following the group discussion, a formal vote was held for maternal and child outcomes. The results were reviewed with further discussion, especially where there was no outcome included for key domains and where there was discrepancy of votes between stakeholder groups. This was followed by four additional rounds of voting. The threshold for inclusion was set before the meeting as ≥80% of yes votes from all participants.

7.4 Results

Changes to the protocol

Changes were made to the systematic literature search, number of rounds for the Delphi survey, the number and scope of the consensus meetings, and the criteria for inclusion in the consensus meetings. The systematic literature search for studies reporting outcomes for pregnant women with multimorbidity from inception to 11th August 2021 identified 18,962 titles. Due to this large yield, study selection and data extraction were performed on a yearly basis until saturation was reached (when no new outcomes were extracted). We encountered difficulties recruiting women and partners for the first Delphi survey. We anticipated that the imbalance of stakeholders may widen with attrition in subsequent surveys. Therefore, we reduced the Delphi surveys from the planned three rounds to two rounds[211] and conducted a post hoc attrition analysis. Despite confirming attendance from equal numbers of stakeholders, there was an imbalance of stakeholder representation at the first consensus meeting. Following the advice of women stakeholders, we additionally included one outcome that was voted in by ≥70% of women stakeholders in the first consensus meeting. Finally, given the long list of included

outcomes at the end of the first consensus meeting, a second consensus meeting was conducted to further prioritise outcomes, and the inclusion threshold was increased to ≥80% of all participants voting for the outcome.

Initial list of outcomes

Chapter 5 presents the PRISMA flow chart for the systematic literature search, characteristics of included studies, reasons for exclusions, extracted outcomes and definitions. The search in COMET and CROWN identified one core outcome set for multimorbidity[132] and two for maternity care, pregnancy and childbirth,[133 134] and five systematic reviews.[130 181 191 215 216] For studies reporting outcomes for pregnant women with multimorbidity, 7534 title and abstracts from 2017 to 2021 were screened, 32 full texts were assessed for eligibility, three additional articles were included from screening the reference list of the included articles. A total of 28 articles were included from 26 studies.[43 44 46-48 63 64 173 217-236]

From the systematic literature search, 185 unique outcomes were identified. The focus groups identified 63 outcomes; when mapped to the systematic literature search, 28 outcomes were new. These 213 outcomes were reviewed in workshops with the research team and patient representatives; 35 outcomes, including seven outcomes from a core outcome set for neonatal research,[273] were added; 86 outcomes were dropped and 35 outcomes were combined with other outcomes, giving a total of 127 outcomes for the first Delphi (Figure 7.1). Supplementary Material 7.2 lists the initial outcomes and rationale for decisions from the research team's workshops.

Delphi surveys

Table 7.1 shows the characteristics of the survey participants. In the first survey, 209 participants took part: 62 women, one partner, 102 health professionals and 44 researchers. In

the second survey, 116 participants took part: 38 women, one partner, 52 health professionals and 25 researchers. In the first survey, 19 women / partner and 77 health professionals / researchers were from non-European countries; in the second survey, 12 women / partner and 34 health professionals / researchers were from non-European countries. The overall attrition rate was 44%: 39% for women, 49% for health professionals and 43% for researchers.

In the first survey, 42 outcomes reached *Consensus in.* The list of additional outcomes suggested by participants is provided in Supplementary Material 7.3. Four outcomes were suggested by two or more participants and were added to the second survey. These were: cephalopelvic disproportion, childhood vaccination, feeding support and neonatal abstinence syndrome. In the second survey, 45 outcomes reached *Consensus in* (Table 7.2). In the attrition analysis, using a 5% significance level, three outcomes reached significance in the Mann-Whitney test, six outcomes reached significance in the Chi squared test. These different scoring patterns did not change whether the outcomes reached *Consensus in* in the first Delphi. Supplementary Material 7.3 presents the percentage of participants that rated the outcomes as *Critically important*, stratified by stakeholder groups and the attrition analysis.

First consensus meeting

From the second survey, 15 *Borderline* outcomes were eligible for discussion at the first consensus meeting. Thirteen participants took part in the meeting: six women and seven health professionals/researchers (Table 7.1). Supplementary Material 7.4 presents the meeting minutes and the votes for these 15 *Borderline* outcomes; seven additional outcomes were included (Table 7.2).

Second consensus meeting

The 52 outcomes included from the second Delphi survey and first consensus meeting were discussed (Table 7.2). Seventeen participants took part: nine women and eight health professionals/researchers (Table 7.1). Supplementary Material 7.5 presents the meeting minutes and the voting results. The final core outcome set included 11 outcomes: five maternal and six child outcomes. Table 7.3 presents the final list of core outcomes and key points from the discussion. These should be considered in the next stage when determining how the core outcomes should be defined and measured.

Consensus meetings key discussion points

In the consensus meetings, participants spoke about the importance of exploring the reasons behind women having a *Termination of pregnancy*, whether women received good support and counselling for this decision, and whether women felt coerced.

Neurodevelopmental conditions (child) reached *Consensus in* in the second survey, whilst *General cognitive ability (child)* was considered *Borderline* and was ultimately not voted in in the first consensus meeting. The opinions for these two outcomes were split in the consensus meetings. Participants who did not support the inclusion of these outcomes were concerned that it will lead to study findings that encourage ableism, place the blame of these child outcomes on women's choices, and limit women's access to certain medication or types of birth. Participants who supported the inclusion of these outcomes felt that having information on these outcomes is important for pregnant women with multimorbidity to make informed decisions for their care during pregnancy. This includes decisions on medications they take during pregnancy and their babies' treatment during the neonatal period.

There was general agreement that the perinatal mental health outcomes needed to be combined and to be included in the core outcome set. However, there were debates on whether the core outcome set should focus on mental health conditions that are severe. Participants raised concerns that, depending on the definition of severe mental health conditions used, this may not capture birth related post-traumatic stress disorder.

Separation of baby from mother overlapped with *Admission to neonatal unit*. Women participants felt very strongly for the former. They were concerned of the long-term impact on the baby if admission to neonatal unit was required, but additionally spoke about the anxiety that came with the separation. *Separation of baby from mother* may also overcome the challenges of international variation in how neonatal care is provided.

7.5 Discussion

Main findings

This paper reports the process of developing a core outcome set for studies of pregnant women with multimorbidity. The final core outcome set included 11 outcomes: five maternal outcomes and six child outcomes. Maternal outcomes covered survival, severe manifestation of maternal complications during pregnancy and childbirth, impact on the women's multiple long-term conditions and mental health, and experiential outcomes. Child outcomes covered survival, gestational age and birth weight, separation of baby and mother at birth for health care needs and longer-term neurodevelopmental and quality of life outcomes.

Comparison with the literature

Outcomes that are of importance to all pregnant women are likely to also be important to pregnant women with multimorbidity. Therefore, we expected an overlap of the current core

outcome set with existing core outcome set for pregnancy, childbirth, and maternity care,[133 134] such as survival of mother and child, gestational age at birth, birth weight, quality, and experience of care. *Severe maternal morbidity* that arises during childbirth, a composite outcome that is frequently used in recent USA based studies of maternal multimorbidity, was also included.[47 66 225 227 229] However, our study additionally included core outcomes specific to pregnant women with multimorbidity such as *Change in existing long-term conditions (physical and mental).*

Strengths and limitations

The core outcome set was developed with a robust multistage approach, balancing the views of all stakeholders including women with multimorbidity, health and social care professionals and researchers. The broad remit of multimorbidity allowed us to work with many national and international patient charities for recruitment. This is reflected in the broad range of study participants, including participants from under-served groups, who provided invaluable perspective on the included outcomes. The multidisciplinary nature of maternal multimorbidity was also reflected in the range of health professionals who participated, including health professionals in women's health, children's health, and mental health, in both primary care and hospital settings.

Our Patient and Public Involvement Advisory Group was involved at all stages of the study. This is a diverse group of women with lived experience of a broad range of health conditions, disabilities, geographical and ethnic representation in the UK. They advised on the scope of the core outcome set, reviewing and piloting the study materials, recruitment, conduct of the study, interpreting the focus group findings, selection of the initial outcomes and participated in the consensus meetings.

However, a key limitation of this study is the representation of stakeholders. Despite having more women stakeholders in the focus groups, only a third of the Delphi surveys participants were women stakeholders. Although a third of women / partner stakeholders who participated in the Delphi surveys were from non-European countries, all women stakeholders at the consensus meeting were based in the United Kingdom. The study findings may not represent the views of participants who do not have digital access or experience care outside of the UK or similar high-income settings.

Despite recruiting for family members, carers, and partners of women with multimorbidity, only two partners participated in the focus groups and one partner participated in the Delphi surveys. We were not able to consider the views of children born to mothers with multimorbidity. It may be possible that some of the women participants met this criteria given the hereditary nature of some health conditions, but this information was not captured. The WRISK study highlighted concerns that current pregnancy risk messaging prioritises fetal health over the women's health outcomes.[275 276] Therefore, this study focuses on maternal and child outcomes that are important to women with multimorbidity and information that will help women make informed decisions for their own care during pregnancy and in the postpartum period.

The attrition rate in the follow up survey was high (44%). Previous studies have reported attrition rates ranging from 21% to 48%.[130 274] The survey burden presented by the long list of outcomes is likely to have contributed to the difficulty in recruitment and retention. To avoid further imbalance of stakeholder representation, we terminated the Delphi survey after the second round. This meant participants did not have the opportunity to reflect on the scores for the four new outcomes added from the first Delphi survey.

Research implications

A core outcome set lists the minimum standard list of outcomes that should be measured ('what to measure'). Once this is agreed through consensus setting methods, a separate piece of work is needed to reach consensus on how the core outcomes should be defined and measured ('how to measure'),[142] following the guidance of the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) initiative.[277] This includes a literature search to identify existing measurement instruments for each of the core outcomes, quality assessment of the instruments, and a consensus process to agree on one instrument per core outcome.[277] In this study, key points were raised in the consensus meetings on defining the core outcomes, these should be taken into consideration when developing a consensus on how to measure the 11 core outcomes. The next step is to disseminate the core outcome set for use in future observational and interventional studies in line with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement and the CROWN initiative.[126] [129] As this core outcome set is also applicable to observational studies using routine health records, it can be considered by those designing data collection tools within the healthcare services. This can provide consistency in data collection across healthcare providers, allowing for clinical audit and secondary analysis.

To reduce the survey burden, some outcomes were combined into broader categories when designing the Delphi surveys. For instance, vaginal, caesarean, and instrumental births were combined as *Types of birth*. Preterm birth, small and large for gestational age are captured by *Gestational age* and *Birth weight.* Some outcomes were considered so important they were kept as standalone outcomes alongside broader outcomes, such as *Cerebral palsy*, *General motor, cognitive* and *social ability* alongside *Neurodevelopmental conditions (child)*; *Post-traumatic stress disorder, Suicide, Self-harm* alongside *Perinatal mental health*. Although we

have grouped all types of *Congenital anomaly* and *Neurodevelopmental conditions* into one outcome respectively, that does not mean they should be researched as one entity. Depending on the research question and granularity of the data source, further subclassification of the types of congenital anomaly and neurodevelopmental conditions may be required.

Some of the outcomes were process measures. The second consensus meeting offered the opportunity to consider whether these process measures or the associated longer-term impact are more important. For instance, the quality of *Care for long-term conditions* and *Perinatal mental health support* would ultimately determine the status of the women's long-term conditions or mental health outcomes; *Requiring intubation / ventilation (neonate)* and *Neonatal resuscitation* matter if the baby required admission to the neonatal unit, is separated from the mother, or develops longer-term complications. Consequently, many of these process measures were not included in the final core outcome set.

In the consensus meeting, some women stakeholders were concerned about the introduction of ableism through child outcomes such as *Neurodevelopmental conditions.* Ableism is a value system that discriminates against people with disabilities.[278] Disabled people have differing views, some may find research aimed at preventing impairment offensive whilst others are supportive.[278] The term neurodevelopmental conditions itself has been widely debated. Within the spectrum of neurocognitive function, there are neurodivergent individuals whose neurocognitive differences fall outside societal norms but are not considered impairment, whilst a diagnosis of neurodevelopmental conditions is for those with significant functional impairment.[279] It is, therefore, imperative to keep an open conversation with disabled people and maintain sensitivity and awareness about this.[280] It is also important to involve people with neurodevelopmental conditions in research about the condition itself.[281]

The inclusion of perinatal mental health outcomes is important as it is one of the commonest complications of pregnancy, with suicide being the leading cause of maternal death, especially in high income countries.[60 282 283] Severe mental health conditions was proposed as an umbrella outcome for perinatal mental health outcome and was discussed at length. Health professionals wanted to focus on mental health conditions that are severe. However, women participants were concerned that this would not capture birth related post-traumatic stress disorder. There is no international consensus on the definition of severe mental illness / health conditions.[284] Conventionally two approaches are being used: narrow (three dimension) and broad (two dimension) operationalised definitions of severe mental health conditions.[284 285] The three dimensions consider: (i) a diagnosis of non-organic psychosis, (ii) duration and (iii) disability.[284 285] The first approach includes a narrower list of health conditions (e.g., bipolar affective disorder, schizophrenia, psychosis) and is widely used in health services and research.[286 287] The second approach uses the latter two dimensions and would include any mental health conditions resulting in serious functional impairment,[288] it was advocated by health professional participants.

As discussed by Zumstein et al, although international consensus for severe mental health conditions can facilitate large scale epidemiological studies, definitions that are context specific may be more useful.[285] For example, in the context of perinatal mental health, health professional participants raised the difficulty with the duration criteria, which may exclude acute perinatal mental health conditions which are nevertheless severe. Ultimately, two of the included core outcomes will capture perinatal mental health outcomes: *Change in existing long-term conditions* will capture improvement, worsening, or relapse of existing mental health conditions; *Development of new mental health conditions* will capture new onset antenatal and postnatal mental health conditions, such as birth related post-traumatic stress disorder, self-harm and suicide attempts, postnatal depression, and puerperal psychosis.

Finally, just because an outcome is not included in the core outcome set does not mean it is not important. Additional study specific outcomes can still be measured depending on the research question. This can be guided by the preliminary list of 52 outcomes prioritised by stakeholders through the Delphi surveys and first consensus meeting. For instance, studies of medication safety in pregnant women with multimorbidity may want to include *Congenital anomaly (child).*[272] As more studies are conducted for pregnant women with multimorbidity, an update of this core outcome set may be indicated in the future.[142]

Conclusion

Multimorbidity in pregnancy is a new and complex clinical research area. Developing a core outcome set for studies of pregnant women with multimorbidity requires broader inclusion of participants. Following a rigorous process this complexity was meaningfully reduced to a core outcome set that balances the views of a diverse stakeholder group. It included outcomes for obstetrics, maternity services, perinatal mental health, maternal long-term conditions, and child outcomes, reflecting the multidisciplinary nature of multiple long-term conditions in pregnancy.

DECLARATIONS

Ethics approval and consent to participate

This study has received ethical approval from the University of Birmingham Science, Technology, Engineering and Mathematics Ethical Review Committee (ERN_20-1264). Participants provided consent to participate in the Delphi surveys, focus groups and consensus meeting.

Consent for publication

Participants consented for publication of study findings.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary materials.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SIL: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data Curation, Writing - Original Draft, Visualization, Project administration, Funding acquisition

MB: Conceptualization, Methodology, Validation, Investigation, Resources, Writing - Review & Editing, Supervision, Funding acquisition

KN, ST: Conceptualization, Methodology, Resources, Writing - Review & Editing, Supervision, Funding acquisition

RP: Conceptualization, Methodology, Validation, Resources, Writing - Review & Editing, Funding acquisition

SH, ZV, MS: Methodology, Validation, Investigation, Resources, Writing - Review & Editing

KAE, NM, AAL, AS, BT, CNP, CY, CM, DOR, HH, KMA, LL, PB, SB: Conceptualization, Methodology, Resources, Writ–ng - Review & Editing, Funding acquisition

CDM, HD, ML, GS: Methodology, Resources, Writing - Review & Editing, Funding acquisition

CG, KP, SPBHS: Methodology, Resources, Writing - Review & Editing,

AFF, LK, MM, SM, SW: Methodology, Writing - Review & Editing

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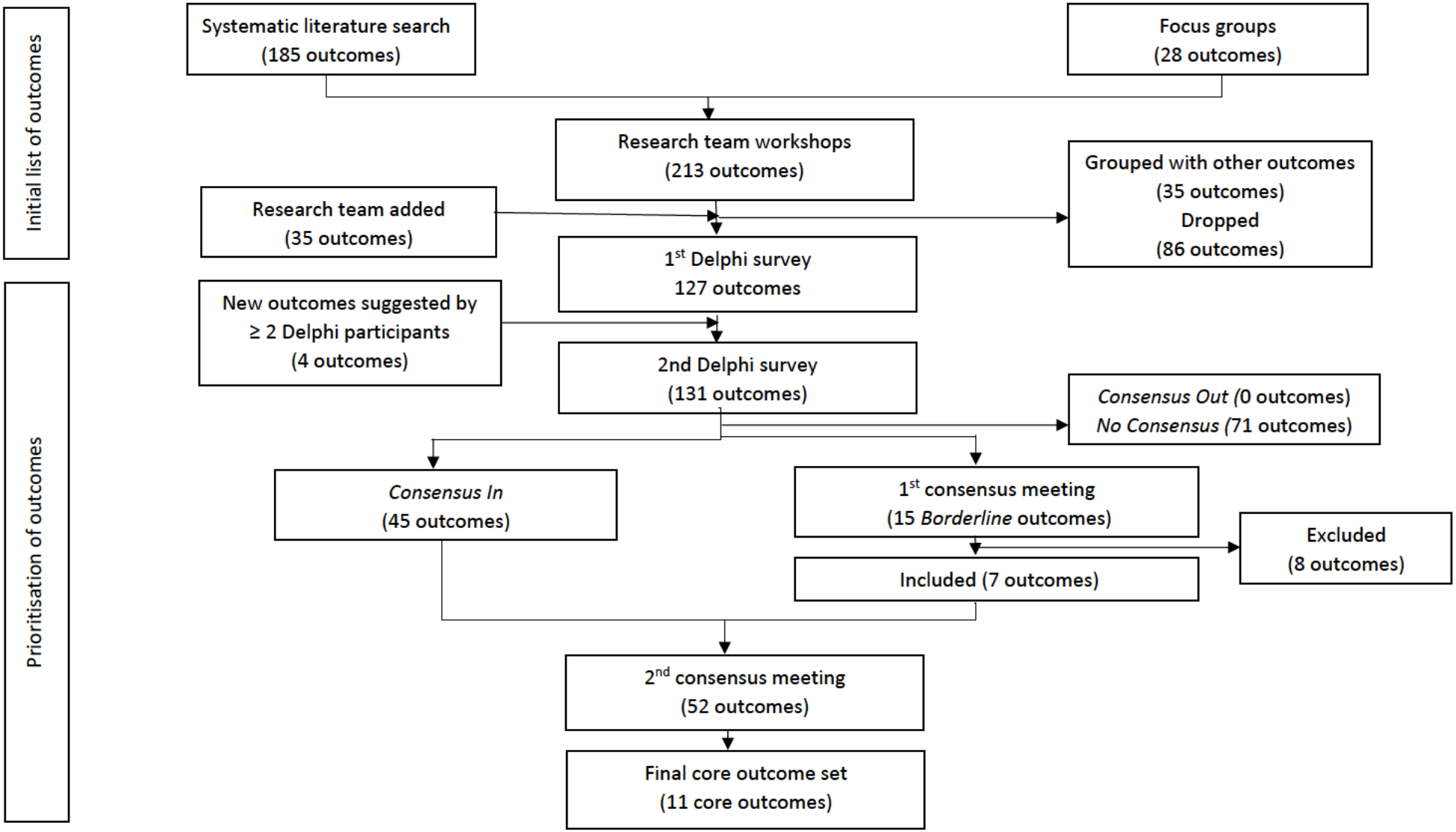
Epilepsy Foundation of America, Epilepsy Society, Fair Treatment for the Women of Wales, Fibromyalgia Action UK, General Practitioners Championing Perinatal Care, Global Kidney Foundation, Graham Mcllroy, Haemophilia Foundation Australia, Hereditary Spastic Paraplegia Support Group, Institute of Health Visiting, International League Against Epilepsy (Africa), Irish Neonatal Health Alliance, Juvenile Diabetes Research Foundation, Katie's Team, Kidney Patient Involvement Network, Kidney Wales, LGBT Mummies, MacDonald Obstetric Medicine Society, Malaysian Obstetric Medicine, Maternity and Midwifery Forum, MIDIRS Midwifery Digest, Midlands Maternal Medicine Network, Milena Forte, MQ Mental Health Research, Multiple Sclerosis Australia, Mums Like Us, Mum's Pride, Mumsnet, Muslim Women's Network UK, National Childbirth Trust, National Human Immunodeficiency Virus Nurses Association, National Kidney Federation, National Rheumatoid Arthritis UK, Newport Yemeni Community Association, Niina Kolehmainen, Obsessive Compulsive Disorder Action, Obstetric Anaesthetists' Association, Organisation for Sickle Cell Anaemia Relief and Thalassaemia Support Birmingham, Parathyroid UK, Parent Voices in Wales, Parents 1st, Positive East, Positive Life Northern Ireland, Postural Tachycardia Syndrome UK, Psoriasis Association, Raham Project, Royal College of Midwives, Royal Surrey County Hospital Maternity Voices Partnership, Scottish Perinatal Network, Scottish Research Nurse, Midwife & Coordinators' Network, Section for Women's Mental Health Institute of Psychiatry, Psychology and Neuroscience (King's College London), Sjogern's India, Society of Obstetric Medicine of Australia and New Zealand, Society of Obstetric Medicine (India), Somerville Heart Foundation, Sophia Forum, South African Nephrology Society, South Asian Health Foundation, South London Applied Research Collaboration Maternal and Perinatal Mental Health Research Patient and Public Involvement, Stockport Foundation Trust, Taraki, The Black Wellbeing Collective, The International Marcé Society for Perinatal Mental Health, The Pituitary Foundation, Thyroid Patients Canada, Tommy's, Turner Syndrome Support Society UK, UK Audit and Research Collaborative in Obstetrics and Gynaecology, UK Preconception Early-and Mid-Career Researchers Network, UK Teratology Information Service, University of Bristol Centre for Academic Primary Care and Patient and Public Involvement Panel, Vasculitis Ireland Awareness, Verity Polycystic Ovarian Syndrome UK, Wales Perinatal Mental Health Network. We would also like to thank Clare Evans for her input in reviewing this manuscript.

Figure 7.1: Flowchart of outcomes selection



Consensus in is when ≥70% of all participants across all stakeholders rated an outcome as *Critically important. Consensus out* is when ≥70% of all participants rated an outcome as *Not important. No consensus* is for any other scores. *Borderline* is when in the second survey: (1) ≥70% of all participants rated an outcome as *Important but not critical*, or (2) when ≥70% of one stakeholder group (women/partner or health professionals/researchers) have rated an outcome as *Critically important* but *Consensus in* was not reached. In the consensus meeting, *Borderline* outcomes that were voted in by ≥70% of all participants or ≥70% of women participants were additionally included in the core outcome set. For the second consensus meeting, an outcome is included if ≥80% of all participants voted for inclusion.

Table 7.1: Characteristics of participants

Characteristics	1st Delphi, n	2nd Delphi, n	1st consensus meeting, n	2nd consensus meeting, n
Total	209	116	13	17
Stakeholders				
Service users: Women with multiple long-term conditions	62	38	6	9
Service users: Partner	1	1	-	-
Service providers: Health or social care professionals	102	52	7	8
Researchers	44	25	(5 health professionals have dual roles as researchers)	(8 health professionals have dual roles as researchers)
Consensus meeting recruitment				
From focus group and Delphi surveys participants	-	-	8	11
From research team	-	-	3	1
From Patient and Public Involvement Advisory Group	-	-	2	5
Geography				
Africa	51	20	1	1
Asia	23	14	-	-
Australia and New Zealand	7	5	-	-
Europe	112	70	12	16
Middle East	3	1	-	-
North America	11	5	-	-
South America	1	1	-	-
Prefer not to say	1	-	-	-
Urban / Rural				
Urban	169	97	11	15
Rural	35	15	2	1
Prefer not to say	5	4	-	1
Ethnicity				
Asian	40	26	-	1
Black, Caribbean, or African	48	21	1	2
Mixed or multiple ethnic groups	3	1	-	-
White	110	66	11	13
Other	4	-	-	-
Prefer not to say	4	2	1	1
Age in years				
Median (interquartile range)	36 (31 to 44)	37 (32 to 47)	42 (32 to 44)	41 (34 to 46)
Range	22 to 70	23 to 70	28 to 70	28 to 61
Prefer not to say / missing	4	3	1	1

Woman stakeholders				
Pregnant in the last 5 years	54	33	3	3
Planning a pregnancy	8	5	1	1
Patient and Public Involvement Advisory Group	-	-	2	5
Number of health conditions (median, IQR)	3 (2 to 4)	3 (2 to 4)	4 (2 to 6)	3 (2 to 4)
Number of health conditions (range)	2 to 11	2 to 11	2 to 11	2 to 11
Health conditions				
Mental health conditions	29	17	4	4
Rheumatology / musculoskeletal	21	13	4	3
Gastroenterology	16	6	-	1
Endocrine	15	10	-	-
Respiratory	13	8	1	1
Neurology	12	8	2	3
Women's health	12	7	-	1
Cardiovascular	12	6	1	-
Dermatology / allergies	11	5	-	1
Other	5	3	1	2
Neurodevelopmental	5	2	1	2
Haematology	4	4	1	1
Genetic	4	3	-	-
Under-served characteristics (Includes addiction, asylum seeker, disabled, homeless / supported accommodation, LGBTQ+, migrant, victims of domestic abuse, other)	18	14	5	8
Education				
Primary	1	1	-	-
Secondary	10	7	-	1
Tertiary	46	27	6	7
Vocational	4	2	-	1
Other	-	-	-	-
Prefer not to say	1	1	-	-
Health or social care professional stakeholders				
Midwife / nurse / health visitor	39	19	4	3
Obstetrician / maternal and fetal medicine specialist	19	9	1	1
Obstetric physician / physician / anaesthetist	15	10	-	1
Family medicine / general practitioner	9	5	1	1
Paediatrician / neonatologist	7	4	1	1
Psychiatrist / perinatal mental health specialist / psychotherapist	5	2	-	1
Other	5	1	-	-
Not stated	3	2	-	-
Researcher stakeholders' area of research				
Maternal & infant health / midwifery / obstetrics / women's / reproductive health	24	14	5	4
Epidemiology / pharmacoepidemiology	6	-	-	-

Primary care / nursing	3	3	-	1
Medical specialties	2	2	-	2
Psychiatry / psychology	2	2	-	1
Not stated	7	4	-	-

IQR: interquartile range; LGBTQ+: lesbian, gay, bisexual, transgender, queer and others

Table 7.2: Fifty-two preliminary outcomes included in the second Delphi survey and first consensus meeting

Maternal outcomes	Children's outcomes
Survival	***Survival***
1. Maternal death	1. Death before birth (intrauterine death, stillbirth, perinatal death)
	2. Death after birth (neonatal death, infant death)
Clinical: antenatal	
2. Miscarriage*	***Clinical: fetal***
3. Termination of pregnancy*	3. Fetal growth restriction
4. Pre-eclampsia, eclampsia, HELLP syndrome	
5. Placenta abruption	***Clinical: neonatal***
6. Placenta insufficiency	4. Gestational age at birth
7. Venous thromboembolism	5. Apgar score
	6. Birth weight
Clinical: peripartum	7. Neonatal resuscitation required
8. Preterm premature rupture of membrane	8. Requiring intubation / ventilation
9. Severe maternal morbidity	9. Neonatal birth injury
10. Postpartum haemorrhage	10. Neonatal sepsis
11. Hysterectomy	11. Brain injury on imaging
12. Maternal infection	12. Neonatal respiratory distress syndrome
	13. Necrotizing enterocolitis
Clinical: postpartum and longer term	14. Retinopathy of prematurity
13. Development of new long-term conditions	15. Neonatal abstinence syndrome
14. Impact on long-term conditions	16. Meconium aspiration syndrome
	17. Separation of mother from baby*
Resource use / care related outcomes	
15. Admission to intensive care unit	***Clinical: infant***
16. Involvement in care decisions (overall care)	18. Chronic lung disease / bronchopulmonary dysplasia
17. Involvement in care decisions (types of birth)*	
18. Postpartum admission / readmission	***Clinical: longer term***
19. Quality & experience of care*	19. Congenital anomaly
20. Care for long-term conditions*	20. Cerebral palsy
	21. Children mental health & behavioural disorder
Mental health	22. Need for complex care
21. Suicide (perinatal)	23. Neurodevelopmental conditions
22. Post-traumatic stress disorder	
23. Perinatal mental health	***Life impact / functioning***
24. Self-harm (perinatal)	24. Visual impairment / blindness
25. Perinatal mental health support	25. Quality of life*
	Resource use
	26. Admission to neonatal unit (including intensive care)
	27. Neonatal readmission to hospital

HELLP: Haemolysis, elevated liver enzymes and low platelets

* The seven *Borderline* outcomes that were included after discussion in the first consensus meeting.

Table 7.3: Eleven core outcomes in the final core outcome set for studies of pregnant women with multimorbidity

Core outcomes	Concepts of the outcomes and key points for consideration in the next stage of defining outcomes
Maternal outcomes	
1. Maternal death	Important to document timing and cause of death.
2. Severe maternal morbidity	Many of the pregnancy complications that were initially included were removed from the core outcome set as severe maternal morbidity would represent the severe manifestation of the pregnancy complications.
3. Change in existing long-term conditions (physical and mental)	Includes the worsening, relapse, or improvement of pre-existing long-term physical and mental health conditions.
4. Quality and experience of care	Important to include whether women were involved in their care decisions.
5. Development of new mental health conditions	This would include the development of new onset mild, moderate, and severe mental health conditions that are acute or chronic.
Child outcomes	
1. Survival of baby	To include early pregnancy loss (miscarriage) and death of the baby at different time points (e.g., intrauterine fetal demise, stillbirth, perinatal death, neonatal death, infant death). Important to include the time frame, e.g., death within 28 days for neonatal death.
2. Gestational age at birth	This outcome together with birth weight and sex can be used to derive other outcomes, such as preterm / post-term birth, small / large for gestational age, fetal growth restriction.
3. Neurodevelopmental conditions / impairment	Important to determine what is the definition, what conditions to include, and the severity level at which it impairs function. Important to ensure research is conducted ethically.
4. Quality of life	Will need the development of measurement tools to measure this outcome in very young babies.
5. Birth weight	Studies should also document the sex of the baby alongside this outcome to enable meaningful interpretation.
6. Separation of baby from mother for health care needs	This would be a proxy for baby or mother needing additional care, such as admission to neonatal unit or intensive care unit.

Chapter end summary

Following the study protocol in Chapter 4, this chapter prioritised the long list of outcomes identified in Chapters 5 (systematic literature search) and 6 (focus groups) using Delphi surveys and consensus meetings and agreed on a final core outcome set. The next step would be to develop consensus on how these 11 core outcomes should be defined and measured. This is discussed in the next chapter's future research section.

Chapter 8: General discussion

Thesis overview

Maternal multimorbidity is increasingly important as women are getting pregnant older with higher body mass index, and as the prevalence of multimorbidity and maternal long-term conditions increase.[8 26 28 31 32] Recent evidence suggests that maternal multimorbidity increases the risk of adverse pregnancy outcomes.[66] However, this is a relatively new area of research, with its importance first raised by Beeson et al in 2018.[178]

This thesis aimed to describe the epidemiology of multimorbidity in pregnancy and to develop a core outcome set for studies of pregnant women with multimorbidity. Chapter 3 estimated the prevalence of pre-existing maternal multimorbidity in pregnancy that started in 2018 in the United Kingdom. Chapter 4 outlined the study protocol for the development of a core outcome set for studies of pregnant women with multimorbidity. The core outcome set was developed following a systematic literature search (Chapter 5), focus groups with stakeholders (Chapter 6), Delphi surveys and consensus meetings (Chapter 7).

Chapter overview

This final chapter will summarise the main findings, strengths, and limitations of this thesis. Detailed discussions can be found in the respective chapters. This chapter will focus on the clinical implications of the study findings and propose future research following on from this thesis.

8.1 Summary of findings

Epidemiology of pre-existing maternal multimorbidity in pregnancy

For the first time, Chapter 3 described the prevalence of multimorbidity in pregnant women using contemporary routine health records from different care settings across the devolved nations in the United Kingdom. Multimorbidity is highly prevalent in pregnant women. One in five pregnant women had two or more long-term physical or mental health conditions that required active management prior to conception. Mental health conditions and atopic conditions were highly prevalent. Smoking and higher body mass index preconception were associated with pre-existing maternal multimorbidity in pregnancy.

Core outcome set for studies of pregnant women with multimorbidity

The majority of the outcomes identified in Chapter 5's systematic literature search were clinical outcomes, with severe maternal morbidity frequently reported as a composite outcome. In Chapter 6's focus groups with stakeholders, care process related outcomes (e.g., personalised care, consistency of care) were valued by women with multimorbidity, whilst clinicians also suggested non-physiological outcomes (e.g., quality of life, financial implications) and longer-term outcomes (e.g., child's developmental outcomes). In Chapter 7, after two rounds of Delphi surveys and two consensus meetings, the final core outcome set consisted of 11 outcomes. The five maternal outcomes were: maternal death, severe maternal morbidity, change in existing long-term conditions (physical and mental), quality and experience of care, and development of new mental health conditions. The six child outcomes were: survival of baby, gestational age at birth, neurodevelopmental conditions / impairment, quality of life, birth weight, and separation of baby from mother for health care needs.

8.2 Comparison with previous literature

8.2.1 Prevalence of multimorbidity in pregnant women

As discussed in Chapter 1, the prevalence of multimorbidity in the general population varied widely depending on the number of conditions used to measure multimorbidity.[9] The number of conditions used to measure multimorbidity ranged from two to 285.[55] Pooled estimates of multimorbidity prevalence from systematic reviews were 37% to 42%.[9 10]

In contrast, the prevalence of pre-existing multimorbidity in pregnant women was lower but findings also varied widely from 0.5% of women who gave birth to 27% of reproductive aged women.[40 41] The number of health conditions used to determine multimorbidity status was also lower and varied from seven to 25.[42 43] Chapter 3 included three times more conditions (n=79) to measure multimorbidity, which may explain the higher prevalence of multimorbidity in pregnancy (44% and 46% in primary care datasets and 20% in secondary care and linked community prescription dataset in 2018). This higher number of included conditions is more in line with recent multimorbidity literature, where a ceiling effect was observed at over 50 conditions for the reproductive age group.[56]

Chapter 3's prevalence of multimorbidity in pregnant women using primary care data is closer to the prevalence of multimorbidity in the general population in a recent primary care records study in England (53% in 2019).[8] To date, there is only one other study reporting the prevalence of multimorbidity specifically in pregnant women in United Kingdom (21%), this study used secondary dataset from one English tertiary hospital.[44] This prevalence is similar to the 20% estimated from secondary care dataset in Tayside and Fife (Scotland) in Chapter 3. This prevalence was halved that observed using primary care records, as the latter also captured common mild-moderate long-term conditions that are managed in primary care.

8.2.2 Prevalence of individual health conditions in pregnant women

The prevalence of mental health conditions reported in Chapter 3 was similar to that reported in the last Adult Psychiatry Morbidity Survey in England (common mental health disorder 17%) and the Health Survey for England from 2014 (depression 19%).[167 289] A more recent study using CPRD found the prevalence of depression in mothers to be 18.4% and anxiety 7.9%.[290]

The prevalence of physical health conditions such as diabetes mellitus, asthma, chronic kidney disease, epilepsy and breast cancer were comparable to Kuan et al's seminal paper on the prevalence of 308 conditions across the life course.[65] Age related conditions, such as cardiovascular disease and chronic kidney disease were less prevalent, as would be expected in a pregnant population cohort aged <50. In contrast, Kuan et al's paper also found that mental health, atopic, gynaecological and dermatological conditions were common in the younger age group of 10-39 years.[65] Although some of these common physical conditions are not life-threatening, they are associated with an increased risk of comorbid mental health conditions and adverse health outcomes.[291-293] For instance, psoriasis is associated with cardiovascular disease, whilst gynaecological disorders and migraine are the leading causes of disability in women of reproductive age.[294 295]

8.2.3 Overlaps with existing core outcome sets

Core outcome sets are already available for pregnancy in general[133 134] and for multimorbididty,[132] but there is no core outcome set specifically for pregnant women with multimorbidity. Some degree of overlap with these existing core outcome set is expected for the outcomes identified in the development of one for pregnant women with multimorbidity.

In Chapter 6's focus groups, outcomes that overlapped with existing core outcome sets for pregnancy, childbirth and maternity care included: maternal and neonatal death, types of birth,

postnatal depression (perinatal mental illness), birth experience, active participant in care decisions, gestational age at birth, birth weight, congenital anomaly and neonatal admission to special / intensive care unit.[133 134] Outcomes that overlapped with existing core outcome set for multimorbidity included: shared decision making, treatment burden (number of appointments and tests), adherence and quality of health care.[132] Similar overlap was observed in Chapter 7's final core outcome set. However, the final core outcome set additionally included outcomes that reflect the impact of pregnancy on women's multimorbidity (*Changes to existing long-term physical and mental health conditions*).

8.2.4 Core outcome sets related to pregnancy and childbirth

Österberg et al's systematic review on core outcome sets related to pregnancy and childbirth identified 27 published studies and 42 ongoing studies to date.[131] Within the published studies, there were limited core outcome sets developed for pre-existing long-term conditions in pregnancy; namely rheumatological conditions, diabetes mellitus and epilepsy.[131] The core outcome set developed in Chapter 7 addressed the need for one that is applicable to pregnancy with maternal multimorbidity.

Österberg et al's systematic review also reported the number of outcomes in the core outcome sets ranged from 6 to 51, with a median of 13 outcomes.[131] Only six out of 27 included core outcome sets had 10 or less core outcomes.[131] The large number of core outcomes may be a barrier to the uptake of core outcome sets.[131] Hence, the authors suggested core outcome set developers to consider pre-setting a maximum limit of outcomes to overcome this.[131] The core outcome set development in Chapter 7 faced similar challenges, and a second consensus meeting had to be held to further narrow down the number of included outcomes.

8.3 Strengths and limitations

8.3.1 Strengths of the epidemiology study

Novelty of the study

For the first time, Chapter 3 provided a comprehensive and contemporary description of the epidemiology of multimorbidity specifically in a pregnant population, using routine health records from both primary and secondary care, from all four devolved nations in the United Kingdom. The CPRD primary care-based pregnancy register included pregnant women regardless of the pregnancy outcomes. As discussed in Chapter 1, most existing literature describing the epidemiology of multimorbidity in pregnancy used data from hospital admissions. This would miss long-term conditions that are managed in primary care, such as mild to moderate depression or migraine. Most studies also included women who have given birth as the denominator, excluding those with pregnancy loss and thus potentially underestimating the prevalence of multimorbidity.

As discussed in Chapter 1, current multimorbidity literature and lists of conditions to measure multimorbidity focus on the general population or older adults. The only existing index for maternal multimorbidity by Bateman et al used 20 conditions, it included both pre-pregnancy long-term conditions and pregnancy complications.[64] The candidate conditions were selected based on relevant literature and clinical plausibility.[64] In contrast, Chapter 3 used a comprehensive list of 79 pre-pregnancy long-term conditions to measure multimorbidity. These conditions were initially based on Ho et al's list of 59 conditions compiled through an international Delphi process,[58] with modifications made to reflect the reproductive age range of the pregnant population. Crucially, the list of conditions in Chapter 3 was finalised with women with lived experiences of multimorbidity and pregnancy, and clinicians, ensuring its relevance to stakeholders.

Strength of using routine health records

A key strength of using routine health records for the epidemiological study is being able to access contemporary data for a large population. Less resources were required compared to setting up a cohort or a representative survey. The method also enabled large number of health conditions to be examined simultaneously, allowing a comprehensive list of long-term conditions to define multimorbidity, selected by patients and clinicians. The incorporation of regular prescription data further refined the phenome definitions for the long-term conditions.

Strength of the data sources

A unique strength of the study in Chapter 3 is the access to three different data sources. CPRD's primary care-based pregnancy register represented pregnant women from all four devolved nation in the United Kingdom and included women with pregnancy loss; SAIL provided population level coverage of the Welsh population; the Scottish dataset provided an alternative perspective using hospital admission data linked to community prescriptions.

Where similar findings were replicated in different datasets, this increased the confidence in the validity of the study findings. Exploring the utility of primary (CPRD and SAIL) and secondary care (Scottish data) database increased our understanding of the respective strengths and weaknesses. Primary care datasets were good for identification of common mild conditions managed in the community. This suggests that primary care may be a good starting place to identify women for preconception health optimisation. Indeed, a systematic review found that primary care was considered the most appropriate place for the delivery of preconception care, although there was no agreement which professional group the responsibility should lie with.[296] A recent systematic review found that primary care based preconception care was effective in improving health knowledge and reducing preconception risk factors.[297] In contrast, identifying health conditions from secondary care and prescription data can be a marker of disease severity.

8.3.2 Limitations of the epidemiology study

Inclusion criteria

Chapter 3 included pregnant women of reproductive age 15 to 49 years old. Although this reproductive age range is commonly used in official statistics,[298-300] the lower limit excludes teenage pregnancies (pregnancies aged <18)[301] for those on the extremely young age spectrum (10 to 15). The number of pregnancies in this age group is likely to be small. The conception rate for under-16s is a third of what it was a decade ago, at 2.1 conceptions per 1000 women in 2021.[26] Under-18s constituted 1% of mothers in the 2017 Maternity Services Dataset in England.[31] As multimorbidity increases with age, the prevalence of multimorbidity in this age group is likely to be small too. However, this is an important omission as teenage pregnancies are associated with adverse outcomes.[302]

The data quality check required patients to have at least one year of recorded data. This inclusion criterion is likely to have excluded pregnant women with social risk factors who may frequently move location and change general practice registration. This may result in the underestimation of the prevalence of multimorbidity and underrepresentation of women with under-served characteristics who may have worse outcomes.

Missing data

As discussed in Chapter 2, missing data and unmeasured confounders are key limitations of using routine health records. This is because data were not collected with the primary intention of a research study and may lack rigour. Data were missing for ethnicity, index of multiple deprivation, body mass index and smoking status in Chapter 3. These are unlikely to be missing completely at random. Pregnant women of ethnic minority and deprived background may be less likely to engage with maternity services to have sociodemographic factors collected. Body mass index and smoking status data may be more likely to be collected in women with a clinical

indication, such as risk assessment for contraception or existing long-term conditions. Equally, women who smoke or have high body mass index may not volunteer that information or engage with health services due to social desirability bias. These missing data were treated as separate missing categories in the logistic regression examining risk factors for maternal multimorbidity, which may lead to biased estimates.

Sensitivity analysis was conducted using CPRD, substituting the missing data using other observed data. Missing ethnicity data in CPRD was substituted with linked hospital episodes statistics ethnicity data where available. Sheikh et al recently demonstrated high levels of agreement (93%) between ethnicity recorded in CPRD and linked hospital episodes statistics, although this was lower in the mixed and other ethnic group.[303] Missing patient level deprivation data was substituted with practice level deprivation data. However, this assumes that patients experience the same level of deprivation as the small area their general practices are situated in.[304] Moreover, Mahadevan et al found poor agreement of social economic status data between patient and practice level data in CPRD.[304]

Multiple imputation is the preferred method to handle missing data as it imputes the missing values based on observed data and accounts for uncertainty.[305] This method will be used in the outcome study proposed in Supplementary Material 8.1.

Limitations of the data sources

Unlike SAIL, CPRD Gold does not have whole population coverage, it comprises of general practices that have agreed to contribute data. As of June 2023, CPRD Gold covers just under 5% of the United Kingdom's population.[306] Nevertheless, it is broadly representative of the United Kingdom population when compared to the census.[153] Linked small area data for patient level index of multiple deprivation and hospital episodes statistics are only available for a

subset of English practices.[153] Nine percent of the pregnancy episodes in the CPRD pregnancy register conflicted with another episode (overlapping dates).[307]

The SAIL study cohort was identified from the Welsh National Community Child Health Database. This means it may not capture pregnancies that resulted in early pregnancy loss. This is likely to have contributed to the different gravidity distribution compared to the other datasets, observed in Chapter 3. For the Scottish Morbidity Records, data was only available for two regions, Tayside and Fife. This resulted in a smaller sample size compared to CPRD and SAIL. In addition, medical history data only date back to 2005, potentially missing any long-term conditions diagnosed and last managed before 2005. Additional file 5 (supplementary materials) in Chapter 3 details the limitations specific to each dataset.

Recorded diagnosis

For a diagnosis to be captured in the medical records, a patient first has to present to their clinicians with symptoms and subsequently receiving a diagnosis. There are many factors that can influence the journey to receiving a diagnosis, including ability to access an appointment, the patients' attitude toward medical consultation and beliefs in the cause of their symptoms, and the clinical decisions made by the clinician.[138] As observed in Chapter 3, barriers to accessing health care for stigmatised condition may result in underestimation of the prevalence when using routine health records.

Simple count to measure multimorbidity

Using simple count to measure multimorbidity also means the study in Chapter 3 was not able to account for disease severity. Attempts were made to separate quiescent episodic conditions from conditions needing active management. However, the method would not distinguish between well controlled asthma and brittle asthma or diet-controlled diabetes from insulin dependent diabetes. Multimorbidity is treated as a single entity, with the dose response

relationship limited to increasing counts of long-term conditions. The effect size may consequently be diluted by the larger numbers of milder conditions. Subgroup analysis for specific clusters or combinations of severe health conditions may partially overcome this shortcoming.

8.3.3 Strengths of the core outcome set study

Core outcome set development is a relatively new field, with the COMET initiative first launched in 2010, and the COMET handbook published in 2017.[142 180] The core outcome set developed in this thesis followed the robust methods and the four key steps outlined in the COMET handbook.[142] The scoring process and criteria were described a priori in the study protocol (Chapter 4) and the study was registered on the COMET database.[185] Patient and public involvement representatives were consulted and closely involved throughout the study as described in Chapter 2.

Qualitative component

The initial list of outcomes that are put forward in the Delphi surveys had traditionally been identified through systematic reviews.[143] More recent core outcome set development work has started to incorporate qualitative research to ensure outcomes that are important to service users and service providers are included in the Delphi surveys.[143] The guidance on qualitative methods to inform Delphi surveys in core outcome set development was recently published in 2016.[143] In the latest COMET annual systematic review on core outcome set development studies, 39% of the included studies considered both patients and health professionals views when compiling the initial list of outcomes.[308]

Therefore, the qualitative component (focus groups, Chapter 6) is a strength in this core outcome set development study. It explored outcomes that were important to women with

multimorbidity, their partners and health care professionals. The focus groups allowed participants to hear other's experience and opinions and empowered women and partners to share their experience, be it positive or negative. This shared experience stimulated illuminating discussions. The convening of a multidisciplinary clinical group allowed different specialties to hear each other's perspective when helping women with multimorbidity navigate their pregnancy journey.

Positive outcomes

The concept of salutogenic (positive) outcomes first emerged in the literature search in Chapter 5. Smith et al proposed a shift from risk aversion and prevention to promoting health and understanding what constitutes and contributes to optimum health and well-being in maternity research.[216] Positive framing of outcomes was raised again by health professionals in Chapter 6's focus group. Subsequently, in Chapter 7, pregnancy loss and early childhood deaths were reframed positively as *Survival of the baby* by study participants in the consensus meeting and included in the final core outcome set.

8.3.4 Limitations of the core outcome set study

Challenges encountered in agreeing on a core outcome set

Getting the concept of 'core outcomes' across was a challenge. The focus group discussion often centred on women and clinicians' experience and suggestions on how maternity care could be improved for pregnant women with multimorbidity. This resulted in many care components being identified as 'outcomes', such as 'preconception care', 'postnatal care' and 'perinatal mental health support'. Participants also considered what good care would look like as 'outcomes', such as 'holistic care', 'personalised care' and 'continuity of care'. These can be considered as patient reported experience measures (PREM).[134] Future work is needed to

determine how best to measure them, such as measuring 'satisfaction' or 'quality' of the different care components. As discussed in Chapter 7, the second consensus meeting offered the opportunity to consider the relative importance of process measures compared to long-term outcomes as a result of these process measures. Ultimately participants voted in favour of the latter. Nevertheless, these findings offer some insights to what good care looks like to pregnant women with multimorbidity and their clinicians.

In Chapter 4, the prespecified scope of the core outcome set was broad. It covered both maternal and offspring outcomes. A life course approach was taken spanning all stages of pregnancy and offspring's life course. The core outcome set was to be used in both observational and interventional studies. The outcomes that emerged in Chapters 5 and 6 were therefore categorised using this prespecified framework of maternal and offspring outcomes across different time frame. This framework helped consideration of coverage of key outcome domains in the consensus meetings in Chapter 7.

The challenge of incorporating a broad range of outcomes in a concise core outcome set was observed in Chapter 7, where the initial list at the end of the Delphi surveys first consensus meeting included 52 outcomes (inclusion threshold 70% of all participants). This necessitated the conduct of a second consensus meeting with a higher inclusion threshold (80%) which resulted in 11 final core outcomes.

The number of core outcomes will be higher in obstetric research where both maternal and children's outcomes are considered. This is also the case for core outcome sets with a broad scope and applicability. Devane 2007's core outcome set for maternity care included 48 outcomes;[133] Nijagal 2018's for pregnancy and childbirth included 24 outcomes.[134] In Österberg et al's systematic review, amongst the 27 published core outcome set related to pregnancy and childbirth, the number of core outcomes ranged from six to 51, with a median

of 13.[131] Only six of the core outcome set had 10 or less core outcomes, most studies used a 70% inclusion threshold.[131] Österberg et al's review highlighted the need for future consideration and guidance on how extensive the scope of core outcome sets can be and the optimal number of core outcomes to increase the usability of core outcome sets.[131]

Representation in the core outcome set study

Under-served communities

The sampling matrix outlined in Chapter 4 included social risk factors for pregnant women as discussed in Chapter 1. This included under-served characteristics such as survivors of domestic abuse, migrants, disabled people, and people who misuse substance and alcohol. However, we did not ask for participants' postcodes to determine social deprivation indices. Education level was used as a proxy instead. As the inclusion criteria to ensure data quality in Chapter 3 likely under-represented pregnant women with social risk factors, the recruitment strategy in Chapters 6 and 7 engaged with organisations and charities that support pregnant women with under-served characteristics (see Acknowledgement section in the respective chapters).

Recruitment through organisations, charities, support groups and social media

Although focus groups and consensus meeting participants were reimbursed, we were not able to reimburse organisations for supporting recruitment. The nature of multimorbidity meant needing to reach out to a large number of organisations for health conditions and for under-served communities. This can have huge cost implications. Some small charities are run by unpaid volunteers and therefore do not have the capacity to support research recruitment.

The potential of social media in study recruitment has been documented in the literature. Darmawan et al's scoping review on the role of social media in clinical trial recruitment included 33 studies; the proportion of participants enrolled through social media ranged from

0% to 86%.[309] Baker et al shared their experiences of social media recruitment for an eczema online monitoring trial.[310] The social media platforms recruited an ethnically diverse participant population (12% Asian, 5% mixed ethnicity, 4% black) and a wide geographical reach.[310] Pekarsky et al recruited 324 pregnant women to a longitudinal observational study over a seven months period in Canada however women with lower education and income were under-represented.[311] All these studies were based in English-speaking high-income countries.

Conducting research online

Despite the digital exclusion that comes with social media recruitment and the online research platforms, it enabled wide geographical reach and much flexibility to participants. Some of the focus group participants chose to switch off their cameras and use the chat functions to express their views.

With the acceleration of online study methods during the COVID-19 pandemic, attention has been drawn to fraudulent participation driven by financial incentives. Ridge et al listed indicators of potential imposter participants, such as specific patterns of email responses and timings, vague and generic answers in interviews, preferring video interview options with cameras turned off and reticence to disclose telephone number.[312]

However, given the vulnerability of participants with social risk factors, some will have legitimate reasons for wanting to maintain their anonymity in group meetings. As financial incentives were not offered for Chapter 7's Delphi surveys and given the time commitment required to complete the long surveys, fraudulent responses were less likely to have occurred.

Generalisability limited to high-income English-speaking countries and participants

The initial aim was to develop a core outcome set for studies of pregnant women with multimorbidity that is applicable to all settings. The literature search to generate the initial list

of outcomes was not limited to English language. However, the focus groups were conducted in the United Kingdom. Although efforts were made to recruit internationally for the Delphi surveys and consensus meeting, there was still limited representation from low- and middle-income countries, especially from patient stakeholders. The survey and consensus meetings were conducted in English and online, limiting participation to those who are fluent in English and have digital access. In addition, the epidemiology of long-term conditions is likely to differ in developed and developing countries, with non-communicable disease dominating in the former and communicable disease in the latter. Therefore, the resulting core outcome set is more applicable to a high-income country setting.

Attrition

As discussed in Chapter 7, the attrition rate for the Delphi surveys was high but not dissimilar to that observed in other core outcome set studies.[130] The high attrition rate risked responder bias where the opinions of those who were loss to follow up may differ from those who completed the study. As we anticipated further widening of the imbalance in stakeholder with further attrition, we shorten the Delphi surveys to two rounds instead of three. Attrition analysis in Chapter 7 examined the first Delphi survey scoring pattern for those who did or did not complete the second Delphi survey. The observed different scoring patterns did not change whether the outcomes reached *Consensus in* in the first Delphi. Strategies that future studies can consider include keeping the Delphi survey to the minimum two rounds.[142] Future studies can also consider using a 5-point Likert scale instead of a 9-point Likert scale to improve the viewing experience on portable devices.

8.4 Clinical, policy and research implications

8.4.1 High prevalence of maternal multimorbidity

Maternal medicine network for complex pregnancies

Chapter 3 found one in five pregnant women had pre-pregnancy multimorbidity. This high prevalence has implications for maternity service provision to meet the needs of this population before, during and after pregnancy. The Ockenden report recommended that women with pre-existing medical conditions should have access to specialist preconception care.[112] It also recommended the development of maternal medicine specialist centres as a regional hub and spoke model for the management of complex pregnancies.[112]

Subsequently, the Maternal Medicine Network was established in 2021 to provide regional clinical leadership, integrate local relevant networks (e.g. perinatal mental health network, neonatal networks) and host multidisciplinary meetings to discuss complex high risk pregnancies.[114] The model would ensure multidisciplinary team working consisting of maternal medicine obstetrician, obstetric physician and midwives.[114]

Care pathways depended on the complexity of the medical conditions and local expertise, (see Chapter 1.6 for examples) and should remain as local as compatible with the care needs.[114] The referral criteria should reflect the increased vulnerability of women with social risk factors.[114] Some of the health conditions in Chapter 3 on its own may not qualify a referral, but may do so in the context of multimorbidity. Future work is needed to incorporate maternal multimorbidity in the Maternal Medicine Network referral criteria.

As of March 2023, there is at least one specialist centre in every region of England, enabling pregnant women with pre-existing medical conditions to access help quickly if needed.[313]

However, the final Ockenden report acknowledged the shortfall of obstetric physicians and the need for sustainable workforce training and planning.[112]

Maternal multimorbidity in current context

Chapter 3 reported the prevalence of maternal multimorbidity in 2018. The analysis was conducted in 2020-2021. Decision was made to avoid using data from the COVID-19 pandemic period, as changes in health seeking behaviour and health service configuration would affect the observed health patterns. Indeed analysis using CPRD and SAIL data showed a fall in new diagnosis of long-term conditions post-2020 when compared to expected rates.[314 315] In SAIL (2020-2021), the largest deficit in incidence was in chronic obstructive pulmonary disorder (38%), followed by depression, type 2 diabetes, hypertension, anxiety disorders, and asthma.[314] A general practice with 10000 patients may have over 400 undiagnosed long-term conditions.[314]

The delay in diagnosis and management of new long-term conditions is likely to lead to worse outcomes.[315] Untreated conditions can lead to development of additional downstream long-term conditions and contribute to multimorbidity, for example untreated hypertension or atrial fibrillation can lead to heart failure.[315] Moreover, given the upward trend of multimorbidity in general, maternal age, maternal obesity and maternal single long-term conditions,[8 26 28 31 32] it is likely that the prevalence of maternal multimorbidity is even higher in present times.

The delivery of maternity services was also affected during the COVID-19 pandemic, a recurring theme being reduction in antenatal appointments and increase in remote consultation.[316-320] A national survey that included just under half of all United Kingdom obstetric units found 89% reported using remote consultation method.[317] However, as we move out of the pandemic, a key message from MBRRACE 2022 for the care of pregnant women

with multimorbidity was the need to triage appropriate assessment method for those with mental health needs.[60] Face-to-face assessment may be necessary in some circumstances.[60]

8.4.2 Maternal mental health conditions

In Chapter 3, mental health conditions had the highest prevalence in pregnant women, one in five pregnant women had depression or anxiety. This reaffirms the importance of maternal mental health. Improving access to perinatal mental health services is one of ten national programme work streams in the Maternity Transformation Programme.[109] It is also one of the commitment of the National Health Service Long Term Plan.[111] As such, specialist perinatal mental health community services are now available in all local National Health Services area in England.[321]

However, the prevalence of mental health conditions was lower in ethnic minority groups. This suggest there may be inequality in accessing health care to manage these conditions. This is especially significant as psychiatric and cardiac conditions were both leading causes of maternal death in the MBRRACE 2022 report.[60] In Chapter 6, a focus group participant spoke about mental illness being a taboo in certain ethnic minority groups. This was also a key learning point from MBRRACE 2022.[60] Therefore, health and social care professionals need to be aware that cultural stigma may influence the willingness of the women and her family to disclose mental health concerns.[60]

In Chapter 3, amongst pregnant women with multimorbidity, 70% had mental health conditions. In Chapter 6's focus group, participants discussed about how physical health conditions impact on mental health conditions, and vice versa. However, MBRRACE 2022 demonstrated the general lack of consideration of the interaction between physical and mental symptoms amongst health care professionals.[60] Therefore the findings from this thesis and the

MBRRACE report emphasise the importance of non-mental health specialist (in MBRRACE's case, diabetes specialist) being able to recognise and manage non-severe mental health conditions and make timely referral to psychiatry where indicated.[60]

8.4.3 Smoking and raised body mass index

Chapter 3's logistic regression examining risk factors for maternal multimorbidity unexpectedly did not find an association with social deprivation. However post hoc analysis suggests that this partially may have been due to some common conditions being less prevalent in deprived population, likely due to inequality of health care access. Post hoc analysis also found the association with social deprivation was attenuated when smoking and body mass index were adjusted for. This suggests that smoking and body mass index may mediate the association of social deprivation with maternal multimorbidity; these factors were on the causal pathway instead of being confounders.

These risk factors are already known to be present in the general pregnant population, with higher rates in deprived population. Data from the English Maternity Services Dataset showed that 13% of pregnant women were current smokers and 22% were obese at their booking appointment.[31] Smoking and obesity rates at booking appointment were higher in the most deprived than the least deprived area (25% versus 4% for smoking, 24% versus 14% for obesity).[31] In addition to this, Chapter 3 showed that pregnant women with multimorbidity were more likely to have smoked and have high body mass index than those without multimorbidity.

The cross-sectional design of the study limits the ability to draw any conclusions on causality. The last recorded smoking and body mass index data before index pregnancy was used and may not necessarily reflect the status at conception. Nevertheless, smoking and obesity are

modifiable risk factors for adverse pregnancy outcomes,[169 170] and for multimorbidity in the general population.[322 323] Chapter 3's findings reaffirm the importance of addressing these risk factors in preconception care, especially for women with multimorbidity. Smoking cessation and weight management interventions in the preconception period may help prevent progression to maternal multimorbidity and reduce the risk of adverse pregnancy outcomes in pregnant women with multimorbidity. This needs to be evaluated in future intervention studies.

8.4.4 Medication during pregnancy

In Chapter 6's focus groups, women spoke at length about wanting information about medication safety during pregnancy and having preconception planning on when to change or stop their regular medications. Health care professionals spoke about women stopping their regular medications, such as psychotropic medications, as soon as they find out they are pregnant or to breastfeed. Health care professionals were mindful to provide a balanced view of the risks and benefits of stopping clinically indicated medications during pregnancy as uncontrolled long-term conditions can also lead to adverse outcomes for the pregnant woman and her unborn child.

A study using CPRD prescribing data from 2000 to 2019 found that one in two pregnant women with multimorbidity were prescribed two or more medications during the first trimester; 13% were prescribed five or more medications.[249] Prescribing data cannot capture whether the medication was actually taken, or taken together, and the medications studied included those used for acute and chronic conditions.[249] Nevertheless, this shows that the challenges related to medication in pregnancy are particularly pertinent to pregnant women with multimorbidity.

MBRRACE recommended that any changes to medications in pregnancy, especially for managing existing conditions, should only be made after careful consideration of the risks and benefits to both mother and child.[60] However, a recent survey and interview study in the United

Kingdom highlighted the difficulty women faced to negotiate medication use during pregnancy due to their own and health care professionals' fear of harm to the fetus.[324] A precautionary approach was taken and prescribing was more restrictive than national guidance.[324] In some instances this led to adverse impact on pre-existing long-term conditions (e.g. stopping asthma medication leading to hospitalisation).[324] This fear stems from the lack of information on medication safety in pregnancy: 73% of medications have no safety information in pregnancy, as pregnant women are often excluded from clinical trials.[24] The Healthy Mum, Healthy Baby, Healthy Future report calls for effective advocacy of safe medicines evaluation and development in pregnancy.[325] For pregnant women with multimorbidity, this includes evaluation of medication interaction in polypharmacy.

8.4.5 Experience of maternal care and experiential outcomes

In Chapter 6's focus groups, health care professionals shared their experience of providing care to pregnant women with multimorbidity, and women with multimorbidity shared their experience of receiving care in the preconception, antenatal, intrapartum, and postpartum period. Many of these experiences and expectations of what constitute good quality maternity care are universal regardless of whether a woman has multimorbidity or not.[108 326] Findings in Chapter 6 overlapped with the key tenets of maternity care set out in Better Births, the National Maternity Review (2016) in England. These included: personalised care, continuity of carer, better postnatal and perinatal mental health care, and multi-professional working.[108] The latest English Care Quality Commission National Maternity Survey 2022 showed improvement in perinatal mental health support, however there remains area of improvement for postnatal care.[326] The importance of continuity of carer and birth experience are illustrated as follows.

In a Cochrane review (2016) that included 15 trials, women who had midwife-led continuity models of care were less likely to experience preterm birth (average relative risk [RR] 0.76,

95% CI 0.64 to 0.91) and fetal loss or neonatal death (average RR 0.84, 95% CI 0.71 to 0.99).[327] It also had higher rates of maternal satisfaction (narrative synthesis).[327] Despite high quality evidence of positive benefit, this model of care is commonly contested and there are barriers to its implementation.[328-330] Concerns of staffing level has led to it being suspended following the Ockenden review.[112]

Bell et al's systematic review included 15 studies (12 quantitative and three qualitative) and found that women's birth experience was associated with maternal care giving attitude and behaviours. Negative birth experience and poor quality of care led to poor maternal infant bonding, maternal anxiety, low maternal confidence and attempts to overprotect or overcompensate.[331]

The World Health Organisation recognised positive antenatal, intrapartum and postnatal experience as significant end points for all pregnant women, upon which its guidelines for maternal and newborn care were based on.[332-334] This was informed by a systematic review of women's view on what matters in pregnancy.[335] Eight databases were searched, all continents were represented except Australia.[335] A positive pregnancy experience mattered across all cultural and sociodemographic context.[335] Positive experience laid the foundation for improved short and long-term health and wellbeing and motherhood.[332 334]

Despite the importance of these patient reported measures, a systematic review in 2019 did not identify any PROM suitable and specific for assessing quality of care during pregnancy or after childbirth.[336] In their pregnancy and childbirth core outcome set work, Nijagal et al also noted the lack of PROM in routine maternity care, and mapped their core outcomes to PROM used in general, non-maternity populations or those proven useful in research studies.[134] The systematic literature search in Chapter 5 did not identify any studies related to PROM for

pregnant women with multimorbidity. Future work to reach consensus on how to define and measure the core outcomes in Chapter 7 should consider PROM.

Although the focus groups' main aim was not to explore the experience of maternity care for pregnant women with multimorbidity, some key findings are relevant to how maternity care can be improved. Compared to women with no multimorbidity, the need for a holistic management of all their multimorbidity and medications, coordination of appointments and continuity of the care team is particularly important for pregnant women with multimorbidity. The MuM-PreDiCT team is formally investigating this through an interview study with service users and service providers. The key lessons learned would be used to coproduce a list of recommendations of how maternity care can be improved for pregnant women with multimorbidity and their family. Leading on from this, further work is required to develop interventions to optimise disease control for women with multimorbidity prior to conception, and to provide support in the postnatal and longer-term period both for managing their long-term conditions and their role as a mother.

8.4.6 Societal pressure on mothers

In Chapter 6, women and health care professionals spoke about women's pressure to be the perfect mother and to breastfeed. They also spoke of the guilt women felt due to having multimorbidity and needing to take medications during pregnancy. As described by a study participant, the attitude and language used by health care professional can also add to these negative emotions.

Schmidt et al's scoping review examined the social norms of motherhood in western society and mothers' responses to them.[337] It searched for literature from the last two decades and included 115 studies.[337] The review identified five norms: (i) the *present mother* (expected to provide best care to child), (ii) the *future oriented* mother (ensure child's success), (iii) the

working mother (integrate employment into motherhood), (iv) the *public mother* (being in control), and (v) the *happy mother* (being contented).[337] For example, mothers were expected to breastfeed which is considered a non-negotiable natural phenomenon by campaigns.[337] Guilt was the emotional response most prominently described in included studies, when mothers feel they do not meet the expectations and when reconciling her own needs and her child's needs.[337]

Although these do not translate easily to measurable outcomes, they capture the aspect of experience that are important to pregnant women with multimorbidity. Health care professionals can help by using respectful language, being alert to these negative emotions, provide psychological support and signpost to relevant services.

8.4.7 Partners of pregnant women with multimorbidity

The core outcome set study in Chapters 6 and 7 aimed to involve partners, family members and carers as stakeholders. Patient and public representatives advised having partners attending the focus groups alongside their pregnant partner to focus the discussion on pregnant women with multimorbidity. They also advised on the design of the recruitment materials to target this stakeholder groups, e.g., having a poster targeting fathers, and having images of different family members in the posters. We engaged with father specific organisations, such as Dad Matters, to help with recruitment. Despite this, very few partners were recruited: two in Chapter 6 and one in Chapter 7. Nevertheless, in Chapter 6's focus group where partners participated, participants spoke about partner's dual role as carers, the anxiety they experienced and the need to keep them informed and involved in the care of pregnant women with multimorbidity.

A study examined the association of marital status and multimorbidity in middle aged adults aged 50 to 60 years.[338] The nationally representative sample included 23641 adults from four longitudinal studies in the United Kingdom, United States, Europe and China.[338] People who were not married had higher odds of multimorbidity (socioeconomic and lifestyle factors aOR

1.14, 95% CI 1.08 to 1.21).[338] Another Australian longitudinal study of 13714 women examined the association of social relationship satisfaction (partner, family members, friends, work and social activities) with multimorbidity.[339] Women with the lowest satisfaction score had the highest odds of developing multimorbidity (aOR 2.35, 95% CI 1.94 to 2.83).[339] Both studies used only eight and 11 conditions to measure multimorbidity respectively; self-reporting of marital status and social relationship are prone to social desirability bias. Nevertheless, these findings suggest that social relationship and having a partner may influence whether someone develops multimorbidity.

The role of partners in supporting pregnant women and the importance of their involvement is recognised in Better Births and MBRRACE report.[60 108] The Ockenden report recommends that the care of the mental health and wellbeing of mothers, their partners and the family as a whole should be integral to maternity services.[112] Partly driven by father's mental health campaigns, mental health checks are now conducted for partners of women who access perinatal mental health services.[321 340]

8.5 Future research

8.5.1 Clustering of health conditions

Chapter 3 provided a current snapshot of how pre-pregnancy multimorbidity is distributed in the United Kingdom. As discussed, multimorbidity is highly heterogenous with different combinations of health conditions, disease severity and health consequences. Amongst the combination of health conditions, some tend to co-exist more frequently than others, leading to disease clusters.[1]

The specific combination of health conditions that a person has is important, as illustrated by the concept of concordant and discordant conditions discussed in Chapter 1. In disease

management, concordant clusters may lead to better quality of care due to synergistic care.[341] A patient with diabetes who undergoes annual eye checks may have age related macular degeneration detected earlier.[342] Conversely, discordant clusters may result in competing priorities in disease management and competition for resources.[341] It can alter a treatment regime's risk and benefit ratio and reduce management options.[342] For example, beta blockers may not be suitable for manging heart failure in a patient with asthma.[342]

One way to start understanding how health conditions accumulate or relate to each other is through clustering analysis. This was identified as a research priority by The Academy of Medical Sciences in their report on multimorbidity research priorities.[1] Conditions that cluster together may share causal factors and risk factors.[1] Interventions to target these shared causal factors can prevent the development of health conditions within these multimorbidity clusters in a stepwise or simultaneous manner.[1] Service pathways may also be developed tailored to multimorbidity clusters with the greatest needs.

For example, Zhu et al analysed linked primary and secondary care data in England and identified 20 clusters across four age strata.[343] They further identified that for adults aged 18 to 64, the cluster with the highest mortality comprised psychoactive substance and alcohol misuse; the cluster with the highest service use comprised depression, anxiety and pain.[343] Similarly, Soley-Bori et al's analysis of primary care records in London (England) also found the cluster with the highest rate of increase in primary care consultations when an additional long-term condition develops comprised of alcohol and substance misuse and human immunodeficiency virus infection, followed by the cluster comprised of anxiety and depression.[344]

There are currently many clustering analysis methods available,[345] and attempts at identifying the optimal clustering analysis methods.[346] Most clustering analysis focused on older aged

adults, where cardiometabolic clusters emerged as the dominant cluster with significant health impact.[341] Important multimorbidity clusters are likely to differ in the pregnant population within the reproductive age range. Colleagues within the MuM-PreDiCT wider study group developed clustering methods capable of handling large numbers of health conditions for a pregnant population.[347] The next step would be to further consolidate clustering analysis for pregnant women with multimorbidity and examine the associated impacts on maternal and child outcomes as outlined in a study protocol in Supplementary Material 8.1.

8.5.2 Measurement of core outcomes

Once a core outcome set is developed, the next step is to develop consensus on how each of the core outcomes should be defined or measured.[142] Having one outcome measured in multiple different ways will still preclude meaningful evidence synthesis. For example, following the completion of a core outcome set for pre-eclampsia,[274] Duffy et al conducted another consensus study to standardise the definitions for each of the core outcomes.[348] Eighty-six definitions for the 20 core outcomes were discussed in a consensus meeting.[348] A systematic review on outcome measurement instrument selection for core outcome sets found that of the 337 core outcome set development studies identified from the annual COMET review, only 118 included recommendations on both what and how to measure.[349]

A future consensus study is required to standardise the definitions and measurement instruments for the core outcome set developed in Chapter 7. This can be guided by the COSMIN/COMET guideline which outlines four key steps in selecting outcome measurement instruments (Table 8.1).[277] Some of the key discussion points in the consensus meetings (Chapter 7) would inform Step 1: *Conceptual consideration*. The COSMIN initiative also developed relevant resources including: search filters for finding studies on measurement

properties, protocols, databases for systematic reviews of outcome measurement instruments, and the COSMIN checklist to evaluate the quality of studies on measurement properties.[350]

Table 8.1: Four steps in the selection of outcome measurement instruments for core outcome sets

Steps	**Tasks**
Step 1: C*onceptual consideration*	Consider the construct to be measured and the target population
Step 2: *Finding existing outcome measurement instruments*	Conducting systematic reviews, literature searches or consulting expert opinions
Step 3: *Quality assessment of the outcome measurement instruments*	Evaluate the measurement properties and the feasibility aspects
Step 4: *Generic recommendations*	Selecting only one measurement instrument for each core outcome Using a consensus process for the selection of measurement instruments Applying the minimum selection criteria of high-quality evidence for good content validity, internal consistency, and feasibility

Adapted from Prinsen CA, Vohra S, Rose MR, et al. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" - a practical guideline. Trials 2016;17(1):449.

8.5.3 Association of maternal multimorbidity with maternal and child outcomes

With the guidance of the core outcome set and with the experience gained from the epidemiological study, the next step is to conduct observational studies to quantify maternal and child outcomes for pregnant women with multimorbidity. As highlighted in the focus groups, women and their family want information on the risks of pregnancy to them and their babies. Being armed with information will help them mentally prepare to face possible adverse outcomes. Such information is also crucial for women to make informed decisions on whether to get pregnant, and for their preconception, pregnancy, and postpartum care plans with their health care professionals.

Outcome studies can be conducted with longitudinal cohorts with linked data. One example is the Born in Bradford, a cohort of 13500 children and their parents, born at Bradford Royal Infirmary between 2007 and 2010.[351] Observational studies can also be conducted using linked routine health and social administrative data such as CPRD and SAIL. A study protocol utilising these datasets is outlined in Supplementary Material 8.1.

8.5.4 Other considerations for outcome studies

Participants from the focus groups have also raised important considerations for future studies. One participant discussed the need for exploring ethnic inequality in outcomes. This is pertinent given that recent studies have highlighted ethnic inequality in adverse pregnancy outcomes including maternal death,[76 352] stillbirth,[353] fetal growth restriction[353] and postpartum haemorrhage.[354] Another participant considered whether outcomes could be framed positively. This concept was previously discussed by Smith et al who examined salutogenically focused outcomes of intrapartum interventions in systematic reviews.[216] The authors suggested shifting towards optimum or positive outcomes (health and wellbeing) instead of focusing on averting

adverse outcomes; examples include: maternal satisfaction with care, positive relationship with infant and intact perineum.[216] This approach was taken in Chapter 7 with *Survival of the baby* being used to capture loss or death of the baby at different time points.

8.6 Personal reflection

This doctoral thesis transcends maternal health, health informatics and consensus setting with multistakeholder groups. Here I share my experience and outline some of the key lessons learned that will shape how I practise as a public health physician and a researcher in the future.

8.6.1 My journey

Prior to this PhD, I completed my general practice training before joining the public health training scheme. My time as a general practitioner exposed me to clinical decision support tools such as QRISK that guides decision on starting cardiovascular disease prevention medications.[355] Such tools were developed using primary care routine health records, 'big data'.[356] I learned that real world data can provide useful evidence in circumstances where clinical trials are not possible or challenging, such as in pregnant women. At that time, one area of interest for me was medication safety in pregnancy. As a general practitioner I experienced first-hand the uncertainty of medication use in pregnancy due to the lack of evidence. My interest in health informatics and maternal health led me to join the MuM-PreDiCT consortium, a collaboration between eight universities to study multimorbidity in pregnancy.

8.6.2 Grant application and study coordination skills

In the first year of my PhD, I joined the MuM-PreDiCT team when they were preparing the collaborative grant application. I participated in the process from start to finish. This included

contributing to the grant writing process, especially the work package related to the core outcome set (Chapters 4-7) and outcome study (Supplementary Material 8), participating in patient and public involvement meetings to shape the research questions, preparing materials to support the team in the panel interview, and drafting responses to panel queries.

I gained organisational skills by coordinating meetings, hosting a multidisciplinary workshop to determine what health conditions to include in measuring maternal multimorbidity, setting up the study website,[189] and hosting a virtual dissemination event.[357] I also worked closely with data scientists and clinicians across institutions to harmonise the phenome definitions and data analysis across three datasets for the epidemiology study in Chapter 3. This provided preliminary data to support the grant application.

When the team was successful in the grant application, I joined as a clinical research fellow to lead on one of the work package (Chapters 4-7, Supplementary Material 8). The academic skills and relationships built throughout my PhD will stand me in good stance for future fellowship applications.

8.6.3 Social media and patient and public involvement

Earlier in my career, I was aware of the importance of engaging with social media to build a research profile. However, I was apprehensive after hearing other people's negative experience. The need to recruit attendees to MuM-PreDiCT's first dissemination event, and later study participants, was the catalyst for me to harness social media for research purposes. To do so, I attended relevant webinars hosted by the university, but I learned the most from MuM-PreDiCT's PPI co-investigators. They taught me how to write effective tweets using infographics, relevant hashtags and short and sharp summaries of research findings. Engaging with Twitter also allowed me to keep up to date with relevant new research publications and

events. Beyond Twitter, MuM-PreDiCT's PPI also prompted me to recruit and disseminate research findings on Facebook and Instagram and to write blog posts for the MuM-PreDiCT website.

The greatest joy was working with patient representatives, support groups and charities. As multimorbidity comprises a wide range of health conditions, I was able to work with a large number of health condition focused organisations. Some charities have established process in place for researchers to access research involvement support, such as Crohn's and Colitis UK,[358] Psoriasis Association[359] and Epilepsy Action.[360] This involves filling in an application form, writing lay summaries and liaising with passionate research support staffs. When MBRRACE published their findings that black women were five times more likely to die of childbirth,[361] FIVEXMORE was established to campaign for safe maternity care for black women.[362] Therefore, beyond health condition orientated organisations, I also reached out to maternity advocacy groups for different ethnic groups.

I hosted the first consensus meeting in Chapter 7, and observed two senior clinical academics host the second consensus meeting. Through working closely with PPI members, I learned the importance of pre- and post-meeting preparation and briefing. Strong divergent views were expressed in the stakeholder consensus meeting. I discussed and reflected on how best to resolve these with senior academics. This experience will be invaluable in my future role as a public health clinician, co-producing service pathways with service users.

8.6.4 Language matters

Desexed language

Language used in research or when delivering health and social care matters, as it is integral to people's experience.[363] [364] I was first introduced to the controversy surrounding the use of

desexed language by MuM-PreDiCT's PPI co-investigators. We used additive language 'pregnant women and birthing people' in our research and public facing documents to be inclusive to people who are pregnant or have given birth but do not identify as women.

However, Gribble et al discussed the implications of using desexed language in inherently sexed process such as pregnancy, birth and breastfeeding.[365] One of the consequences includes imprecision and causing confusion, for example, whether '1 in 10 people have endometriosis' includes female only or people of all sexes in the denominator.[365] My correspondence with some potential participants indicated confusion over the term 'birthing people', whether this meant 'birthing partners'. Gribble et al suggested potential strategies such as using explicit inclusivity statements as a rider to documents, as used in the English National Institute for Health and Care Excellence guidelines for antenatal and postnatal care,[365-367] and in this thesis.

Types of birth

Another important report that was published during my PhD was the Re:Birth consultation project by the Royal College of Midwives.[364] Re:Birth aimed to find language around labour and birth that could be shared between maternity service providers and service users.[364] This was driven by the controversy and ambiguity around the term 'normal birth'.[364] The consultation involved nearly 8000 people across the United Kingdom.[364] 'Birth' was widely preferred over 'delivery' as it acknowledges the active part women play.[364] The preferred terms that should be used in clinical and research communications were: spontaneous vaginal birth, induced / augmented labour, birth with forceps / ventouse, and caesarean birth.[364]

Ethnicity and person-centred language

I also learned that the terms 'BAME' (black, Asian and minority ethnic) and BME (black and minority ethnic) should be avoided as they emphasis certain minority groups and exclude others.[368] Where possible, individual ethnic groups should be described instead.[368] Another

resource that I found useful was the English National Institute for Health and Care Excellence style guide.[369] It emphasises person-centred language, such as 'people with diabetes' instead of 'diabetics', with the exception of 'disabled people' and 'autistic people'; people have health conditions, they do not 'suffer' from them.[369]

8.6.5 Ableism and disability

Despite being disabled myself, I first came across the concept of ableism through participants in Chapters 6 and 7. It is a system that values able bodied people.[370] Following the biomedical model of medicine, ableism views a disabled state as needing to be fixed or prevented; whilst the social disability model recognises that disabled people are limited by society's attitude and external environmental factors.[370]

To help me understand participants' perspective more, I read *We've got this: essays by disabled parents*, a book describing the experiences of disabled parents,[371] and wrote a reflective blog post for the MuM-PreDiCT website.[372] Even with the best intentions, health professionals need to be aware of how language used, such as 'wheelchair bound', is perceived negatively by disabled people. In the context of maternity care, ableist language include suggesting termination of pregnancy to a woman whose unborn child was found to have inherited the woman's conditions on antenatal tests; or questioning a disabled woman's ability for motherhood,[371] as highlighted in Chapter 6. I attended an anti-ableism research webinar and remember vividly a disabled speaker sharing how he felt when he saw a public health campaign poster on road safety, featuring a person in a wheelchair as a deterrent.[373] These exposures sparked my interest in disability activism and disability study, which I hope to explore and incorporate in my future career and research.

8.6.6 Disease registry

My engagement with patient charities has prompted me to be more involved with the support group for my own long-term condition. Through this, I learned that members of the Hereditary Spastic Paraplegia Support Group would very much like to have a disease registry. A disease registry would facilitate recruitment to trials should a new intervention becomes available. Building on group memberships, some patient groups have developed disease registries themselves.[374] Through attending webinars on how to build a patient registry targeted at patient groups,[375] I learned about the English National Congenital Anomaly and Rare Disease Registration Services and their co-production of disease registries with patient groups. This is a future piece of work I will embark on after this doctoral thesis, continuing the theme of long-term conditions, albeit in rare diseases, and health informatics.

8.7 Conclusion

There is a high prevalence of pre-pregnancy maternal multimorbidity in the United Kingdom. A core outcome set has been developed using consensus methods to guide future studies of pregnant women with multimorbidity. The next step is to quantify the risks associated with pregnancy in women with pre-existing multimorbidity. This will provide information for women and clinicians to make informed decisions.

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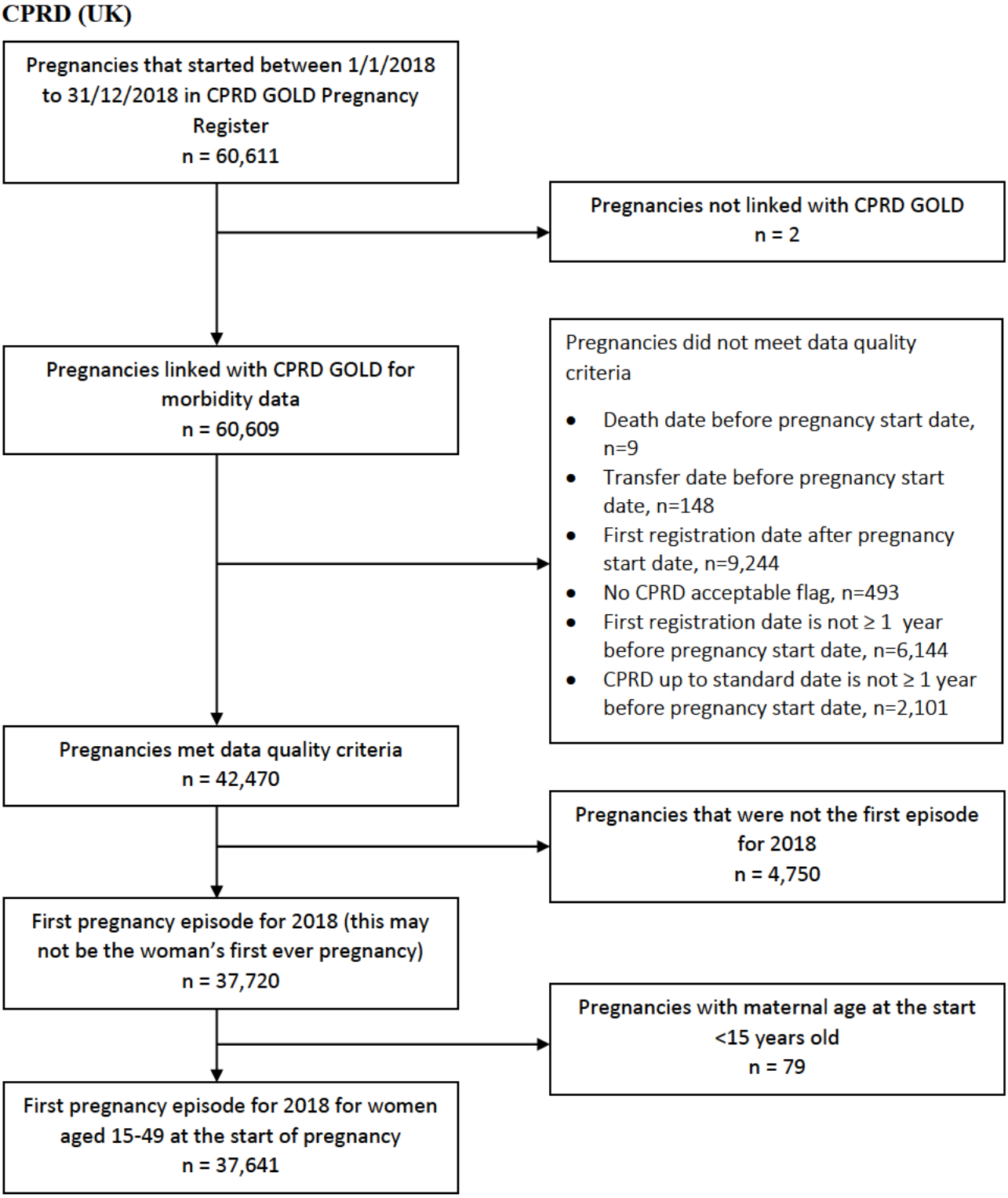
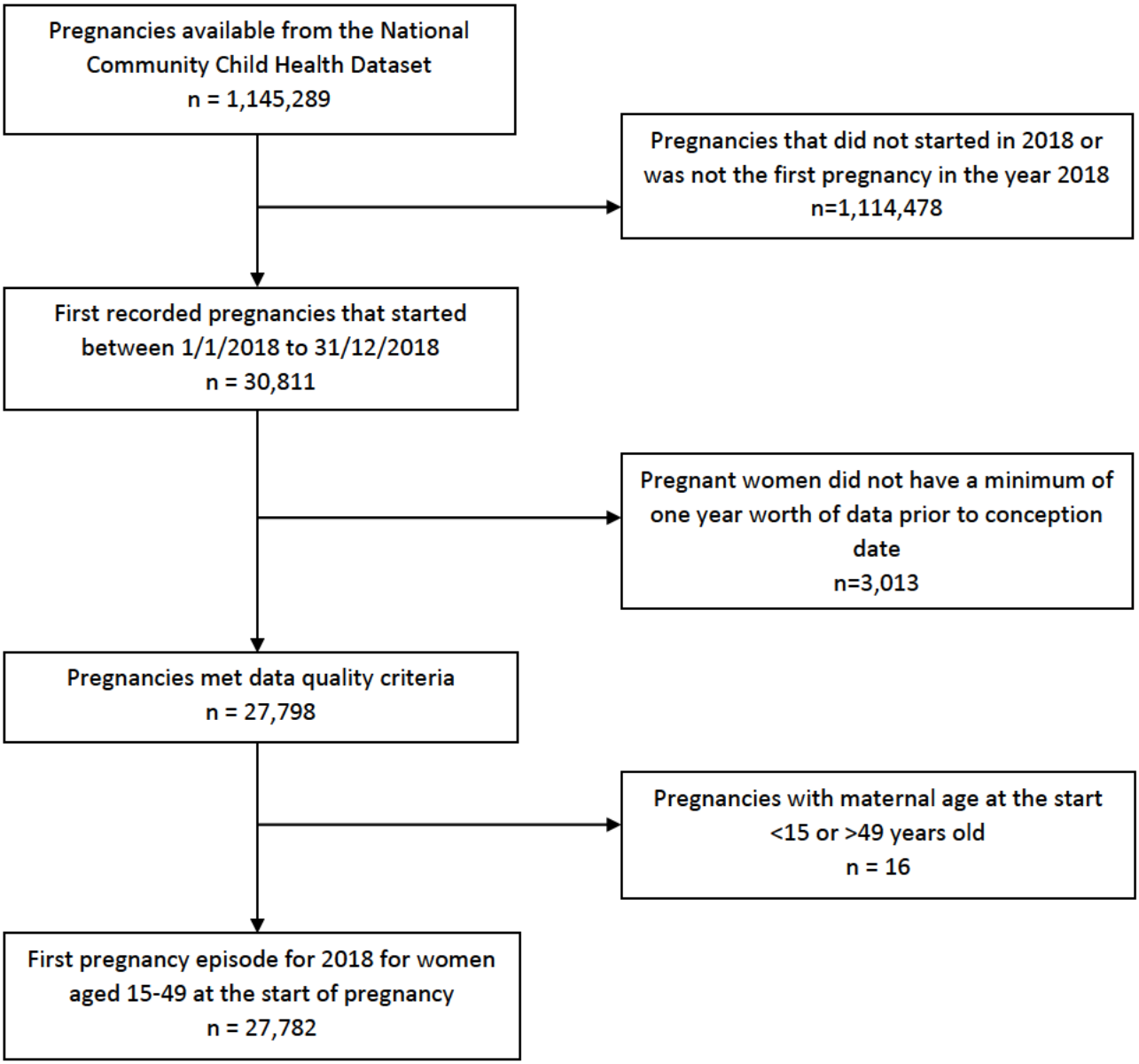
10. Supplementary materials

Chapter 3

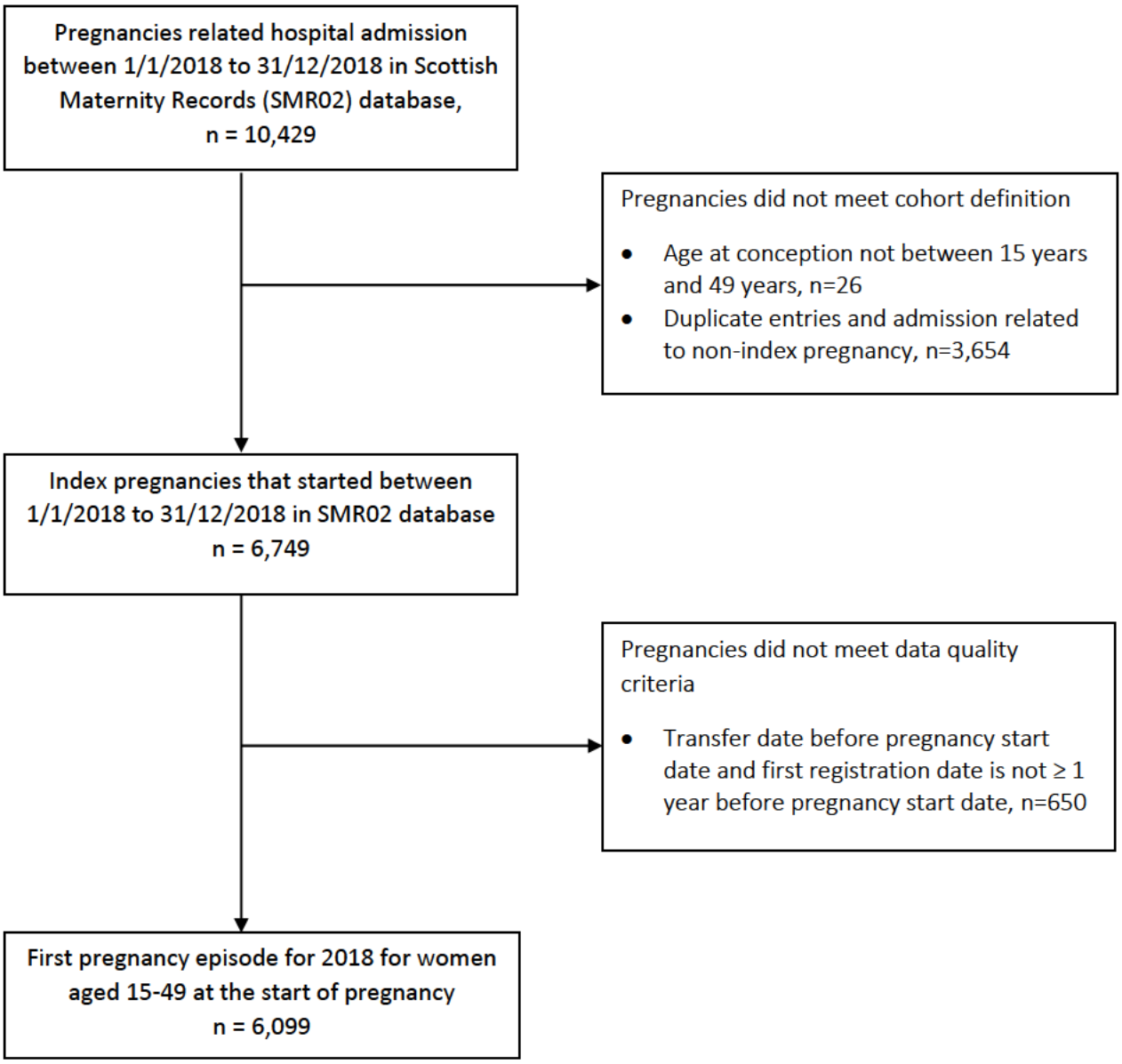
Additional Figure 3.1: Flow chart for selection of study population



SAIL (Wales)


Pregnancies available from the National Community Child Health Dataset
n = 1,145,289
Pregnancies that did not started in 2018 or was not the first pregnancy in the year 2018
n=1,114,478
First recorded pregnancies that started between 1/1/2018 to 31/12/2018
n = 30,811
Pregnant women did not have a minimum of one year worth of data prior to conception date
n=3,013
Pregnancies met data quality criteria
n = 27,798
Pregnancies with maternal age at the start <15 or >49 years old
n = 16
First pregnancy episode for 2018 for women aged 15-49 at the start of pregnancy
n = 27,782

SMR (Scotland: Tayside and Fife)



Additional Table 3.1: Practice level index of multiple deprivation (IMD) quintile by nations in the CPRD 2018 pregnancy cohort

	Patient level*, n (%)		Practice level, n (%)							
Index of multiple deprivation quintile	**England (n=13075)**		**England (n=13075)**		**Northern Ireland (n=2984)**		**Scotland (n=12559)**		**Wales (n=9023)**	
1, least deprived	2326	17.79%	2274	17.39%	284	9.52%	2142	17.06%	1472	16.31%
2	1835	14.03%	2247	17.19%	392	13.14%	2842	22.63%	801	8.88%
3	1878	14.36%	2288	17.50%	718	24.06%	2214	17.63%	2003	22.20%
4	1853	14.17%	2462	18.83%	277	9.28%	2690	21.42%	2244	24.87%
5, most deprived	1908	14.59%	3804	29.09%	1313	44.00%	2671	21.27%	2503	27.74%
Missing	3275	25.05%	-	-	-	-	-	-	-	-

*Available for England only

Additional Table 3.2: Percentage of pregnant women by the total morbidity count in CPRD, SAIL, SMR in 2018

Number of pre-existing long-term health conditions per pregnant woman	Percentage of pregnant women, % (95% confidence intervals)		
	CPRD, n=37641	SAIL, n=27782	SMR, n=6099
0	29.70 (29.24 - 30.17)	31.94 (31.39 - 32.49)	61.99(60.66 - 63.10)
1	26.09 (25.64 - 26.53)	21.90 (21.41 - 22.39)	18.33 (17.36 - 19.30)
2	19.03 (18.63 - 19.43)	17.71 (17.26 - 18.16)	10.18 (9.42 - 10.94
3	11.71 (11.38 - 12.04)	12.54 (12.16 - 12.94)	5.08 (4.53 - 5.63)
4	6.56 (6.31 - 6.81)	7.47 (7.16 - 7.78)	2.43 (2.04 - 2.82)
5	3.51 (3.33 - 3.70)	4.16 (3.93 - 4.41)	1.02 (0.77 - 1.27)
6	1.91 (1.77 - 2.05)	2.26 (2.09 - 2.45)	0.59 (0.40 - 0.78)
7	0.85 (0.76 - 0.95)	1.08 (0.96 - 1.20)	0.20 (0.09 - 0.31)
≥8	0.65 (0.57 - 0.74)	0.95 (0.84 - 1.07)	0.29 (0.16 - 0.42)

Additional Table 3.3: Prevalence of pre-existing multimorbidity in pregnant women in CPRD, SAIL, SMR in 2018 by women's characteristics

Characteristics	Percentage of pregnant women affected by multimorbidity, % (95% confidence intervals)		
	CPRD (UK), n=37641	SAIL (Wales), n=27782	SMR (Scotland), n=6099
All pregnant women	44.21 (43.71 - 44.71)	46.17 (45.58 - 46.75)	19.79 (18.79 - 20.81)
Age categories (5 yearly)			
15-19	27.39 (25.66 - 29.17)	30.38 (28.09 -32.75)	16.11 (12.74 - 19.98)
20-24	40.81 (39.62 - 42.01)	41.72 (40.39 -43.05)	22.23 (19.86 - 24.75)
25-29	44.84 (43.87 - 45.81)	45.69 (44.63 -46.75)	20.77 (18.93 - 22.70)
30-34	45.11 (44.16 - 46.06)	48.83 (47.74 -49.93)	18.56 (16.76 - 20.46)
35-39	49.85 (48.57 - 51.13)	52.61 (50.95 -54.26)	19.18 (16.51 - 22.07)
40-44	53.15 (50.52 - 55.77)	58.21 (54.16 -62.18)	16.67 (10.87 - 23.95)
45-49	58.99 (51.38 - 66.29)	62.86 (44.92 -78.53)	23.07 (5.03 - 53.81)
Gravidity			
1	36.81 (35.93 - 37.70)	42.33 (41.48 -43.18)	16.00 (14.34 - 17.78)
2	41.02 (40.05 - 42.00)	46.79 (45.81 -47.78)	17.22 (15.58 - 18.95)
3	46.24 (45.05 - 47.44)	52.52 (50.79 -54.25)	19.82 (17.51 - 22.29)
4	49.00 (47.44 - 50.56)	58.16 (55.09 -61.19)	25.17 (21.69 - 28.91)
≥5	59.33 (58.03 - 60.63)	66.73 (62.49 -70.78)	33.89 (30.25 - 37.88)
Missing	- - -	- - -	25.00 (0.63 - 80.59)
Ethnicity			
Asian / South Asian[a]	33.78 (31.17 - 36.47)	33.25 (28.75 -38.00)	10.74 (6.30 - 16.85)
Black	46.97 (43.79 - 50.16)	24.16 (18.07 -31.13)	17.39 (4.95 - 38.78)
Mixed	40.00 (34.46 - 45.74)	44.63 (35.59 -53.94)	25.00 (3.18 - 65.09)
Other	33.52 (29.50 - 37.73)	24.45 (19.03 -30.55)	14.29 (7.83 - 23.19)
White	45.97 (45.30 - 46.65)	50.92 (50.17 -51.66)	21.22 (20.04 - 22.40)
Missing	42.80 (41.97 - 43.64)	38.90 (37.91 -39.89)	14.16 (11.97 - 16.58)

Characteristics	Percentage of pregnant women affected by multimorbidity, % (95% confidence intervals)		
	CPRD, n=37641	SAIL, n=27782	SMR, n=6099
BMI (kg/m^2)			
Underweight (<18.5)	45.85 (43.02 - 48.70)	50.82 (48.05 -53.58)	22.83 (14.72 - 32.75)
Normal Weight (18.5-24.9)	42.80 (41.99 - 43.61)	49.33 (48.32 -50.34)	15.70 (13.88 - 17.65)
Overweight (25-29.9)	47.80 (46.71 - 48.90)	53.57 (52.26 -54.88)	19.60 (17.20 - 22.18)
Obese (30+)	55.57 (54.41 - 56.73)	60.52 (59.20 -61.83)	26.97 (24.56 - 29.50)
Missing	30.52 (29.42 - 31.63)	20.25 (19.24 -21.29)	18.35 (16.77 - 20.01)
Smoking			
Non-Smoker	39.92 (39.28 - 40.57)	41.25 (40.29 -42.21)	15.85 (14.64 - 17.13)
Ex-Smoker	52.13 (50.82 - 53.43)	56.07 (54.98 -57.16)	21.67 (18.96 - 24.57)
Smoker	54.55 (53.46 - 55.63)	60.56 (59.37 -61.74)	32.37 (29.53 - 35.31)
Missing	17.82 (15.78 - 20.01)	4.57 (3.85 -5.38)	17.97 (15.43 - 20.72)
Patient level deprivation quintiles (IMD)	**Patient level IMD data only available for England[b]**		
1, least deprived	45.79 (43.75 - 47.84)	49.30 (48.07 -50.52)	11.36 (9.14 - 13.90)
2	44.47 (42.18 - 46.78)	45.70 (44.37 -47.03)	14.53 (12.44 - 16.83)
3	45.69 (43.42 - 47.97)	46.64 (45.22 -48.07)	19.20 (16.78 - 21.81)
4	45.33 (43.05 - 47.63)	43.01 (41.47 -44.55)	25.54 (23.14 - 28.05)
5, most deprived	44.81 (42.56 - 47.08)	46.22 (44.63 -47.81)	23.96 (21.70 - 26.33)
Missing	43.27 (41.56 - 44.98)	43.89 (42.17 -45.62)	18.90 (16.18 - 21.83)

[a] South Asian for CPRD, Asian for SAIL and SMR

[b] Aggregate IMD quintiles cannot be provided for UK as each nation has its specific IMD; data presented here is patient level IMD for England only (n=13075).

BMI: body mass index, CPRD: Clinical Practice Research Datalink, IMD: Index of Multiple Deprivation, SAIL: The Secure Anonymized Information Linkage databank, SMR: Scottish Morbidity Records

Additional Table 3.4: Sensitivity analysis of CPRD England study cohort (n=13,075) with substitution of missing ethnicity and deprivation data

Substituted data

Missing ethnicity data in CPRD Gold was substituted with ethnicity data from linked Hospital Episodes Statistics. Missing patient level Index of Multiple Deprivation (IMD) was substituted with practice level IMD from the same patient.

Additional Table 3.4a: Substituted data for ethnicity and deprivation data in CPRD England study data

Characteristics	**Original data**		**Substituted data**	
	n	%	n	%
Ethnicity				
Black	490	3.75	525	4.02
Mixed	214	1.64	252	1.93
Other	336	2.57	420	3.21
South Asians	843	6.45	912	6.98
White	8302	63.50	10126	77.45
Missing	2890	22.10	840	6.42
Patient level deprivation quintiles (IMD)				
1, least deprived	2326	17.79	2905	22.22
2	1835	14.03	2275	17.40
3	1878	14.36	2279	17.43
4	1853	14.17	2816	21.54
5, most deprived	1908	14.59	2800	21.41
Missing	3275	25.05	-	-

Additional Table 3.4b: Logistic regression of multimorbidity with substituted ethnicity and IMD data in CPRD England cohort

Characteristics	CPRD (England), n=13075					
	Unadjusted OR (95% CI)			Adjusted OR (95% CI)		
Age categories (5 yearly)						
15-19	Ref	-	-	Ref	-	-
20-24	1.60	(1.34	1.90)	1.19	(0.99	1.44)
25-29	1.80	(1.52	2.12)	1.23	(1.02	1.48)
30-34	1.84	(1.56	2.17)	1.28	(1.07	1.54)
35-39	1.95	(1.64	2.32)	1.30	(1.07	1.58)
40-44	2.55	(2.04	3.20)	1.65	(1.29	2.10)
45-49	2.98	(1.74	5.11)	1.82	(1.04	3.18)
Gravidity						
1	Ref	-	-	Ref	-	-
2	1.07	(0.97	1.18)	0.98	(0.89	1.08)
3	1.35	(1.22	1.50)	1.18	(1.05	1.31)
4	1.52	(1.35	1.72)	1.29	(1.14	1.47)
≥5	2.11	(1.90	2.35)	1.68	(1.50	1.89)
Ethnicity						
Black	0.72	(0.60	0.86)	0.69	(0.57	0.83)
Mixed	0.88	(0.69	1.14)	0.94	(0.73	1.22)
Other	0.49	(0.40	0.61)	0.54	(0.44	0.67)
South Asian	0.60	(0.52	0.69)	0.65	(0.56	0.75)
White	Ref	-	-	Ref	-	-
Missing	0.54	(0.46	0.62)	0.62	(0.53	0.73)
BMI (kg/m^2)						
Underweight (<18.5)	0.89	(0.73	1.07)	0.93	(0.76	1.13)
Normal Weight (18.5-24.9)	Ref	-	-	Ref	-	-
Overweight (25-29.9)	1.20	(1.10	1.31)	1.16	(1.06	1.27)
Obese (30+)	1.69	(1.53	1.86)	1.60	(1.44	1.76)
Missing	0.60	(0.54	0.67)	0.74	(0.65	0.83)
Smoking						
Non-Smoker	Ref	-	-	Ref	-	-
Ex-Smoker	1.62	(1.47	1.78)	1.40	(1.27	1.55)
Smoker	1.69	(1.54	1.84)	1.57	(1.43	1.73)
Missing	0.31	(0.24	0.41)	0.50	(0.37	0.66)
Patient level deprivation quintiles (IMD)						
1, least deprived	Ref	-	-	Ref	-	-
2	0.88	(0.79	0.99)	0.88	(0.79	0.99)
3	1.03	(0.93	1.15)	0.97	(0.86	1.08)
4	0.94	(0.85	1.05)	0.89	(0.79	0.99)
5, most deprived	0.98	(0.88	1.08)	0.90	(0.81	1.01)

Additional Table 3.5: Post hoc logistic regression with multimorbidity defined using list of 31 conditions from Barnet et al's paper

Our study did not observe that multimorbidity was associated with increasing levels of social deprivation. To explore whether this is due to the list of conditions we used to define multimorbidity, we repeated the logistic regression in a model where multimorbidity was defined by the list of conditions used in Barnet et al's seminal paper [6].

Barnet et al's study found that multimorbidity increased with social deprivation across different age groups. However, their study included both male and female as well as the elderly population. We included the list of conditions that overlapped with our study and where possible used similar phenome definitions.

Additional Table 3.5a: List of conditions in the post hoc analysis with multimorbidity defined using list of 31 conditions from Barnet et al's paper.

31 conditions that were included in this post hoc analysis	**Conditions that were not included in this post hoc analysis**	
	Present in Barnet et al's study but not in this study	**Present in this study but not in Barnet et al's study**
Hypertension	Painful conditions	Congenital heart disease
Active depression	Treated constipation	Valvular disease
Active asthma	Diverticular disease	Cardiomyopathy
Ischemic heart disease/ myocardial infraction	Peripheral vascular disease	Autoimmune skin conditions
Peptic ulcer disease	Prostate disorders	Other skin conditions
Diabetes mellitus	Glaucoma	Allergic rhinoconjunctivitis
Hyper/hypothyroidism	Dementia	Cataract
Systemic lupus erythematosus/Inflammatory arthritis/Spondylarthritis	Chronic sinusitis	Diabetic retinopathy
Profound deafness	Parkinson's disease	Inflammatory eye disease
Chronic obstructive pulmonary disease		Retinal detachment
Active anxiety		Coeliac disease
Irritable bowel syndrome		Cholelithiasis
Active cancer in last 5 years		Polycystic ovarian syndrome
Substance misuse		Endometriosis
Alcohol misuse		Leiomyoma (fibroids)
Stroke / transient ischemic attack		Female infertility
Chronic kidney disease		Venous thromboembolism
Atrial fibrillation		Primary thrombocytopenia
Heart failure		Haemophilia
Epilepsy		Pernicious anaemia
Severe mental illness		Sickle cell disease
Active eczema / psoriasis		Neurodevelopmental disorder (Attention deficit hyperactive

		disorder, autistic spectrum disorder)
Inflammatory bowel disease		Other mental health conditions
Active migraine		Scoliosis
Severe blindness		Vertebrae disorders
Eating disorder		Osteoarthritis
Learning disability		Chronic back pain
Bronchiectasis		Osteoporosis
Multiple sclerosis		Other chronic headaches
Chronic viral hepatitis		Spina bifida
Chronic liver disease		Idiopathic intracranial hypertension
		Peripheral neuropathy
		Obstructive sleep apnoea
		Interstitial lung disease
		Pulmonary hypertension
		Cystic fibrosis
		Sarcoidosis
		Urolithiasis
		Hyperparathyroidism
		Pituitary disorder
		Adrenal benign tumours
		Human immunodeficiency virus infection / acquired immunodeficiency syndrome
		Turner’s syndrome
		Marfan’s syndrome
		Solid organ transplant

* Active disease phenome definition as outlined in Additional File 3.3.

Additional Table 3.5b: Logistic regression models with multimorbidity defined using 31 conditions in Barnet et al's paper,[6] in CPRD England (n=13,075)

Model	Index of multiple deprivation (IMD) quintiles	Odds ratio (95% confidence intervals)	p value
Model 1	1, Least deprived	Reference	-
Patient level IMD	2	1.09 (0.91 to 1.31)	0.354
	3	1.24 (1.03 to 1.48)	0.021
	4	1.32 (1.11 to 1.58)	0.002
	5, Most deprived	1.28 (1.07 to 1.53)	0.006
	Missing	1.06 (0.90 to 1.25)	0.493
Model 2	1, Least deprived	Reference	-
Model 1 + Maternal age	2	1.11 (0.92 to 1.33)	0.279
	3	1.27 (1.06 to 1.52)	0.010
	4	1.36 (1.14 to 1.63)	0.001
	5, Most deprived	1.34 (1.11 to 1.60)	0.002
	Missing	1.08 (0.91 to 1.27)	0.376
Model 3	1, Least deprived	Reference	-
Model 2 + Ethnicity	2	1.11 (0.92 to 1.34)	0.266
	3	1.28 (1.07 to 1.54)	0.008
	4	1.45 (1.21 to 1.74)	<0.001
	5, Most deprived	1.43 (1.20 to 1.72)	<0.001
	Missing	1.10 (0.94 to 1.30)	0.235
Model 4	1, Least deprived	Reference	-
Model 3 + Gravidity	2	1.10 (0.91 to 1.33)	0.302
	3	1.24 (1.03 to 1.48)	0.024
	4	1.35 (1.12 to 1.62)	0.001
	5, Most deprived	1.30 (1.08 to 1.57)	0.005
	Missing	1.06 (0.90 to 1.25)	0.504
Model 5	1, Least deprived	Reference	-
Model 4 + Body mass index categories	2	1.08 (0.89 to 1.30)	0.435
	3	1.19 (0.99 to 1.43)	0.068
	4	1.26 (1.05 to 1.51)	0.015
	5, Most deprived	1.22 (1.02 to 1.47)	0.033
	Missing	1.02 (0.86 to 1.20)	0.809
Model 6	1, Least deprived	Reference	-
Model 5 + Smoking status	2	1.03 (0.85 to 1.25)	0.753
	3	1.10 (0.92 to 1.33)	0.303
	4	1.13 (0.94 to 1.36)	0.194
	5, Most deprived	1.05 (0.87 to 1.27)	0.583
	Missing	0.97 (0.82 to 1.14)	0.702

Additional Table 3.6: Post hoc logistic regression removing conditions that were associated with less deprived IMD quintiles in CPRD England study cohort (n=13,075)

This post hoc analysis was performed to further test our hypothesis that the lack of association of multimorbidity with social deprivation may be due to the health conditions used to define multimorbidity.

To identify health conditions that were associated with less deprived social economic status, the list of 79 health conditions in this study was each tested with linear regression against patient level index of multiple deprivation (IMD) quintiles (1 being least deprived, 5 being most deprived, missing values not substituted). IMD quintiles were treated as continuous variables in the linear regression to produce a single effect size.

The following eight health conditions were found to be associated with less deprived socio-economic background. The logistic regression was repeated using the remaining 71 health conditions in the CPRD England dataset.

Additional Table 3.6a: Linear regression of eight health conditions that were significantly, negatively associated with the Index of Multiple Deprivation

Health conditions	Coefficient	95% confidence intervals		p value
Endometriosis	-0.004	-0.006	-0.002	<0.001
Irritable bowel syndrome	-0.008	-0.012	-0.004	<0.001
Female infertility	-0.006	-0.009	-0.003	<0.001
Polycystic ovarian syndrome	-0.006	-0.009	-0.003	0.001
Hyper/hypothyroidism	-0.003	-0.006	-0.001	0.009
Anxiety	-0.007	-0.012	-0.002	0.012
Vertebrae disorders	-0.002	-0.003	-0.000	0.014
Inflammatory arthritis	-0.002	-0.003	-0.000	0.024

Additional Table 3.6b: Logistic regression with multimorbidity defined by 71 health conditions in the CPRD England dataset.

Model	IMD quintiles	Odds ratio (95% confidence intervals)	p value
Model 1	1, Least deprived	Reference	-
Patient level IMD	2	1.07 (0.94 to 1.22)	0.326
	3	1.12 (0.99 to 1.28)	0.082
	4	1.22 (1.07 to 1.39)	0.002
	5, Most deprived	1.25 (1.10 to 1.42)	0.001
	Missing	1.01 (0.90 to 1.14)	0.807
Model 2	1, Least deprived	Reference	-
Model 1 + Maternal age	2	1.08 (0.95 to 1.24)	0.234
	3	1.15 (1.01 to 1.31)	0.041
	4	1.26 (1.10 to 1.44)	0.001
	5, Most deprived	1.30 (1.14 to 1.49)	<0.001
	Missing	1.03 (0.92 to 1.16)	0.616
Model 3	1, Least deprived	Reference	-
Model 2 + Ethnicity	2	1.09 (0.95 to 1.24)	0.225
	3	1.16 (1.01 to 1.32)	0.032
	4	1.32 (1.15 to 1.50)	<0.001
	5, Most deprived	1.37 (1.20 to 1.57)	<0.001
	Missing	1.05 (0.93 to 1.18)	0.419
Model 4	1, Least deprived	Reference	-
Model 3 + Gravidity	2	1.08 (0.94 to 1.23)	0.283
	3	1.12 (0.98 to 1.28)	0.103
	4	1.23 (1.08 to 1.41)	0.002
	5, Most deprived	1.26 (1.10 to 1.44)	0.001
	Missing	1.01 (0.90 to 1.14)	0.859
Model 5	1, Least deprived	Reference	-
Model 4 + Body mass index categories	2	1.05 (0.92 to 1.20)	0.501
	3	1.06 (0.93 to 1.21)	0.392
	4	1.14 (1.00 to 1.31)	0.053
	5, Most deprived	1.18 (1.03 to 1.36)	0.015
	Missing	0.97 (0.86 to 1.09)	0.595
Model 6	1, Least deprived	Reference	-
Model 5 + Smoking status	2	1.02 (0.89 to 1.17)	0.773
	3	1.01 (0.88 to 1.16)	0.873
	4	1.07 (0.93 to 1.23)	0.328
	5, Most deprived	1.08 (0.94 to 1.24)	0.284
	Missing	0.94 (0.83 to 1.06)	0.308

Additional Table 3.7: Prevalence of individual health conditions in pregnant women aged 15-49 years in CPRD, SAIL, SMR in 2018

No	Health conditions[a]	Percentages, %		
		CPRD, n=37641	SAIL, n=27782	SMR, n=6099
	Cancer			
1	All cancers	0.51	0.60	0.57
	Primary breast cancer	0.07	0.06	<0.08
	Primary lung cancer	<0.01	0.00	<0.08
	Primary bowel cancer	<0.01	<0.02	<0.08
	Primary cervical cancer	0.03	0.03	0.08
	Primary ovarian cancer	<0.01	0.03	<0.08
	Primary uterine cancer	<0.01	<0.02	<0.08
	Primary thyroid cancer	0.05	0.03	<0.08
	Primary skin cancer (excluding basal cell carcinoma)	0.18	0.27	0.15
	Lymphoma	0.07	0.08	<0.08
	Leukaemia	0.03	0.04	<0.08
	Metastatic cancer	<0.01	<0.02	0.10
	Cardiovascular			
2	Hypertension	0.87	0.67	0.93
3	Ischemic heart disease	0.07	0.18	<0.08
4	Heart failure	0.07	0.07	<0.08
5	Stroke / transient ischemic attack	0.20	0.17	<0.08
6	Atrial fibrillation	0.05	0.03	<0.08
7	Congenital heart disease	0.67	0.76	<0.08
8	Valvular heart disease	0.15	0.14	<0.08
9	Cardiomyopathy	0.05	0.02	<0.08
	Dermatology			
10	Atopic eczema	3.06	3.97	6.35
	Atopic eczema (active)	1.58	1.80	3.36
11	Psoriasis	3.90	3.62	0.71
	Psoriasis (active)	1.46	1.20	0.36
12	Autoimmune skin conditions	0.73	0.86	<0.08
	Vitiligo	0.26	0.30	<0.08
	Alopecia areata	0.48	0.57	<0.08
13	Other skin conditions	5.47	5.71	0.31
	Other skin conditions (active)	1.46	1.43	-
	Seborrheic dermatitis	2.60	3.02	<0.08
	Seborrheic dermatitis (active)	0.79	0.87	-
	Rosacea	2.22	1.98	<0.08
	Rosacea (active)	0.45	0.33	-
	Hidradenitis suppurativa	0.80	0.90	0.15
	Hidradenitis suppurativa (active)	0.24	0.26	-

	Lichen planus	0.10	0.08	<0.08
	Lichen planus (active)	0.01	<0.02	-
	Ear nose throat			
14	Allergic Rhinoconjunctivitis	16.35	18.53	7.56
	Allergic Rhinoconjunctivitis (active)	1.27	3.17	3.34
15	Profound deafness	0.19	0.32	0.16
	Eye			
16	Severe blindness	0.02	0.21	<0.08
17	Cataract	0.11	0.18	<0.08
18	Diabetic eye disease *(retinopathy, maculopathy)*	0.39	0.34	<0.08
19	Inflammatory eye conditions *(uveitis, scleritis, episcleritis)*	0.55	0.65	<0.08
20	Retinal detachment	0.09	0.09	<0.08
	Gastrointestinal			
21	Inflammatory bowel disease	0.60	0.58	0.38
	Crohn's disease	0.33	0.28	0.25
	Ulcerative colitis	0.31	0.34	0.18
22	Irritable bowel syndrome	7.97	7.83	3.16
23	Coeliac disease	0.41	0.40	<0.08
24	Peptic ulcer disease *(or gastroesophageal reflux disease for SMR)*	0.21	0.14	6.98
25	Cholelithiasis	2.02	2.11	2.15
26	Chronic liver disease	0.42	0.34	<0.08[b]
	Chronic hepatitis B, C	0.22	0.13	<0.08
	Autoimmune liver disease	<0.01	0.03	<0.08
	Chronic alcoholic liver disease	<0.01	<0.02	<0.08
	Non-alcoholic fatty liver disease	0.12	0.10	0.13[b]
	Cirrhosis	0.02	0.04	<0.08
	Gynaecology			
27	Polycystic ovarian syndrome	4.66	3.96	0.25
28	Endometriosis	1.68	1.31	1.05
29	Leiomyoma	0.61	0.33	0.26
30	Female infertility	3.81	-	1.18
	Haematology			
31	Venous thromboembolism	0.65	0.60	0.10
32	Primary thrombocytopenia	0.14	0.19	<0.08
33	Haemophilia	<0.01	<0.02	<0.08
34	Pernicious anaemia	0.20	0.20	<0.08
35	Sickle cell disease	0.01	<0.02	<0.08

	Mental health conditions			
	Common mental health disorders (diagnosis code)			
36	Depression	23.43	24.07	1.71
37	Anxiety	18.98	23.05	1.36
	Anxiety	18.59	22.74	-
	Post-traumatic stress disorder	0.76	0.78	-
	Depression OR Anxiety	30.97	32.26	-
	Common mental health disorders (drug phenome)			
	4 prescriptions in 12 months	20.28	21.99	22.66
	2 prescriptions, minimum 1 month apart, in 6 months[c]	25.23	26.33	28.43
	Common mental health disorders (diagnosis / drug)			
	Diagnosis code OR 4 prescriptions in 12 months for depression or anxiety	35.69	36.22	-
	Common mental health disorders (active)			
	CMHD (drug phenome)	-	-	21.79
	Depression (diagnosis code + drug)	11.50	12.03	-
	Anxiety (diagnosis code + drug)	9.47	11.34	-
	Severe mental illness (diagnosis code)			
	SMI	0.71	0.75	0.46
	Bipolar disorder / affective psychosis	0.47	0.45	0.23
	Schizophrenia / non-affective psychosis	0.33	0.40	0.28
	Severe mental illness (drug phenome)			
	4 prescriptions in 12 months	2.12	1.81	2.26
	2 prescriptions, minimum 1 month apart, in 6 months[c]	2.23	1.87	2.28
	Severe mental illness (diagnosis/drug)			
38	Diagnosis code OR 4 prescriptions in 12 months	2.42	2.07	-
	Improving access to psychological therapies (IAPT, diagnosis code)	0.32	0.00	-
39	Eating disorder	1.88	1.80	<0.08
	Alcohol misuse/dependency			
	Diagnosis code	0.95	2.25	0.59

40	Diagnosis code OR 4 prescriptions in 12 months	0.97	2.25	0.62
	Diagnosis code OR 2 prescriptions, minimum 1 month apart, in 6 months)[c]	0.98	2.26	-
	Substance misuse/dependency			
	Diagnosis code	1.98	2.20	0.89
41	Diagnosis code OR 4 prescriptions in 12 months	1.98	2.20	1.23
	Diagnosis code OR 2 prescriptions, minimum 1 month apart, in 6 months[c]	1.98	2.20	-
42	Neurodevelopmental disorder	0.79	0.93	0.38
	Attention deficit hyperactivity disorder	0.39	0.57	0.10
	Autism	0.17	0.13	<0.08
	Learning difficulty	0.29	0.32	0.15
43	Other mental health conditions	8.85	9.43	4.84
	Other mental health conditions (active)	1.78	1.83	-
	Obsessive compulsive disorder	0.73	0.70	<0.08
	Obsessive compulsive disorder (active)	0.07	0.07	-
	Personality disorder	1.09	0.98	0.36
	Self-harm/suicide	7.83	8.40	4.64
	Self-harm/suicide (active)	0.63	0.60	-
	Dissociative disorder	0.10	0.27	<0.08
	Rheumatology			
44	Systemic lupus erythematosus	0.09	0.07	<0.08
45	Spondylarthritis	0.19	0.16	<0.08
	Psoriatic arthritis	0.14	0.11	<0.08
	Ankylosing spondylitis	0.05	0.05	<0.08
46	Inflammatory arthritis	1.46	1.40	0.57
	Rheumatoid arthritis	0.16	0.12	0.16
	Raynaud's disease	1.25	1.23	0.08
	Sjogren's disease	0.03	0.02	<0.08
	Systemic sclerosis	<0.01	<0.02	<0.08
	Primary systemic vasculitis	0.03	0.04	<0.08
47	Ehlers's Danlos Syndrome (EDS) Type 3 (Hypermobile EDS)	0.53	0.45	0.13
	Orthopaedic			
48	Scoliosis	0.60	0.54	0.13
49	Vertebrae disorder	0.78	0.84	0.23
	Intervertebral disc disorder	0.57	0.54	0.18
	Spondylolisthesis	0.05	0.06	<0.08
	Spondylosis	0.17	0.23	<0.08
	Collapsed vertebrae	0.02	0.03	<0.08
	Spinal stenosis	<0.01	0.03	<0.08

50	Chronic back pain	0.74	0.67	0.67
51	Osteoporosis	0.09	0.13	<0.08
52	Osteoarthritis	0.31	0.29	0.28
	Neurological			
53	Migraine	12.71	13.47	3.69
	Migraine (active)	3.08	1.62	2.49
54	Other chronic headaches	3.53	6.60	0.13
	Other chronic headaches (active)	0.29	0.52	-
	Tension type headache	3.22	6.35	0.11
	Tension type headache (active)	0.25	0.49	-
	Cluster headache	0.29	0.23	<0.08
	Cluster headache (active)	0.04	0.03	-
	Other chronic headaches	0.08	0.17	0.13
	Other chronic headaches (active)	0.02	<0.02	-
55	Epilepsy	1.44	1.30	1.57
56	Multiple sclerosis	0.15	0.09	<0.08
57	Spina bifida	0.08	0.11	-
58	Idiopathic intracranial hypertension	0.19	0.22	0.11
59	Peripheral neuropathy	0.46	0.62	0.16
60	Somatoform disorder	1.14	1.14	0.21
	Chronic fatigue syndrome	0.36	0.48	<0.08
	Fibromyalgia	0.61	0.53	0.13
	Chronic Pain	0.25	0.41	<0.08
	Respiratory			
61	Asthma	14.63	17.17	10.49
	Asthma (active)	7.09	7.13	8.26
62	Chronic obstructive pulmonary disease	0.06	0.08	0.23
63	Obstructive sleep apnoea	0.28	0.28	<0.08
64	Interstitial lung disease / pulmonary fibrosis	<0.01	<0.02	<0.08
65	Pulmonary hypertension	0.02	<0.02	<0.08
66	Bronchiectasis	0.10	0.21	<0.08
67	Cystic fibrosis	0.02	0.02	<0.08
68	Sarcoidosis	0.05	0.05	<0.08
	Renal			
69	Chronic kidney disease stage (CKD) 3-5	0.12	0.09	<0.08
	CKD by diagnosis codes	0.10	0.06	<0.08
	CKD by eGFR	0.06	0.06	-
	Dialysis	0.03	<0.02	<0.08
70	Urolithiasis	0.40	0.33	0.46
	Endocrine			
71	Diabetes mellitus (DM)	0.99	0.84	0.79
	Type 1 DM	0.56	0.49	-

	Type 2 DM	0.71	0.68	-
72	Thyroid disorder	3.34	2.45	3.12
	Hyperthyroidism	0.73	0.55	-
	Hypothyroidism	2.82	2.07	-
73	Pituitary disorder	0.35	0.27	<0.08
	Prolactinoma	0.07	0.06	-
74	Adrenal benign tumour	<0.01	0.02	<0.08
75	Hyperparathyroidism	0.02	<0.02	<0.08
	Other			
76	Turner syndrome	0.02	0.02	<0.08
77	Marfan syndrome	0.03	<0.02	<0.08
78	Solid organ transplant	0.03	0.09	<0.08
79	Human immunodeficiency virus infection (HIV) / acquired immunodeficiency syndrome (AIDS)	0.06	-	<0.08

[a] Constituent health conditions may not add up to the total in the combined categories either because there may be overlaps or not all constituent health conditions have been presented in this table.

[b] For SMR, chronic liver disease includes chronic hepatitis B & C, alcoholic liver disease, autoimmune liver disease, cirrhosis

[c] Sensitivity analysis of the prevalence of individual health conditions when using a drug phenome of 2 prescriptions, minimum 1 month apart, in 6 months

NB: active diseases were active in the last 12 months

Additional File 3.1: Cohort selection and data quality checks

Cohort selection

- Index pregnancy is the pregnancy with a start date from 1st Jan 2018 to 31st December 2018.
- When a woman has more than one pregnancy episode in that time frame, the first recorded pregnancy will be used
- Age at pregnancy start date of 15 to 49 years old
- Women of these pregnancies need to have at least one year worth of data recorded preceding index pregnancy

Pregnancy start date

- England - CPRD Pregnancy Register generated pregnancy start dates using primary care pregnancy records following a hierarchical algorithm [152]
- Wales – obtained from National Community Child Health Dataset (NCCHD), when data is not available from NCCHD, pregnancy start date was estimated as 40 weeks before the offspring's date of birth
- Scotland – last menstrual period date for index pregnancy

CPRD GOLD Pregnancy Register (UK)

- Acceptable patient metric and Up To Standard (UTS) time as practice metric as defined by CPRD [153]
- Death date should be after index pregnancy start date
- Date the patient transferred out of the data-contributing practice should be after index pregnancy start date
- Date of the last data collection for the data-contributing practice should be after index pregnancy start date
- Patient's first registration date should be at least one year before index pregnancy start date
- UTS date should be at least one year before index pregnancy start date

SAIL (Wales)

- Mothers and children with valid status codes from anonymized matching. The codes that were utilized were:
  - 1 National health service (NHS) number passes check digit test
  - 2 NHS number derived through external linkage, i.e., Clinical Research Network match on Patient Episode Database for Wales
  - 4 Surname, first name, post code, date of birth and gender code match exactly to the Administrative Register
  - 39 Surname, post code, date of birth and gender code match exactly to the Administrative Register. First name matches on Lexicon (known variants) or Fuzzy Matching probability >= 0.9.
- Patients need to have a full year of continuous GP practice/s registration in the year

prior to conception. A patient's GP practice/s registration was considered to be continuous if there was no more than 30 days gap between registration with a new GP practice.

- Codes with event dates prior to the week of the patient's birth or after index pregnancy date were not considered valid for this study.
- Patient's death date must not be prior to the index pregnancy date.

Scotland (SMR)

- Anonymized linked dataset within a Safe Haven environment was created and maintained using internationally accepted privacy-preserving protocols by Health Informatics Centre (HIC).
- Death date should be after index pregnancy start date
- Date the patient transferred out of the data-contributing health board should be after index pregnancy start date
- Date of the last data collection for the data-contributing health board should be after index pregnancy start date
- Patient's registration date in the health board should be at least one year before index pregnancy start date

Additional File 3.2: Read codes and International Classification of Disease-version 10 (ICD-10) codes for health conditions

https://github.com/mumpredict/Read-codes-and-ICD-10-codes

These diagnostic codes were based on existing literature and code list repositories,[65 376-379] and when not available, were generated by clinicians in the research team

Additional File 3.3: Phenome definitions of health conditions

Health conditions

- 79 health conditions that will count towards the multimorbidity status were identified in a workshop with women representatives and a multidisciplinary team.
- The multidisciplinary team consisted of generalists (GP) and specialists (obstetric, obstetric, and fetal medicine, perinatal mental health, public health).
- These are health conditions that pre-existed at baseline prior to the conception of index pregnancy.
- All historical medical records that were available in the datasets, before the index pregnancy, contributed to the identification of multimorbidity, unless specified otherwise. Absence of a health condition was considered when there were no relevant Read or ICD-10 codes.
- Additional phenome definition by community prescriptions and event dates were used to: (i) improve the detection of health conditions (e.g. identifying mental health conditions with relevant prescriptions), (ii) improve the accuracy of morbidity detection (e.g. regular topical steroids for atopic eczema), and (iii) limit childhood morbidities that may resolve in adulthood (e.g. asthma only considered if still present from age 11 years onwards.[290]

Transient conditions limited to childhood / episodic conditions

Certain childhood conditions are likely to resolve and not continue in adulthood, for example viral induced wheeze, cradle cap, atopic eczema. This is especially the case for atopic conditions and dermatological conditions. There are also conditions that are less likely to occur in very early childhood, such as mental health conditions and chronic headache (except neurodevelopmental disorder and migraine). We anticipate the documentation of these conditions will be high or over-diagnosed in primary care records and therefore have agreed on additional phenome definitions with our clinical colleagues.

We would be less interested in conditions that were transient in childhood and subsequently never active again in a woman's lifetime. To define disease in adulthood, we have taken into account that age 16 is the age for lawful consent and where a patient may transition to adult health care services. However, using a definition of disease occurring in adulthood (aged >16) would discount recent medical history for the youngest pregnant women in the study cohort. Therefore, we have chosen aged 11 (5 years before 16 years old) as the cut off for these conditions.

The following health conditions will only be considered if the latest related health record is when the woman is aged 11 and above:

- all mental health conditions (excluding neurodevelopmental disorders),
- atopic eczema,
- other skin conditions (seborrheic dermatitis, rosacea, hidradenitis suppurativa, lichen planus),
- allergic rhino-conjunctivitis,
- asthma
- chronic headache (cluster headache, tension headache, chronic type headache)

Analysis of mental health conditions

Common mental health disorders (CMHD)

Depression and anxiety diagnoses were treated as separate morbidities. Mixed depression and anxiety is the most common mental health disorder,[380] but as the maternal outcome may differ for these conditions,[381] we analysed them separately where possible.

Medications used to manage mental health conditions often are used in more than one health condition. For instance, selective serotonin reuptake inhibitors are used in both depression and anxiety. Therefore, the prescription phenome for depression and anxiety were combined as common mental health disorders (CMHD) medications.

In the absence of a diagnosis code, it is not possible to determine whether the CMHD prescription was used for anxiety or depression. CMHD prescription phenome if present, will contribute as one morbidity, only when neither a depression nor anxiety diagnosis code is present.

Severe mental illness (SMI)

As the diagnosis codes and drugs used in bipolar disorder, schizophrenia and psychosis may overlap, and given that it is very uncommon for bipolar disorder and schizophrenia to co-occur, these conditions were combined as severe mental illness if a diagnosis or prescription code is present.

Improving access to psychological therapies (IAPT)

It was not possible to determine what mental health conditions a woman was referred to IAPT for. For mild-to-moderate mental illness, a woman may not be on medication and is referred to low-intensity psychosocial intervention (IAPT) instead.[382] IAPT was included to improve the detection rates of mental illnesses. Therefore, IAPT Read codes if present, will contribute as one morbidity, only when depression diagnosis, anxiety diagnosis, CMHD prescription phenome, SMI diagnosis or prescription phenome were not already present.

Alcohol misuse/dependence, substance misuse/dependence
Both these conditions were considered to be present if a diagnosis code or prescription code is present.

Mental health conditions phenome definitions

Mental health conditions	Phenome definitions[a]	Prescription BNF chapters	Phenome by prescriptions[b]
Common mental health disorders (CMHD) ● *Depression* ● *Anxiety* *(includes phobia, panic disorder, post-traumatic stress disorder)*	● Diagnosis code ● Prescription code: CMHD prescriptions ● Improving access to psychological therapy (IAPT) program	**CMHD prescriptions** ● 4.3: Antidepressant drugs (excluding amitriptyline) ● 4.1.2 Anxiolytics ● Propranolol 10mg, 40mg	4 CMHD prescriptions within 12 months *AND* no lifetime SMI prescriptions
Severe mental illness (SMI) ● *Bipolar disorder* ● *Schizophrenia* ● *Affective psychosis* ● *Non affective psychosis*	● Diagnosis code ● Prescription code: SMI prescriptions ● Improving access to IAPT program	**SMI prescriptions** **Group A:** 4.3: Antidepressant drugs (excluding amitriptyline) 4.1.2 Anxiolytics **Group B:** 4.2.1: Antipsychotic drugs (excluding prochlorperazine) 4.2.2: Antipsychotic depot injections	4 group A prescriptions within 12 months AND any lifetime group B/C prescriptions *OR* 4 group B prescriptions within 12 months *OR*

		Group C: 4.2.3: Drugs used for mania and hypomania (lithium, asenapine)	4 group C prescriptions within 12 months
Alcohol misuse/dependence	• Diagnosis code • Prescription code	4.10.1 Alcohol dependence (acamprosate, disulfiram, nalmefene)	4 prescriptions within 12 months
Substance misuse/dependence	• Diagnosis code • Prescription code	Methadone	4 prescriptions within 12 months
Eating disorder	• Diagnosis code	-	-
Neurodevelopmental disorder • *Attention deficit hyperactivity disorder* • *Autism* • *Learning difficulties*	• Diagnosis code • Prescription code (SMR only)	Methylphenidate	4 prescriptions within 12 months

Other mental health conditions ● *Obsessive compulsive disorder* ● *Personality disorder* ● *Dissociative disorder* ● *Self-harm (including suicide)*	● Diagnosis code	-	-

[a] Latest diagnosis code and prescription codes at aged 11 or above, except for neurodevelopmental disorder
[b] Sensitivity analysis uses the same criteria but for 2 scripts, minimum 1 month apart, within 6 months, this is presented in Additional Table 3.7.
BNF: British National Formulary

Physical health conditions phenome definitions

Health conditions	CPRD, SAIL	SMR	British National Formulary chapters for phenome by prescriptions
Cancers			
All cancers	Diagnosis code	Diagnosis code	
Cardiovascular disease			
Hypertension	Diagnosis code	Diagnostic OR prescription code. 4 prescriptions in 12months anytime.	2.2.1: Thiazides and related diuretics; 2.6.2: Calcium-channel blockers; 2.5.5: Renin-angiotensin system drugs; 2.5.4: Alpha-adrenoceptor blocking drugs
Ischemic heart disease & myocardial infarction	Diagnosis code	Diagnosis code	
Heart failure	Diagnosis code	Diagnosis code	
Stroke	Diagnosis code	Diagnosis code	
Atrial fibrillation	Diagnosis code	Diagnosis code	
Congenital heart disease	Diagnosis code	Diagnosis code	
Valvular heart disease	Diagnosis code	Diagnosis code	
Cardiomyopathy	Diagnosis code	Diagnosis code	
Dermatology			
Atopic eczema	Diagnosis code AND topical steroid prescription (4 script in 12months) aged 11+	Topical steroid prescription OR diagnostic code aged 11+. 4 prescriptions in 12months.	13.4: Topical corticosteroids

Psoriasis	Diagnosis code	4 prescriptions in 12months	13.5.2: Preparations for psoriasis
Autoimmune skin disease (vitiligo, alopecia areata)	Diagnosis code	Not available	
Other skin conditions (Seborrheic dermatitis, Rosacea, Hidradenitis suppurativa, Lichen planus)	Diagnosis code aged 11+	Diagnosis code	
Ear, nose throat			
Allergic rhinoconjunctivitis	Diagnosis code OR prescription (2 prescriptions in 6 months) aged 11+	2 prescriptions in 6 months aged 11+	12.2.1 Nasal allergy topical antihistamines, cromoglicate, topical corticosteroids
Profound deafness	Diagnosis code	Diagnosis code	
Eye			
Severe blindness	Diagnosis code	Diagnosis code	
Inflammatory eye disease (scleritis, episcleritis, uveitis)	Diagnosis code	Diagnosis code	
Cataract	Diagnosis code	Diagnosis code	
Diabetic eye disease (retinopathy, maculopathy)	Diagnosis code + Diabetes Diagnosis code	Diagnosis code	
Retinal detachment	Diagnosis code	Diagnosis code	
Gastroenterology			

Irritable bowel disease	Diagnosis code	Diagnosis code OR prescription 4 prescription in 12 months	1.2: Antispasmodics and other drugs altering gut motility
Inflammatory bowel disease (ulcerative colitis, Crohn's disease)	Diagnosis code	Diagnosis code	
Coeliac disease	Diagnosis code	Diagnosis code	
Chronic liver disease (chronic hepatitis B & C, alcoholic liver disease, autoimmune liver disease, cirrhosis)	Diagnosis code	Diagnosis code	
Non-alcoholic fatty liver disease	Diagnosis code	Diagnosis code	
Peptic ulcer disease	Diagnosis code	Diagnosis code OR prescription 4 prescription in 12 months	1.3.1: H2-receptor antagonists, 1.3.5: Proton pump inhibitors
Cholelithiasis	Diagnosis code	Diagnosis code	
Gynaecology			
Polycystic ovarian syndrome	Diagnosis code	Diagnosis code	
Endometriosis	Diagnosis code	Diagnosis code	
Leiomyoma (fibroids)	Diagnosis code	Diagnosis code	
Female infertility	Diagnosis code	Diagnosis code	
Haematology			
Venous thromboembolism (VTE)	Diagnosis code	Diagnosis code	

(deep vein thrombosis, pulmonary embolism, other VTE)			
Primary thrombocytopenia	Diagnosis code	Diagnosis code	
Haemophilia	Diagnosis code	Diagnosis code	
Pernicious anaemia	Diagnosis code	Diagnosis code	
Sickle cell anaemia	Diagnosis code	Diagnosis code	
Rheumatology			
Systemic lupus erythematosus	Diagnosis code	Diagnosis code	
Spondylarthritis (psoriatic arthritis, ankylosing spondylitis)	Diagnosis code	Diagnosis code	
Inflammatory arthritis (rheumatoid arthritis, Sjogren's syndrome, Raynaud's syndrome, systemic sclerosis, primary systemic vasculitis)	Diagnosis code	Diagnosis code	
Ehlers's Danlos Syndrome (EDS): Type 3 (Hypermobile EDS)	Diagnosis code	Diagnosis code	
Orthopaedic			
Scoliosis	Diagnosis code	Diagnosis code	
Vertebral disorder	Diagnosis code	Diagnosis code	

(intervertebral disc disorder, spondylosis, spondylolisthesis, collapsed vertebrae, spinal stenosis)			
Chronic back pain	Diagnosis code	Diagnosis code	
Osteoporosis	Diagnosis code	Diagnosis code	
Osteoarthritis	Diagnosis code	Diagnosis code	
Neurology			
Migraine	Diagnosis code	4 prescriptions in 12 months	4.7.4: Antimigraine drugs
Other chronic headaches (cluster headache, tension headache)	Diagnosis code aged 11+	Not available	
Epilepsy	Diagnosis code	Diagnostic code OR Prescription: antiepileptics specific to epilepsy	4.8.1: Control of epilepsy (exclude Gabapentin [0408010G0], Pregabalin [0408010AE] and Topiramate [040801050])
Multiple sclerosis	Diagnosis code	Diagnosis code	
Spina bifida	Diagnosis code	Diagnosis code	
Idiopathic intracranial hypertension	Diagnosis code	Diagnosis code	
Peripheral neuropathy	Diagnosis code	Diagnosis code	
Somatoform disorder (chronic fatigue syndrome / myalgic encephalomyelitis, fibromyalgia, chronic pain syndrome [chronic regional pain syndrome, myofascial pain syndrome])	Diagnosis code	Diagnosis code	

Respiratory			
Asthma	Diagnosis code aged 11+	4 scripts in 12 months aged 11+	3.1.1: Adrenoceptor agonists OR 3.2: Corticosteroids
Chronic obstructive pulmonary disease	Diagnosis code	Not available	
Obstructive sleep apnoea	Diagnosis code	Diagnosis code	
Pulmonary fibrosis, interstitial lung disease	Diagnosis code	Diagnosis code	
Pulmonary hypertension	Diagnosis code	Diagnosis code	
Bronchiectasis	Diagnosis code	Diagnosis code	
Cystic fibrosis	Diagnosis code	Diagnosis code	
Sarcoidosis	Diagnosis code	Diagnosis code	
Renal			
Chronic kidney disease, dialysis	Diagnosis code OR two eGFR <60, 90 days apart	Diagnosis code	
Urolithiasis	Diagnosis code	Diagnosis code	
Endocrine			
Type 1 diabetes mellitus	Diagnosis code	Diagnosis code OR prescription 4 prescription in 12 months	6.1.1: Insulin
Type 2 diabetes mellitus	Diagnosis code	Diagnosis code OR prescription 4 prescription in 12 months AND no insulin	6.1.2: Antidiabetic drugs (exclude Metformin Hydrochloride (0601022B0) due to its use for infertility

Hyperthyroidism	Diagnosis code	Diagnosis code OR prescription 4 prescription in 12 months	6.2.2: Antithyroid drugs
Hypothyroidism	Diagnosis code	Diagnosis code OR prescription 4 prescription in 12 months	6.2.1: Thyroid hormones
Pituitary disorder	Diagnosis code	Diagnosis code	
Adrenal benign tumour	Diagnosis code	Diagnosis code	
Hyperparathyroidism	Diagnosis code	Diagnosis code	
Other			
Human immunodeficiency viral (HIV) infection / AIDS	Diagnosis code	Diagnosis code	
Turner's syndrome	Diagnosis code	Diagnosis code	
Marfan's syndrome	Diagnosis code	Diagnosis code	
Solid organ transplant	Diagnosis code	Diagnosis code	

NB: Drug codes for SAIL databank were generated based on British National Formulary chapters

Phenome definitions to limit common transient / episodic conditions to the 12 months preceding index pregnancies

Health conditions	Phenome definitions	CPRD BNF Chapters	Scotland BNF Chapters
Atopic eczema	Meets main criteria AND at least 1 prescription of topical steroid in the 12 months before index pregnancy	13040000 Topical corticosteroids, 13040100 Topical corticosteroids with antimicrobials, 13040200 Mild topical corticosteroids, 13040300 Moderate topical corticosteroids, 13040400 Potent topical corticosteroids, 13040500 Very potent topical corticosteroids	13.4: Topical corticosteroids
Psoriasis	Meets main criteria AND at least 1 prescription of (topical steroid OR topical psoriasis treatment) in the 12 months before index pregnancy	Topical steroids as above, 13050000 Preparations for eczema and psoriasis, 13050200 Preparations for psoriasis, 13050202 Topical preparations for psoriasis	13.5.2: Preparations for psoriasis
Seborrheic dermatitis	Meets main criteria AND at least 1 prescription of (topical steroid OR topical antifungal treatment) in the 12 months before index pregnancy	Topical steroids as above, 13100200 Antifungal preparation (topical): included ketoconazole, miconazole, clotrimazole	-
Rosacea	Meets main criteria AND at least 1 prescription of (topical OR oral rosacea treatment) in the 12 months before index pregnancy	*Topical* 13060300 Topical preparations for rosacea, 13100102 Antibacterial preparations also used systemically	-

		(for skin conditions): included topical metronidazole, 13060101 Benzoyl peroxide and azelaic acid for acne: included azelaic acid. *Oral* 03060201 Oral antibacterial for acne: included doxycycline, oxytetracycline, tetracycline, erythromycin, 13060000 acne and rosacea: doxycycline 40mg	
Hidradenitis suppurativa	Meets main criteria AND at least 1 prescription of oral antibiotics for hidradenitis in the 12 months before index pregnancy	Lymecycline, metronidazole, clarithromycin, clindamycin, rifampicin, 13060201 Oral antibacterial for acne: included doxycycline, erythromycin.	-
Lichen planus	Meets main criteria and latest diagnosis code in the 12 months before index pregnancy	-	-
Allergic rhinoconjunctivitis	Meets main criteria by diagnosis code and at least 1 prescription for allergic rhinoconjunctivitis in the 12 months before index pregnancy	12020100 Drugs used in nasal allergy 12020101 Corticosteroids used in nasal allergy (spray) 12020150 Antihistamines in nasal allergy (spray)	12.2.1 Drugs used in nasal allergy

		12020151 Cromoglicate in nasal allergy (spray)	
Depression	Meets main criteria by diagnosis code and at least 1 prescription of antidepressant in the 12 months before index pregnancy	04030100 Tricyclic and related antidepressants (excluded amitriptyline), 04030200 Monoamine oxidase inhibitors, 04030201 Reversible monoamine oxidase inhibitors, 04030300 Selective serotonin reuptake inhibitors, 04030400 Other antidepressants	4.3 Antidepressant drug 4.1.1 Anxiolytics propranolol (40 mg or 10 mg)
Anxiety	Meets main criteria by diagnosis code and at least 1 prescription of antidepressant/anxiolytics/propranolol in the 12 months before index pregnancy	Antidepressants as above, 04010000 Hypnotics and anxiolytics: included bromazepam 04010200 Anxiolytics, 04010201 Benzodiazepines Propranolol 10mg, 40mg	4.3 Antidepressant drug 4.1.1 Anxiolytics propranolol (40 mg or 10 mg)
Obsessive compulsive disorder	Meets main criteria and latest diagnosis code in the 12 months before index pregnancy	-	-
Self-harm	Meets main criteria and latest diagnosis code in the 12 months before index pregnancy	-	-
Migraine	Meets main criteria and at least 1 prescription of acute/prophylaxis migraine treatment in the 12 months before index pregnancy	4070401 Acute Migraine, 4070402 Prophylaxis of Migraine	4.7.4: Antimigraine drugs
Other chronic headaches	Meets main criteria and latest diagnosis code in the 12 months before index pregnancy	-	-

Asthma	Meets main criteria and at least 1 bronchodilator or steroid inhaler prescription in the 12 months before index pregnancy	03010000 Bronchodilators, 03010101 Selective Beta 2 Agonists, 03020000 Corticosteroids (For Respiratory Conditions)	3.1.1: Adrenoceptor agonists 3.2: Corticosteroids (respiratory)

BNF: British National Formulary

NB: Drug codes for SAIL databank were generated based on BNF chapters

Additional File 3.4: The RECORD statement

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Background		
Objectives	3	State specific objectives, including any prespecified hypotheses	Background		
Methods					
Study Design	4	Present key elements of study design early in the paper	Methods		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods		

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Methods	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Methods, Figure 3.1, Additional Files 3.1- 3.3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Methods	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Additional Files 3.2- 3.3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods, Additional Files 3.1-3.3		

Bias	9	Describe any efforts to address potential sources of bias	Methods		
Study size	10	Explain how the study size was arrived at	Not applicable as population based routine dataset		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Data analysis		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	Data analysis, Additional Tables 4-6		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Additional File 3.1, Additional Figure 3.1

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Methods
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	Additional Figure 3.1	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Additional File 3.1, Additional Figure 3.1
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarize follow-up time (*e.g.*, average and total amount)	Table 3.1, Additional Table 3.1		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time	Additional Tables 3.2-3.3		

		Case-control study - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 3.2		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results, Additional Tables 3.4-3.6		
Discussion					
Key results	18	Summarize key results with reference to study objectives	Discussion		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion, Additional File 3.5	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing	Additional File 3.5

				eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion		
Generalizability	21	Discuss the generalizability (external validity) of the study results	Discussion		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding statement		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Additional File 3.2

Additional File 3.5: Limitations of CPRD, SAIL, SMR

CPRD

Linked patient level deprivation data were only available for 75% of the study cohort in England. Although practice level IMD was available for all four nations with no missing data, nation specific practice level IMD cannot be combined due to differences in the IMD domains; therefore, only English data were presented for the association analysis for CPRD. Parity (number of pregnancies that progressed beyond 24 weeks) were not readily available in the CPRD pregnancy register and gravidity was used instead across all three datasets.

SAIL

Pregnancy episodes were detected from the National Community Child Health database (NCCHD) and thus does not include pregnancies that resulted in early pregnancy loss. The gravidity generated from the pregnancy episodes identified from the NCCHD is likely to be an under-estimation. Sensitive data, such as human immunodeficiency virus infection and infertility, were not available in the SAIL databank, but is unlikely to have a large effect on the prevalence of multimorbidity.

SMR

Historical data from the SMR datasets used in this study were available from 2005-2019, community prescription data from NHS Fife was available from 2009 onwards. This meant that if a pregnant woman had a history of a health condition prior to this time period, it may not be captured. This, together with the fact that secondary care data are more likely to capture the severe spectrum of health conditions, may have led to the lower prevalence of multimorbidity compared to primary care datasets. This limitation is more likely to affect older women in the SMR pregnancy cohort and may partially account for the lack of association of maternal age with multimorbidity. As the Scottish SMR dataset relied on

community prescription data to define certain health conditions, this can lead to misclassification.

Chapter 4

Supplementary Material 4.1: The Core Outcome Set-STAndardised Protocol Items (COS-STAP) Statement

Sections	No	Items	Location in manuscript
TITLE/ABSTRACT			
Title	1a	Identify in the title that the paper describes the protocol for the planned development of a COS	Title page
Abstract	1b	Provide a structured abstract	Abstract
INTRODUCTION			
Background and objectives	2a	Describe the background and explain the rationale for developing the COS, and identify the reasons why a COS is needed and the potential barriers to its implementation	Background
	2b	Describe the specific objectives with reference to developing a COS	Background
Scope	3a	Describe the health condition(s) and population(s) that will be covered by the COS	Scope of the COS
	3b	Describe the intervention(s) that will be covered by the COS	Scope of the COS
	3c	Describe the context of use for which the COS is to be applied	Scope of the COS
METHODS			
Stakeholders	4	Describe the stakeholder groups to be involved in the COS development process, the nature of and rationale	Table 4.1 and Table 4.2

		for their involvement and also how the individuals will be identified; this should cover involvement both as members of the research team and as participants in the study	
Information sources	5a	Describe the information sources that will be used to identify the list of outcomes. Outline the methods or reference other protocols/papers	Stage 1 Systematic literature search Stage 2 Focus groups
	5b	Describe how outcomes may be dropped/combined, with reasons	Initial list of outcomes
Consensus process	6	Describe the plans for how the consensus process will be undertaken	Consensus meeting
Consensus definition	7a	Describe the consensus definition	Score criteria for consensus
	7b	Describe the procedure for determining how outcomes will be added/combined/dropped from consideration during the consensus process	Score criteria for consensus
ANALYSIS			
Outcome scoring/feedback	8	Describe how outcomes will be scored and summarised, describe how participants will receive feedback during the consensus process	1st-3rd Delphi survey
Missing data	9	Describe how missing data will be handled during the consensus process	3rd Delphi survey
ETHICS and DISSEMINATION			
Ethics approval/informed consent	10	Describe any plans for obtaining research ethics committee/institutional review board approval in relation to the consensus process and describe how informed consent will be obtained (if relevant)	Focus group 1st Delphi Ethics

Dissemination	11	Describe any plans to communicate the results to study participants and COS users, inclusive of methods and timing of dissemination	Dissemination
ADMINISTRATIVE INFORMATION			
Funders	12	Describe sources of funding, role of funders	Funding statement
Conflicts of interest	13	Describe any potential conflicts of interest within the study team and how they will be managed	Conflict of interest

Chapter 5

Supplementary Material 5.1: Reasons for exclusion from the stage 2 searches

No	Full reference	Reason for exclusion
1	Moe HW, Sharma S, Sharma AK. An evaluation of medication appropriateness in pregnant women with coexisting illness in a tertiary care hospital. Perspectives in Clinical Research. 2021;12(1):21-6.	Exposure: not 2 or more long-term conditions that existed before pregnancy
2	Pluym ID, Tandel M, Kwan L, Mok T, Holliman K, Afshar Y, et al. 57 Randomized Control Trial of Postpartum Visits at 2 weeks and 6 weeks. American journal of obstetrics and gynecology. 2021;224(2):S40-.	Population: not pregnant women with multimorbidity or their offspring
3	Little D, Varner C, Park A, Ray J. Emergency department use by pregnant women: A population-based study within a universal healthcare system. Journal of Obstetrics and Gynaecology Canada. 2020;42:680.	Population: not pregnant women with multimorbidity or their offspring. The main purpose was to characterize emergency department visits during pregnancy and number of comorbidities was one of two risk factors examined.
4	Varner CE, Park AL, Little D, Ray JG. Emergency department use by pregnant women in Ontario: a retrospective population-based cohort study. CMAJ open. 2020;8(2):E304-E12.	Population: not pregnant women with multimorbidity or their offspring. The main aim was to characterise emergency department visits by pregnant women.
5	McCauley M, Zafar S, van den Broek N. Maternal multimorbidity during pregnancy and after childbirth in women in low- and middle-income countries: a systematic literature review. BMC Pregnancy & Childbirth. 2020;20(1):637.	Outcomes: No types of outcomes that can be extracted. The review reported on the prevalence of physical, psychological, and social morbidities (exposures) and the association between these.
6	Clapp MA, Little SE, Zheng J, Robinson JN, Kaimal AJ. Case mix and the utility of postpartum readmission rates as a marker of quality in obstetrics. American Journal of Obstetrics and Gynecology. 2018;218:S549-S50.	Exposure: not 2 or more long-term conditions that existed before pregnancy. The exposures were listed as individual diseases, the study identified patients based on low / high admission rates hospital then looked for risk factors for readmissions.
7	Cunningham SD, Magriples U, Thomas JL, Kozhimannil KB, Herrera C, Barrette E, et al. Association Between Maternal Comorbidities and Emergency Department Use Among a National Sample of Commercially Insured Pregnant Women. Academic Emergency Medicine. 2017;24(8):940-7.	Exposure: not 2 or more long-term conditions that existed before pregnancy. The study participants were categorised as one or more comorbidities vs no comorbidities.

Chapter 6

Supplementary Material 6.1: Focus group topic guide

1. Welcome
Welcome everyone, facilitators and participants given opportunity to introduce themselves.

2. What is a Core Outcome Set
Before we start, I would like to share with you a 3 minute video that will explain what a Core Outcome Set is.[180]

3. Aim of the focus group

To find out **what outcomes you want researchers to measure** and report in all studies for pregnant women and birthing people with 2 or more long-term physical and mental health conditions.

The findings from this focus group will help us design the next stage of our study. It will be fed into surveys where we invite people to vote on which outcomes should be included in the final list of core outcomes.

4. Housekeeping

- The session will last **1.5 to 2 hours**.
- Please keep your microphone on **mute** when you are not speaking.
- To give everyone a chance to speak, please use the **raise your hand function** when you would like to share your views.
- Please feel free to use the **chat function** too to share your thoughts
- This is an open discussion, there is no right and wrong answers, and we want to hear the views of everyone here.
- Please **do not** discuss what your fellow participants **shared** in this focus group **beyond this session** today.
- We will start the recording shortly, all discussions will be **recorded** for analysis, you will not be identified in any publications of this research study.
- If at any time you would like to **avoid answering** a question, take a **break or leave** the focus group please do so.

5. How to access support if you become distressed
During the focus group, if you feel unable to continue with the discussion, please let one of our facilitators know so we can support you. If you feel comfortable to do so, you can switch off your camera, send a message to the facilitator. One of the facilitators can meet you in a separate link for some support.

Ask if there are any questions and clarify.

Questioning/prompting by the facilitator is likely to include the following areas; exact wording will vary according to the flow of the conversation and what participants have already shared.

6. Discussions about outcomes
Case scenario

> Jane has multiple long-term health conditions. She takes multiple medications and sees her doctors regularly for her health conditions.
>
> She becomes pregnant. Jane sees her doctors and midwives to plan for her pregnancy care.
>
> Jane would like to know how her health conditions may impact on her pregnancy. Jane would also like to know how having her health conditions and being pregnant may impact on her health, her child and her family.
>
> To answer her questions, Jane's doctors and midwives look at previous studies on people like Jane who has multiple long-term conditions and became pregnant.

- If researchers study a large group of pregnant women with multiple long-term conditions like Jane, **what would you like** to see they **measure** in the study?
- If research found a new treatment / intervention / way of delivering care for people like Jane, what would be the **evidence that it worked**?
- What do you think researchers should measure to know any new treatment / change in care has **made a difference**?
- (If the discussion veers towards suggestions of how care can be improved, then ask: If we improve maternity care for people like Jane, what would you like to see **improve as a result**?)

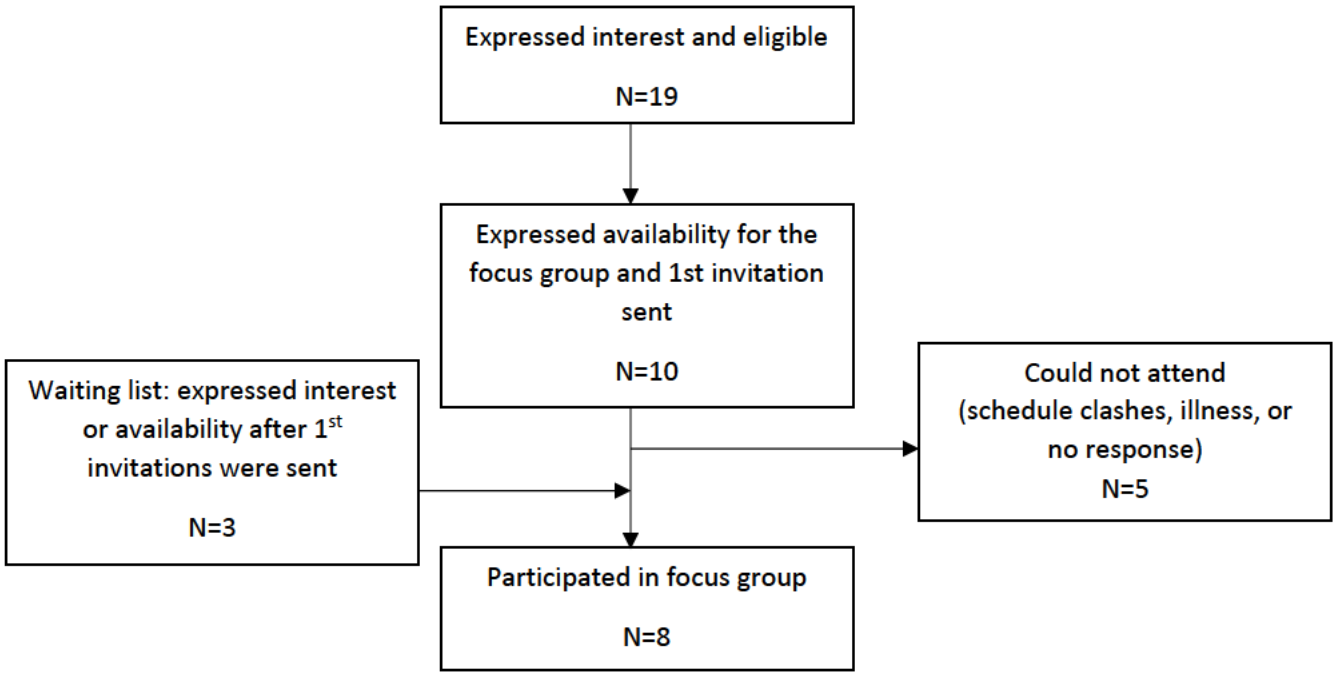
Remind participants the aim of the focus group before the discussion starts:

- We are not asking about suggestions of how maternity care can be improved for pregnant women with multimorbidity, rather we are asking what the end results / ideal pregnancy or birth would look like if changes were made.
- We are interested in broad outcomes generic to all pregnancies with multiple long-term conditions, we are not focusing on outcomes specific to a particular health condition
- Outcomes for the following people: women and birthing people and their children
- Outcomes in the following time periods: pre-pregnancy, during pregnancy, immediately after pregnancy, longer term

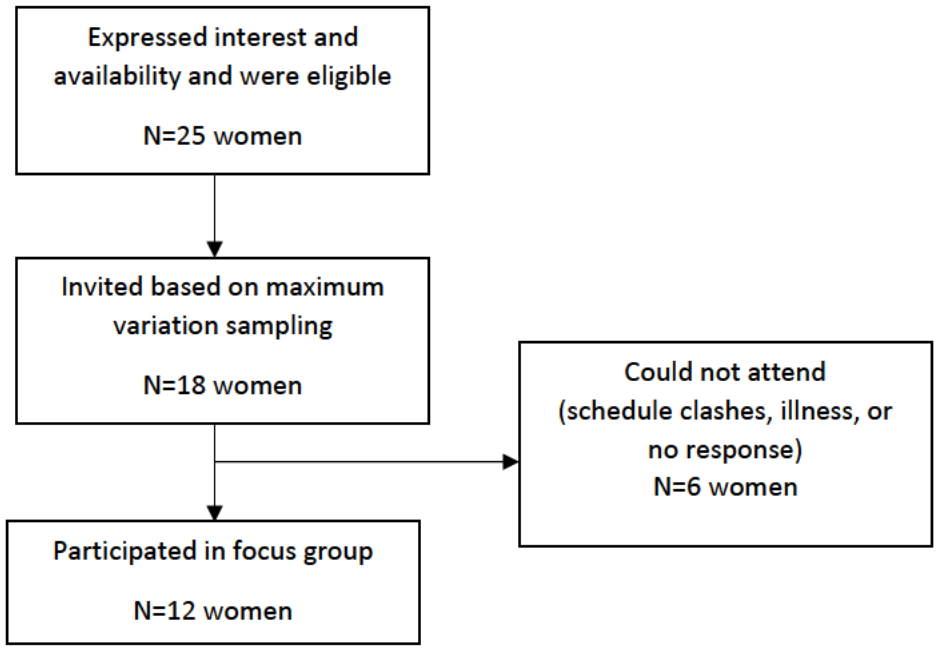
6. Closing remarks
Do you have any further thoughts/ comments?
Thank you for participating in this focus group interview. Your input has been very valuable and will help us design the next stage of your study, which are surveys where people vote for outcomes, they feel are important.

Supplementary Material 6.2: Participant flow chart

Health care professionals



Women


Expressed interest and availability and were eligible
N=25 women
Invited based on maximum variation sampling
N=18 women
Could not attend (schedule clashes, illness, or no response)
N=6 women
Participated in focus group
N=12 women

Supplementary Material 6.3: Supplementary quotes

Maternal outcome: before pregnancy
Fertility "…your condition might make it very difficult to get pregnant and therefore getting pregnant is the achievement…" (Focus group [FG] 1, health care professionals [HCP] 4)
Preconception care ***Uptake of preconception support*** "…It would be interesting to know…it's very rare for somebody to come in, purely for preconceptual counselling." (FG1, HCP7) ***Quality of preconception counselling*** "…it would be interesting to know are there certain conditions where the patients actually do get better counselling than other aspects." (FG1, HCP7) ***Preconception counselling on medications*** "…a lot of my medications is unknown...[Clinicians] recommend coming off it for a year before getting pregnant…if I have to stop this medication…my conditions may get so bad…I then might struggle to get pregnant…that could then take me a year or two…" (FG3, Women [W] 4)
Maternal outcome: during pregnancy
Maternal death "…[my wife] dying…the pressure on her heart…I was very very scared…" (FG3, Partner [P] 2)
Impact on long-term conditions "Anybody with a long-term health condition knows the pregnancy is going to wreck your body...to have some statistics to say…on these medications, X number of women have found that this has happened in their pregnancy, will be a lot more reassuring..." (FG3, W1)
Types of birth **Birth weight / macrosomia** "…size was a big concern for us, especially because I've had wanted a vaginal birth but unfortunately ended up having… c-sections." (FG3, W2)
Miscarriage "…so like miscarriage, which I never thought of beforehand, till we started having regular miscarriages." (FG3, P1)

Birth injuries

"I have [condition] so when it comes to injuries and wound it's so hard to heal and it takes a lot of time. And in the process of healing you may actually acquire another condition that was not there…the risk for injuries…should be measured, just to reduce injuries anytime to mother..." (FG2, W5)

Interventions in pregnancy

"…patients view a normal pregnancy has minimal intervention.…when we're trying to…achieve the best outcome for the mother and for the baby, by intervening with weekly appointments…the woman may feel that she's a failure…but it's nobody's fault, because obviously if we didn't intervene there was something horrific that happened…" (FG1, HCP7)

Limited options
Analgesia
"…term birth, via a normal delivery with no monitoring, minimal analgesic…there is some impacts of their disease…that means, that some of those choices aren't open to them." (FG1, HCP4)

Haemorrhage
Blood pressure

"… the type of birth, the pain relief, the blood pressure. Any haemorrhaging..." (FG1, HCP2)

Maternal outcome: after pregnancy

Postnatal and long-term care

Length of postnatal support

"…it's considering the kind of home care…support packages that we put in place… women are going home, on their own, or may have a partner, and feel the extra pressure…how that support is going to continue beyond the pregnancy element of it." (FG1, HCP5)

Postnatal support for raising a child

"…you need the support, after you've had the baby…your [multiple long-term] conditions, I'm guessing, are probably going to be all over the place…to raise the baby when you're going to need to be up all night and feeding, but actually you still got to care for yourself…" (FG3, W3)

Quality of postnatal support
"But also postnatal [check]… it varies…is there a way of evaluating how efficient that might be….we are the last people to actually see these women…" (FG1, HCP7)

"…it's not just stopping at birth. It's then the follow up…are you being followed up properly, and when you've left the hospital, again is that information being passed through, about your kind of health needs." (FG2, W4)

Emotional support

"…definitely emotional support…I just found that in my pregnancy…it was quite hard because…I gave birth quite early [baby] was premature…" (FG2, W6)

"…my hospital stay and all was quite traumatic and happened very quickly…that all hit me more after I had the baby and…he was safe…abit of a check in at some stage…would be a good thing to consider for people with multiple health condition..." (FG3, W4)

Support for family

"…the community midwives were coming out, we were having hour long meetings…there still wasn't time to cover what happened to [husband]…to [child]. It was mainly focused on me…that is definitely something that needs to change, it needs to be looked at the family unit as a whole..." (FG3, W2)

Perinatal mental health

Postnatal depression
"…postnatal depression…we didn't know where to go, what support was available…I've heard people still don't pick up depression… with ethnic minorities and Asians its quite a taboo subject…" (FG2, W6)

Impact on pre-existing mental illness
"…the high-risk period…in women's mental health cycle…from 36 weeks pregnancy to about six weeks afterwards, so we could look at that period and look at rates of relapse…" (FG1, HCP8)

Emotional and mental wellbeing
"… the trauma of being in hospital and having the baby and having the baby taken away, I probably found it more difficult in the weeks after..." (FG3, W4)

Impact of mental health on physical health
"…something like depression, they will have an effect if they got other…physical problems, they might get so depressed and actually have very poor compliance with the treatment." (FG1, HCP7)

Impact of physical health on mental health
"… how has my mental health regarding my diabetes changed because, when I'm pregnant…I get really, really scared of having high blood sugars because it's so drilled into you how dangerous it is." (FG3, W2)

Experience of perinatal mental health support

"…if you've got multiple health conditions…our brains are already swirling with a million different things, add in to that the anxiety of pregnancy and childbirth and…the unknown…the fact we're not being checked in on." (FG3, W1)
Ability to breastfeed "I wanted to breastfeed straight away, I was told I couldn't…because of the [pregnancy complication]…" (FG3, W2)
Breastfeeding support …I wanted help with the breastfeeding...But I didn't get that... sometimes I used to cry because I can't do it... But you just didn't feel like you got the support…someone being there and helping you and saying it's okay…there's breast pumps available…it takes time…." (FG2, W6)
Establishing feeding **Engaging with healthy behaviour** "…if their mental health is destabilised, they are less likely to engage in positive health behaviours…requirements at different stages of pregnancy…potential disruption to mum, to baby, to the bond…establishing feeding and bonding." (FG1, HCP 8)
Pressure in maternal role "…there's lots of pressure on mothers to be the perfect mother and, about breastfeeding…" (FG1, HCP7)
Maternal guilt "…there's an awful lot of guilt isn't there, when you do have mothers if there's multiple morbidities or the effects of their [medications] or their illness on their child." (FG1, HCP 7) "I felt really guilty... that it was because I had health conditions that [my child] had a problem…So my child is like [x] months now and…I still think about that quite a lot… nobody really spoke to me about that after…" (FG2, W4)
Parent and infant bonding "…[child] has always been a lot more independent…we felt that was the result of having been in special care [when he was a newborn]…he had been away from us for so long…how do we support building a better bond with their parents…" (FG3, W2) "…if a daddy's really struggling with how the baby arrived then…that's going to put up barriers to bonding with the new baby." (FG3, W4)

Skin-to-skin "I think outcomes for babies are things like, was skin to skin preserved, was the golden hour observed as much as possible, how much contact was given between parents and babies, even if baby was in special care..." (FG3, W2)
Recovery time "…even after a C-section…for a healthy person…it's a six-week recovery, it's a major surgery. Put in there all the additional needs, and we have no idea what's going to go on…the services…offered aren't long enough." (FG3, W1) "…with her [health conditions]…will she be able to recover as fast as normal…" (FG3, P1)
Development of new health conditions "…at some point in my life, maybe I'm likely to develop type two diabetes... deep vein thrombosis you're more likely to clot…that information hasn't been shared…Like if you've had a pregnancy and you're overweight or have a higher BMI (body mass index), and you have certain conditions. They should have a checklist that you could say screen for this..." (FG2, W3)
Long-term cardiovascular outcomes "…in terms of long-term outcomes for their risk of developing strokes, MIs (myocardial infarctions)…later on, if they've had really intensive help or support in managing their conditioning well during those nine months, whether that could have a positive outcome on their future long term…cardiovascular health…outcomes." (FG1, HCP1)
Maternal outcome: all stages of pregnancy
Quality and experience of care "…like the GAD-7 (a measuring tool for mental health) where we're talking about mental health, actually about the full experience of pregnancy being looked after under that health profession that would be really quite useful." (FG3, W1)
Change in medication "…if you take this, then you gotta give it up… for…years…we have that with one [medication] that you could have been given, but …we got to wait an entire length of time till it is out of your system…" (FG3, P1)
Holistic care / multidisciplinary coordination of care "…when I came from general medicine into obstetric medicine, it sometimes felt like things were like poetry in motion when someone got pregnant, because you had all of these

services coming together to help them. So, if they had long standing diabetes, they'd suddenly have three or four different people supporting them." (FG1, HCP1)

Shared care decision

"The measurement of does that woman feel as though she's a partner in that care…it's about us not being paternalistic…does she feel as though she was involved?" (FG1, HCP2)

"…the lactation consultant comes to me and says, well, you need to hand express because your baby who's in neonatal intensive care needs breast milk…she didn't discuss the benefits…So I was sort of forced into it. No choices." (FG2, W3)

Continuity of care

Information being passed on

"…what's really important for [women] is the continuity in the transfer of information between those different stages…at certain stages, they get a lot of support and… communication, but…that doesn't happen naturally as they transition back to…general medical services..." (FG1, HCP4)

Seeing the same health care professionals

"…my main concern is, if you introduce me to Dr so and so… am I ever going to see Dr so and so, again..." (FG2, W1)

Social and peer support

"…I find myself … searching the Internet for blogs and anything of women who had the same conditions as me who had gone through pregnancy…it's like finding a needle in a haystack…and when I did find anything, I was like, oh yes that is how I feel." (FG2, W4)

"…consider other clubs and groups because nowadays there's a lot of mum groups …whatsapp groups..." (FG2, W6)

"…having someone who has the same condition as you, being part of the journey, would be a) they can advocate for you when really tricky subject comes up; b) they can take a lot more in because if you're getting shocking news at that time, your focus is not going to be on what the doctors or healthcare providers are talking about; and c) just having someone who has been through it, makes a whole lot of difference." (FG2, W1)

Information provision for preparedness

Informed of potential risks

"…doctors always like trying to make it as nice and cushy as possible…but they're not honest with you about the possible things that could happen." (FG2, W3)

"…I hate being taken by surprise…if I don't know what's coming, then I feel really, really out of control." (FG3, W2)

Informed of care

"…how informed they felt, how kept in the picture they felt even in emergency situations…" (FG2, W2)

"When your baby…go on to CPAP (continuous positive airway pressure)…seeing your baby with this big mask…it's the scariest thing…had I been warned that my child would look like that, maybe I would have felt better…" (FG2, W3)

Informed of support / services available

"People who have multiple medical conditions and planning for pregnancy/baby need more support, we don't know where to get that support and help..." (FG3, W6)

Informed for self-care

"…how can I adapt anything first…how can I adapt routines to help…knowledge is power…we can then sort them out ready for when mother and baby come home." (FG3, P1)

Birth experience

"For me I think the biggest thing would be…birth satisfaction… we had a very, very detailed birth plan…[the health care team] didn't speak to my consultant…it went almost as wrong as it could have gone." (FG2, W2)

Accessibility of services

Physical barriers
"…I ended up having to spend a night, in an inaccessible room…my wheelchair had to be kept outside…I was literally stuck in the bed…" (FG2, W2)

Social barriers
"…I ended up being assigned to a specialist health visitor…who purposely did do home visits, because domestic violence survivors can't go to a lot of the places they had previously gone to…"(FG2, W2)

Communication barriers

"…several friends of mine who are deaf BSL [British Sign Language] users…they had to have their hearing parents, come along for the birth, because the hospital told them they couldn't even get an interpreter." (FG2, W2)

Travel distances

"…I'm not going to travel really far when I'm pregnant…if I need urgent care, I don't have the choice of travel unfortunately." (FG, W3)
Health care professionals' knowledge and skills "… how confident the team is…to be able to care for us…It's their knowledge that's more important. (FG3, W1 and P1)
Health care professionals' knowledge of the women *"*...at every appointment… if I'm introduced to a new [health care professional], I say, have they read my notes before…I want them to be knowledgeable about me… how am I going to trust you to see me through the hardest point in my life, so much pain, so much stress, if I can't even trust that you know who I am.*"* (FG2, W1)
Health care professionals' attitude towards the women "…if the baby does have an issue and requires specialist treatment, how is that mother… who has multiple health conditions…treated...When they were talking about my little boy, they would often say oh he's the baby of the [name of health condition] mother with other health conditions. And then you could almost see the other nurses going hmm." (FG2, W4) "…they said, how are you going to manage to look after your child…because disabled women are seen as…not basically being suitable for having children that we just get completely bypassed. And my needs weren't met... And it's down to the attitudes of doctors, beyond anything else." (FG2, W2) "… I was discriminated and judged…I could not pick up my baby, no one was coming in to look at her, feed her, change her, nothing. I was in a room by myself…I felt like they have put a hazardous sign on my door…" (FG2, W1)
Hospital's facilities / services "…you choose the best hospital to meet your care for that day… the most [complete ones] for when you go in for tests, check-ups and also for the main day of the birth, where things can go wrong, and you want the specialists to all meet…"(FG3, P1)
Personalised care "…Are those discussions being had between the doctor and the patient, or are they just following the guidelines…[For postnatal care]…it was again almost like there was a sheet of guidelines that were being read off and ticked…having that a bit more individualized care, particularly for moms who have multiple health conditions." (FG2, W4)
Consistency of care "…the other thing that gets to me is… the consistency between…health workers…My [child] was born early…they work on an actual uncorrected age…my friends are getting

one set of treatment…but I don't get [the same treatment]…if there's a guideline of what they need to do…if it's all the same for everyone...” (FG2, W3)

Impact on partner

Partner’s caring role

“[my partner] is my carer, he has to physically help me get up and get dressed… The stuff that he has to see now that I’m sure it's traumatized him already…let alone a difficult birth or a birthing plan that goes wrong.” (FG3, W1)

Support for partner

“…because there are times, where I feel like my husband has needed more input than I have. But he's just never been offered it...” (FG3, W2)

Involvement of partner

“…the male is supported as much as the female, the male is included in all of the information, the males not felt that they can't ask questions…”(FG3, W1)

Partner’s mental well being

“…it would be good for fathers to be involved…like how it impacted them. Because I know, during my labour, [my partner] had a really difficult time…there were so many machines going on…so many doctors and anaesthetists…he would still talk about it now, how scary it was...” (FG3, W4)

Expectation of care and outcomes

“…the expectation of what she wanted for herself for that care…the outcomes…what is important to her…Because, sometimes, we…measure it according to our expectations...” (FG1, HCP2)

“…it's really difficult with multiple long-term conditions in pregnancy…the outcomes are so wide… I may recommend you not to get pregnant, because your risk of dying is so high, you may choose to get pregnant, but the satisfaction should be that I support you through that journey and you felt supported, whether your expectation has been met...” (FG1, HCP4)

Compliance with medication

“…interesting…to…find out…how many women have actually stopped taking their medication…” (FG1, HCP7)

“…we often see women who have, stopped their medication automatically as soon as they find out they're pregnant…then explaining to the woman the [impact their untreated] illness could have on the baby, and the pregnancy.” (FG1, HCP8)

Quality of life "…you might want to know the impact of the multiple morbidities on her quality of life..." (FG1, HCP3)
Children's outcome
Timing of birth (preterm birth) **Baby's growth** **Birth defect** **Child's death** "… I'd like to see the outcomes to the birth, what measurements would be for the growth of the baby, stillbirth, outcomes, abnormalities…maybe even type of births, the timing of the birth." (FG1, HCP2) "… the usual stats that are covered regarding…maternity care…maternal mortality and infant mortality…" (FG2, W2) "…any kind of birth…defect statistics…" (FG3, W1)
Separation of mother from newborn baby "…I gave birth to my [child], and she was rushed in to the neonatal intensive care unit because of her gestation…I was having nightmares that my child was looking for me and couldn't find me… it's very traumatic…you should be warned about it… to put you in a maternity ward with the other mothers that have just had their babies and they are so happy and excited and it's the first night. And here you are…babyless." (FG2, W3)
Baby's lung development (respiratory distress syndrome) "…my little boy had problems with his lungs, they hadn't quite developed, which is something that's linked with my [condition] that… I wasn't aware of…and also…delivering a little bit early and having a section, they kinda all added up to, leading to that." (FG2, W4)
Infant mental health "…there's quite a lot of research about infant mental health, quality of the [mother baby] relationship impacting on, development of the baby and how the absence of that relationship can have a negative impact…" (FG1, HCP8)
Impact of medication in pregnancy **Baby's condition at birth** "I had tried to search for more information on the Internet and had consulted with doctors and other people with the same condition around medication, because I wanted to be sure that it was safe, particularly for the baby…" (FG3, W5) "We need education about pregnancy and medication we are using and their side effects from our doctors." (FG3, W6)

"…how the baby could potentially be whenever they were born…that was a massive concern of mine…with all the… extra medications that I was taken during the pregnancy." (FG3, W4)
Neonatal intervention "…if you're looking at what interventions babies have had, hopefully that cascade of interventions that happens when a baby is sick, would be more considered [by health care professionals]." (FG3, W2)
Inheritance of mother's condition "What will happen in my next pregnancy, will my next child be diabetic or something, how will I manage it, and everything is still a worry." (FG2, W5) "…I was saying to my [child] to get that blood test, because sometimes it's inherited…so it can be like family conditions…they should definitely screen through when they do your medical history..." (FG2, W6)
Developmental outcomes "…we often use, again probably not perfect in any shape or form…two-year-old neurodevelopmental outcomes." (FG1, HCP6)
Metabolic syndrome "[regarding outcomes in children]…inflammatory diseases and the effect on metabolic syndrome, in the long term, also neurodevelopmental conditions in the longer term." (FG1, HCP1)
Neonatal morbidity "…so the morbidity would be typically looking at…whether they require intensive care, support in the neonatal period, whether they develop respiratory distress, and or depending on the condition, some of those might have an adverse impact on the cardiovascular function of the baby or the metabolic controls..." (FG1, HCP6)
Participation in society "…some of the long-term outcomes which may be more relevant as to how that child is going to be... be functioning as an adult…to the society as he or she grows." (FG1, HCP6)
Health care utilisation
Admission to neonatal unit "…they don't give you the possibility of [your newborn] going to neonatal intensive care unit (NICU)...(FG2, W3)."

Number of appointments "…my appointments they've made sure…I won't go in on a Monday and then go in on a Wednesday... They tried to have one appointment, at the right time in my pregnancy, so that I see everybody on that day…(FG2, W1)."
Length of hospitalisation "so what they want is some measure of…what is … the length of stay going to be, how long is my care going to need to be in hospital after I have given birth..." (FG1, HCP4)
Number of hospital admission during pregnancy **Financial implications** "…how many times during her pregnancy she requires admission to hospital? Does she require time off of work?" (FG1, HCP3) "…the financial impacts for them that are very worrying, additional visits…" (FG1, HCP4)
Consideration for future studies
Impact of ethnicity "…looking at what impact it would have on them specifically, i.e., from a black or brown perspective…" (FG1, HCP5)

Chapter 7

Supplementary Material 7.1: COS-STAR checklist

Section / Topic	Item No.	Checklist Item	Manuscript
TITLE / ABSTRACT			
Title	1a	Identify in the title that the paper reports the development of a COS	Title: Core outcomes for studies of pregnant women with multiple long-term conditions (multimorbidity) and their children: development of a core outcome set
Abstract	1b	Provide a structured summary	Abstract
INTRODUCTION			
Background and Objectives	2a	Describe the background and explain the rationale for developing the COS.	Background
	2b	Describe the specific objectives with reference to developing a COS.	Last sentence of the Background sentence states the aim of the study.
Scope	3a	Describe the health condition(s) and population(s) covered by the COS.	Methods: Scope
	3b	Describe the intervention(s) covered by the COS.	Methods: Scope
	3c	Describe the setting(s) in which the COS is to be applied.	Methods: Scope
METHODS			
Protocol/Registry Entry	4	Indicate where the COS development protocol can be accessed, if available, and/or the study registration details.	Methods: Study design
Participants	5	Describe the rationale for stakeholder groups involved in the COS development process, eligibility criteria for participants from each group, and a description of how the individuals involved were identified.	Methods: Participants
Information Sources	6a	Describe the information sources used to identify an initial list of outcomes.	Methods: Systematic literature search, Focus groups
	6b	Describe how outcomes were dropped/combined, with reasons (if applicable).	Methods: Delphi surveys

			Supplementary material 7.2: Selection of initial list of outcomes for Delphi surveys (workshop)
Consensus Process	7	Describe how the consensus process was undertaken.	Results: Delphi surveys, Consensus meetings
Outcome Scoring	8	Describe how outcomes were scored and how scores were summarised.	Results: Delphi surveys, Consensus meetings
Consensus Definition	9a	Describe the consensus definition.	Results: Delphi surveys, Consensus meetings
	9b	Describe the procedure for determining how outcomes were included or excluded from consideration during the consensus process.	Results: Delphi surveys, Consensus meetings Figure 7.1
Ethics and Consent	10	Provide a statement regarding the ethics and consent issues for the study.	Declarations: Ethics and consent
RESULTS			
Protocol Deviations	11	Describe any changes from the protocol (if applicable), with reasons, and describe what impact these changes have on the results.	Results: Changes to the protocol
Participants	12	Present data on the number and relevant characteristics of the people involved at all stages of COS development.	Table 7.1: Characteristics of participants
Outcomes	13a	List all outcomes considered at the start of the consensus process.	Supplementary material 7.3: Delphi results
	13b	Describe any new outcomes introduced and any outcomes dropped, with reasons, during the consensus process.	Results: Delphi surveys Supplementary material 7.3: Delphi results
COS	14	List the outcomes in the final COS.	Table 7.3
DISCUSSION			
Limitations	15	Discuss any limitations in the COS development process.	Discussion: Strengths and limitations
Conclusions	16	Provide an interpretation of the final COS in the context of other evidence, and implications for future research.	Discussion: Research implications
OTHER INFORMATION			
Funding	17	Describe sources of funding/role of funders.	Declarations: Funding
Conflicts of Interest	18	Describe any conflicts of interest	Declarations: Competing interest

Supplementary Material 7.2: Initial list of outcomes and decisions from the research team workshops

No	Outcomes	Source	Include for Delphi	Comments
	MATERNAL OUTCOMES			
	Maternal: Mortality / survival			
1	Maternal death	Literature	Y	
	Maternal: Physiological / clinical			
	Antenatal			
2	Fertility	Focus group	N	Population is not reproductive aged women
3	Impact on long-term health conditions	Focus group	Y	
4	Miscarriage	Focus group	Y	
5	Termination of pregnancy	Research team	Y	
6	Antenatal anxiety / depression	Research team	Combine	Combine with 'Perinatal mental health'
7	Pre-eclampsia, eclampsia, HELLP syndrome	Literature	Y	Separate 'Hypertensive disorders of/in pregnancy (gestational hypertension, pre-eclampsia, eclampsia)' into (i) gestational hypertension; (ii) Pre-eclampsia, eclampsia, HELLP syndrome
8	Gestational hypertension	Research team	Y	
9	Obstetric cholestasis	Literature	Y	
10	Gestational diabetes mellitus	Literature	Y	
11	Chorioamnionitis	Literature	Y	
12	Fluid abnormalities on ultrasound (oligohydramnios or polyhydramnios)	Literature	N	Not specific to pregnant women with multimorbidity
13	Oligohydramnios	Literature	N	Not specific to pregnant women with multimorbidity
14	Polyhydramnios	Literature	N	Not specific to pregnant women with multimorbidity
15	Placental abruption	Literature	Y	
16	Placental insufficiency	Literature	Y	PPI representative advised to include
17	Placenta previa	Literature	N	Clinicians commented there is no clinical or biological link between this and multimorbidity.

18	Smoking rate at booking	Literature	N	Risk factor for outcomes
19	Nausea / vomiting / dehydration	Literature	Y	
20	Hyperemesis gravidarum	Research team	Y	
21	Headache	Literature	N	Not specific to pregnant women with multimorbidity
	Peripartum			
22	Type of labour onset (e.g., spontaneous, induced)	Literature	Y	
23	Spontaneous rupture of membranes	Literature	N	Not specific to pregnant women with multimorbidity
24	Preterm premature rupture of membranes	Literature	Y	
25	Mode of birth	Literature	Y	Change to 'Types of birth'
26	Caesarean birth	Literature	Combine	Combine with 'Types of birth'
27	Emergency caesarean section	Literature	Combine	Combine with 'Types of birth'
28	Vaginal birth after previous cesarean section (VBAC)	Literature	Combine	Combine with 'Types of birth'
29	Any instrumental/assisted vaginal birth	Literature	Combine	Combine with 'Types of birth'
30	Normal (i.e., physiological) birth without intervention	Literature	Y	
31	Place of birth	Literature	Y	Changes to original preferred place of birth
32	Anaesthesia with gastric reference (Mendelson's syndrome, etc.)	Literature	N	Non specific
33	Types of analgesia (Use of pharmacological analgesia/anaesthesia)	Literature	Y	Separate 'Use of pharmacological analgesia/anaesthesia' into 2 outcomes: 'Types of analgesia' and 'Types of anaesthesia'
34	Types of anaesthesia	Research team	Y	
35	‘Drugs’ other than analgesics	Literature	N	Non specific
36	Postnatal administration of drugs	Literature	N	Non specific
37	Induction and/or labour augmentation (artificial rupture of membrane/ oxytocin)	Literature	Combine	Combined 'Induction of labour' with 'Types of labour onset'
38	Oxytocin augmentation of labour	Literature	Y	Change to 'Labour augmentation'
39	Number (count) of pregnancy complications	Literature	N	Non specific
40	Adverse event / outcome, serious complication – maternal	Literature	N	Non specific
41	Maternal near miss	Literature	N	Non specific
42	Procedural or anaesthesia complication	Literature	N	Non specific
43	Medication-related serious adverse events	Literature	N	Non specific

44	Obstetric haemorrhage	Literature	Y	
45	Maternal infection	Literature	Y	Infection that led to transfer to ITU / prolonged hospital stay / readmission to hospital / delay in discharge from hospital
46	Cesarean section wound infection	Literature	Combine	Combine with 'Maternal infection'
47	Wound complications	Literature	N	Captured by 'Maternal infection' and 'Recovery time'
48	Placenta (retained, manual removal)	Literature	Y	Change to 'Retained placenta'
49	Ruptured uterus	Literature	N	Not specific to pregnant women with multimorbidity
50	Uterine inversion	Literature	N	Not specific to pregnant women with multimorbidity
51	Uterine (expulsive effort, hyperstimulation, rupture, etc)	Literature	N	Not specific to pregnant women with multimorbidity
52	Laceration (cervical, vaginal, perineal)	Literature	N	Not specific to pregnant women with multimorbidity
53	Perineal/vaginal trauma	Literature	N	Captured by 'Birth injury: 3rd / 4th degree tear'
54	Episiotomy	Literature	N	Captured by 'Birth injury: 3rd / 4th degree tear'
55	Intact perineum	Literature	N	Captured by 'Birth injury: 3rd / 4th degree tear'
56	Third- and fourth-degree tear	Literature	Y	Change to 'Birth injury' and include 'Obstetric fistula'
57	Thromboembolic event (deep vein thrombosis, pulmonary embolism)	Literature	Y	Move to 'Antenatal'
58	Transfusion	Literature	Y	
59	Anaemia	Literature	N	Captured by 'Blood transfusion'
60	Smoking rate at delivery, Smoking cessation in pregnancy	Literature	N	This would be a factor that impact on outcomes, would be treated as a covariate
61	Mobility during labour	Literature	Y	
62	Pregnancy prolongation	Literature	N	Not specific to pregnant women with multimorbidity
63	Labour length/duration	Literature	Y	
64	Comfort	Literature	N	Captured in 'Birth experience'
65	Maternal perception of pain experienced	Literature	Y	Change to 'Involvement in decisions on pain relief: were you offered the type and amount of pain relief you required'
66	Relaxation	Literature	N	Captured in 'Birth experience'
67	Resuscitation measures, arrest, or loss of consciousness	Literature	N	Captured by 'Maternal intensive care admission'
68	Miscellaneous / other	Literature	N	Non-specific, catch all category

69	Blood pressure	Literature	N	Captured by 'Maternal intensive care admission' and 'Pre-eclampsia'
70	Surgical reference, additional operation	Literature	N	Non specific
71	Dilation and curettage for retained products of conception	Literature	N	Not specific to pregnant women with multimorbidity
72	Extension of uterine incision	Literature	N	Not specific to pregnant women with multimorbidity
73	Symphysiotomy	Literature	N	Not specific to pregnant women with multimorbidity
74	Hysterectomy	Literature	Y	
75	Respiratory morbidity	Literature	N	Captured in 'Severe maternal morbidity'
76	Renal impairment	Literature	N	Captured in 'Severe maternal morbidity'
77	Tissue injury (bladder and/or bowel injury)	Literature	N	Captured in 'Severe maternal morbidity'
78	Coagulation abnormalities	Literature	N	Captured in 'Severe maternal morbidity'
79	Hepatic complications	Literature	N	Captured in 'Severe maternal morbidity'
80	Cardiac complications	Literature	N	Captured in 'Severe maternal morbidity'
81	Bowel obstruction	Literature	N	Not specific to pregnant women with multimorbidity
82	Pulmonary oedema	Literature	N	Captured in 'Severe maternal morbidity'
83	Abnormal maternal biomarkers	Literature	N	Non specific
84	Severe maternal morbidity (SMM)	Literature	Y	
85	Non transfusion SMM	Literature	Combine	Combine with 'Severe maternal morbidity'
86	End organ injury	Literature	Combine	Combine with 'Severe maternal morbidity'
	Postnatal and long-term (beyond birth episode)			
87	Recovery time	Focus group	Y	
88	Development of new health conditions	Focus group	Y	
89	Long-term cardiovascular outcome	Focus group	N	Too specific to certain health conditions. Captured in 'Development of new long-term health condition'
	Maternal mental health			
90	Postnatal depression	Literature	Y	Change to 'Perinatal mental health'. Combine all as perinatal mental health and list the individual condition as example. However, keep post-traumatic stress disorder, self-harm, and suicide as standalone outcomes.
91	Puerperal psychosis	Literature	N	Combine all as perinatal mental health and list the individual condition as example. However, keep post-

				traumatic stress disorder, self-harm, and suicide as standalone outcomes.
92	Self-harm	Research team	Y	
93	Suicide	Research team	Y	
94	Post-traumatic stress disorder	Research team	Y	
95	Social and peer support	Focus group	Y	Add 'Perinatal mental health support' as a separate outcome to capture support for emotional and mental health
96	Perinatal mental health support	Research team (literature, focus group)	Y	
	Maternal: Life impact / functioning			
97	Incontinence	Literature	Y	
98	Pain with intercourse	Literature	N	Not specific to pregnant women with multimorbidity
99	Health-related quality of life	Literature	Y	
100	Well-being	Literature	Y	Emotional & mental well-being
101	Mental health	Literature	Combine	Combine as perinatal mental health
102	Treatment burden	Literature	Y	Treatment burden' to capture burden of self-care for the pregnant women, add 'Number of appointments and tests' for both mother and child
103	Number of appointments and tests	Research team (literature, focus group)	Y	
104	Self-rated health	Literature	Combine	Combine with health-related quality of life
105	Self-efficacy	Literature	Y	
106	Self-management behaviour	Literature	Combine	Combine as 'self-efficacy / self-management'
107	Perceived/personal control	Literature	Combine	Combine as 'self-efficacy / self-management'
108	Adherence	Literature	Y	Adherence with medication in pregnancy
109	Change in medication	Focus group	Y	
110	Activities of daily living	Literature	Combine	Combine as 'Physical functioning'
111	Physical functioning	Literature	Y	
112	Social functioning	Research team	Y	
113	Physical activity	Literature	Combine	Combine as 'Physical functioning'

114	Mother-infant attachment, bonding, interaction	Literature	Combine	Combine with 'Parent and infant bonding'
115	Parent and infant bonding	Focus group	Y	
116	Maternal guilt	Focus group	Y	
117	Pressure as a mother	Focus group	Combine	Combine as 'Maternal guilt and pressure'
118	Confidence with role as a mother	Literature	Y	
119	Care giver experience/satisfaction	Literature	N	Captured by impact on partner / family / carer
120	Views (mother's and/or father's)	Literature	N	Non specific
121	Impact on partner / family / carer	Focus group	Y	
	Maternal: Resource use, quality of care			
122	Health care use	Literature	N	Non specific
123	Late maternal complication	Literature	N	Non-specific and would be captured by postnatal readmission
124	High utilisation of perinatal acute care services	Literature	Y	
125	Unscheduled visit to the emergency department or clinic	Literature	N	Captured by 'Perinatal acute care services'
126	Hospitalisation	Literature	N	Captured by 'Postnatal admission and readmission' and 'Hospital length of stay'
127	Emergency department visit	Literature	N	Captured by 'Perinatal acute care services'
128	Readmission	Literature	Y	Change to 'Postnatal admission and readmission'
129	High dependency unit/postnatal stay	Literature	Combine	Combine as 'Postnatal admission and readmission'
130	Maternal intensive care unit admission	Literature	Y	
131	Need for hospital transfer	Literature	Y	
132	Hospital length of stay	Literature	Y	
133	Health care cost	Literature	Y	Add 'Financial implications' as a separate outcome to capture cost from a patient's perspective, e.g., time off work, childcare and travel cost to attend appointments. Also need these 2 outcomes separately for mother and child (in total, add 3 outcomes).
134	Financial implication	Research team	Y	
135	Communication	Literature	Y	Change to 'information provision to support preparation' as advised by PPI
136	Involvement in care decisions on overall care (Shared decision making)	Literature	Y	Change 'Shared decision making' to 'Involvement in care decisions' and as 4 separate outcomes for these 4 domains:

				(i) Overall care, (ii) types of birth, (iii) pain relief, and (iv) infant feeding method.
137	Involvement in care decisions on types of birth	Research team (literature, focus group)	Y	
138	Involvement in care decisions on infant feeding methods	Research team (literature, focus group)	Y	
139	Prioritization	Literature	Combine	Combine with shared decision making
140	Quality health care (patient-rated), satisfaction, confidence in health care provider	Literature	Y	Change to 'Quality of care and experience of care' and add separate outcomes for 'Attitude of health / social care professionals' and 'Confidence in health / social care professionals'
141	Attitude of health / social care professionals	Research team (literature, focus group)	Y	
142	Confidence in health / social care professionals	Research team (literature, focus group)	Y	
143	Consistency of care	Focus group	Combine	Combine with 'Quality and experience of care'
144	Holistic care / multidisciplinary coordination of care	Focus group	Y	Separate 'Holistic / personalised care' from 'Multidisciplinary coordination of care' and combine 'Holistic care' with 'Personalised care'
145	Personalised care	Focus group	Y	
146	Continuity of care	Focus group	Y	
147	Accessibility of services	Focus group	Y	
148	Hospital facilities / services	Focus group	Y	
149	Birth experience	Literature	Y	
150	Expectation of care and outcomes	Focus group	N	Satisfaction of whether expectation was met or managed would be captured by 'Quality of care'
151	Preconception care	Focus group	Y	Keep as separate heading, not to combine under generic quality of care. were you satisfied with the preconception care / felt it was informative?
152	Postnatal and long-term care	Focus group	Y	

153	Support for the family	Research team (literature, focus group)	Y	
154	Care for long-term conditions	Research team	Y	
	OUTCOMES FOR CHILDREN			
	Children: Mortality / survival			
155	Intrauterine fetal demise	Literature	Y	Change to 'Death before birth (fetal, still birth, perinatal death)'
156	Stillbirth	Literature	Combine	Combine as 'Death before birth (fetal, still birth, perinatal death)'
157	Neonatal death	Literature	Y	Change to 'Death after birth (neonatal death, infant death)'
158	Perinatal death	Literature	Combine	Combine as 'Death before birth (fetal, still birth, perinatal death)'
159	Infant death	Research team	Combine	Combine as 'Death after birth (neonatal death, infant death)'
	Children: Physiological / clinical			
	Fetal			
160	Intrauterine growth restriction	Literature	Y	
161	Non-reassuring fetal heart tones	Literature	N	The resulting outcome from this would be Caesarean section or baby's survival and these outcomes are already represented
162	Foetal heart rate monitoring	Literature	N	Process measure
163	Foetal blood sampling	Literature	N	Process measure
164	Foetal position (malpresentation, change, etc.)	Literature	N	No known biological link or clinical observation that this is higher risk in pregnant women with multimorbidity
165	Ultrasound sign	Literature	N	Not specific
166	Abnormal doppler findings on ultrasound	Literature	N	Not specific
167	Twin anaemia-polycythaemia sequence (TAPS)	Literature	N	Limited to twin pregnancy
168	Twin-to-twin transfusion syndrome (TTS) reoccurrence	Literature	N	Limited to twin pregnancy
	Neonatal (first 28 days)			
169	Gestational age at birth	Literature	Y	
170	Preterm birth	Literature	Combine	Combine with 'Gestational age at birth', then explain this is to help identify preterm, term and post term

171	Prematurity	Literature	Combine	Combine with 'Gestational age at birth', then explain this is to help identify preterm, term and post term
172	Apgar score	Literature	Y	
173	Birth weight	Literature	Y	
174	Small for gestational age	Literature	Combine	Combine with 'Birth weight'
175	Low birth weight	Literature	Combine	Combine with 'Birth weight'
176	Large for gestational age	Literature	Combine	Combine with 'Birth weight'
177	Meconium-stained liquor / meconium aspiration syndrome	Literature	Y	
178	Neonatal resuscitation required	Literature	Y	
179	Oxygen dependence	Literature	N	The more severe spectrum is captured by 'Chronic lung disease / bronchopulmonary dysplasia'
180	Neonatal respiratory morbidity	Literature	Y	Change to 'Neonatal respiratory distress syndrome'
181	Birth asphyxia	Literature	N	The consequence is captured by 'brain injury on imaging'
182	Any pH levels <7.20 and BD >12. 0	Literature	N	The consequence is captured by 'brain injury on imaging'
183	Hypoxic ischemic encephalopathy	Literature	Y	Change to 'Brain injury on imaging'
184	Babies with encephalopathy	Literature	Combine	Combine as 'Brain injury on imaging'
185	Intraventricular haemorrhage	Literature	Combine	Combine as 'Brain injury on imaging'
186	Periventricular leukomalacia	Literature	Combine	Combine as 'Brain injury on imaging'
187	Retinopathy of prematurity	Literature	Y	
188	Neonatal fitting/seizures	Literature	N	Captured by 'Brain injury on imaging'
189	Congenital anomaly	Literature	Y	
190	Patent ductus arteriosus	Literature	N	Captured by 'Congenital anomaly'
191	Neonatal infection, sepsis	Literature	Y	Change to 'Neonatal sepsis'
192	Shoulder dystocia	Literature	Y	Move to *Maternal outcomes*
193	Jaundice	Literature	Y	
194	Transition to extra-uterine life	Literature	N	Not specific
195	Necrotizing enterocolitis / bowel perforation	Literature	Y	
196	Intubation /ventilation	Literature	Y	
197	Hypoglycaemia	Literature	Y	
198	Foetal or neonatal anaemia	Literature	Y	
199	Inotropic support / hypotension	Literature	N	Captured by 'Admission to neonatal unit'

200	Birth injury to infant	Literature	Y	Change to 'Neonatal birth injury'
201	Peripheral nerve injury (at discharge from hospital)	Literature	Combine	Combine with 'Birth injury to infant'
202	Basal skull fracture	Literature	Combine	Combine with 'Birth injury to infant'
203	Spinal cord injury	Literature	Combine	Combine with 'Birth injury to infant'
204	Hypothermia	Literature	Y	
205	Decreased response to pain	Literature	N	Capture by 'Brain injury on imaging'
206	Stupor	Literature	N	Capture by 'Brain injury on imaging'
207	Clinically significant genital injury	Literature	N	Captured by 'Neonatal birth injury'
208	Hypotonia	Literature	N	Capture by 'Brain injury on imaging'
209	Coma	Literature	N	Capture by 'Brain injury on imaging'
210	Tube feeding	Literature	N	Capture by 'Need for complex care'
211	Loss to follow-up	Literature	N	Not specific
212	Ischemic injury	Literature	Combine	Combine with 'Birth injury to infant'
213	Amniotic band syndrome	Literature	N	Captured by 'Congenital anomaly'
214	Systemic inflammatory response syndrome	Literature	N	Captured by 'Admission to neonatal unit'
215	Allergic reaction	Literature	N	Not specific
216	Postnatal administration of drugs	Literature	N	Not specific
217	Adverse event	Research team (Neonatal core outcome set)	N	Not specific
218	Composite of infant morbidity outcomes	Literature	N	Not specific in terms of health conditions that will constitute neonatal morbidity
219	Skin to skin contact	Literature	Y	
220	Blood transfusion	Research team	Y	
	Infant (first 1 year)			
221	Method of infant feeding, breastfeeding	Literature	Y	Add 'Informed and supported with methods of infant feeding'. Move to *Maternal outcome.*
222	Feeding difficulty	Research team	Y	
223	Infant mental health	Focus group	Y	Change to 'Children's mental health & behavioural disorder'
	Longer term			
224	Abnormal neurodevelopmental outcome at age 2 years	Literature	Y	Keep 'Neurodevelopmental disorder' as a separate outcome given its importance

225	General gross motor ability (neurodevelopmental)	Research team (Neonatal core outcome set)	Y	Neurodevelopmental disorder' is too broad, need to break it down into the four main categories.
226	General fine motor ability (neurodevelopmental)	Research team	Y	Neurodevelopmental disorder' is too broad, need to break it down into the four main categories.
227	General cognitive ability (neurodevelopmental)	Research team (Neonatal core outcome set)	Y	Neurodevelopmental disorder' is too broad, need to break it down into the four main categories.
228	General social ability (neurodevelopmental)	Research team	Y	Neurodevelopmental disorder' is too broad, need to break it down into the four main categories.
229	Cerebral palsy	Literature	Y	Keep 'Cerebral palsy' as a separate outcome given its importance
230	Faltering growth (previously failure to thrive)	Focus group	Y	
231	Metabolic syndrome	Focus group	Y	
232	Impact of medication during pregnancy	Focus group	N	The specific outcomes resulting from mother taking medication during pregnancy are already captured (e.g., congenital anomaly, low blood sugar)
233	Inheritance of mother's conditions	Focus group	Y	
234	Chronic lung disease / bronchopulmonary dysplasia	Research team (Neonatal core outcome set)	Y	
	Children: life impact / functioning			
235	Quality of life	Research team (Neonatal core outcome set)	Y	
236	Visual impairment or blindness	Research team (Neonatal core outcome set)	Y	
237	Hearing impairment or deafness	Research team (Neonatal core outcome set)	Y	
238	Education attainment	Research team	Y	
239	Participation in society	Focus group	Y	
	Children: Resource use			

240	Neonatal admission to special care and/or intensive care unit	Literature	Y	Change to 'Admission to neonatal unit' as the categorisation of level of care may not be universal, difficult to separate at different level of care. Give examples of different levels of care.
241	Neonate length of stay	Literature	N	Captured by 'separation of mother from baby'
242	Separation of mother from newborn baby	Focus group	Y	
243	Neonatal readmission to hospital	Literature	Y	
244	Transfer to long-term care facility	Literature	Y	Change to 'Need for complex care after neonatal unit', give example, needing home ventilation / home nutritional support
245	Number of appointments and tests	Research team (literature, focus group)	Y	
246	Pain / distress from test / treatment	Research team	Y	
247	Health care cost	Research team	Y	
248	Financial implication	Research team	Y	

Supplementary Material 7.3: Delphi survey results and attrition analysis

First Delphi survey

		% of Participants that rated the outcome as *Critically Important (Consensus In)*			Number of participants that provided a rating for the outcome and included in the analysis		
No	**Outcomes**	**All**	**Women/Partner**	**Clinicians/Researchers**	**Denominator All**	**Denominator Women/Partner**	**Denominator Clinicians/Researchers**
1	Death after birth (child)	97.09%	95.16%	97.92%	206	62	144
2	Death before birth (child)	95.17%	96.77%	94.48%	207	62	145
3	Maternal death	93.69%	88.89%	95.80%	206	63	143
4	Pre-eclampsia, eclampsia, HELLP syndrome	93.56%	91.67%	94.37%	202	60	142
5	Severe maternal morbidity	91.54%	95.16%	89.93%	201	62	139
6	Neonatal birth injury	90.20%	91.80%	89.51%	204	61	143
7	Requiring intubation ventilation (child)	88.24%	83.87%	90.14%	204	62	142
8	Placental abruption	87.50%	88.14%	87.23%	200	59	141
9	Congenital anomaly (birth defect)	87.19%	91.94%	85.11%	203	62	141
10	Neonatal sepsis	87.19%	85.48%	87.94%	203	62	141
11	Neonatal resuscitation required	86.21%	86.89%	85.92%	203	61	142
12	Brain injury on imaging (child)	85.85%	90.32%	83.92%	205	62	143
13	Cerebral palsy (child)	85.43%	81.67%	87.05%	199	60	139
14	Placental insufficiency	84.50%	86.67%	83.57%	200	60	140
15	Admission to intensive care (maternal)	84.31%	79.03%	86.62%	204	62	142
16	Postpartum haemorrhage	83.50%	85.48%	82.64%	206	62	144
17	Necrotizing enterocolitis	82.38%	82.14%	82.48%	193	56	137
18	Suicide attempts (perinatal)	81.16%	80.95%	81.25%	207	63	144
19	Impact on long-term health conditions	81.09%	82.26%	80.58%	201	62	139

20	Admission to neonatal unit	80.77%	83.87%	79.45%	208	62	146
21	Development of new long-term conditions	80.68%	87.30%	77.78%	207	63	144
22	Neonatal respiratory distress syndrome	80.20%	86.89%	77.30%	202	61	141
23	Chronic lung disease / bronchopulmonary dysplasia (child)	79.60%	75.41%	81.43%	201	61	140
24	Perinatal mental health	79.43%	84.13%	77.40%	209	63	146
25	Children's mental health and behavioural disorder	78.05%	67.21%	82.64%	205	61	144
26	Fetal growth restriction	77.56%	81.97%	75.69%	205	61	144
27	Post-traumatic stress disorder	77.40%	87.30%	73.10%	208	63	145
28	Miscarriage	76.21%	84.13%	72.73%	206	63	143
29	Hysterectomy	75.74%	77.78%	74.82%	202	63	139
30	Gestational hypertension	75.61%	67.21%	79.17%	205	61	144
31	Venous thromboembolism	75.38%	75.44%	75.35%	199	57	142
32	Apgar score	75.12%	85.25%	70.83%	205	61	144
33	Gestational age at birth (preterm / post-term)	74.51%	65.57%	78.32%	204	61	143
34	Neonatal readmission to hospital	74.16%	79.37%	71.92%	209	63	146
35	Retinopathy of prematurity	74.09%	66.67%	77.21%	193	57	136
36	Preterm premature rupture of membranes	74.02%	72.13%	74.83%	204	61	143
37	Meconium aspiration syndrome (child)	73.74%	70.18%	75.18%	198	57	141
38	Neurodevelopmental disorder (child)	73.66%	68.85%	75.69%	205	61	144
39	Gestational diabetes	73.63%	70.49%	75.00%	201	61	140
40	Self-harm (perinatal)	72.82%	71.43%	73.43%	206	63	143
41	Need for complex care (child)	71.71%	72.58%	71.33%	205	62	143

42	Visual impairment / blindness (child)	70.73%	66.67%	72.41%	205	60	145
43	Care for long-term conditions (maternal)	69.42%	79.03%	65.28%	206	62	144
44	Maternal infection	69.08%	70.97%	68.28%	207	62	145
45	Involvement in care decisions on overall care	68.93%	77.78%	65.03%	206	63	143
46	Quality of life (child)	68.78%	70.97%	67.83%	205	62	143
47	Birth injury (e.g., 3rd /4th degree tear, obstetric fistula)	68.63%	66.67%	69.44%	204	60	144
48	Birth weight	68.63%	55.74%	74.13%	204	61	143
49	Hearing impairment / deafness (child)	68.14%	58.33%	72.22%	204	60	144
50	Inheritance of mother's health conditions (child)	67.32%	70.00%	66.21%	205	60	145
51	Postpartum admission / readmission	66.67%	80.65%	60.69%	207	62	145
52	Failure to thrive (child)	66.50%	68.33%	65.73%	203	60	143
53	Separation of mother from newborn baby	66.18%	73.02%	63.19%	207	63	144
54	Perinatal mental health support	65.85%	74.19%	62.24%	205	62	143
55	General cognitive ability (child)	65.52%	51.67%	71.33%	203	60	143
56	Postpartum and long-term support	64.56%	75.41%	60.00%	206	61	145
57	Multidisciplinary coordination of care	64.53%	73.33%	60.84%	203	60	143
58	Fetal / neonatal anaemia	64.50%	60.66%	66.19%	200	61	139
59	Shoulder dystocia	64.36%	65.00%	64.08%	202	60	142
60	Accessibility of services	64.25%	59.68%	66.21%	207	62	145
61	Hypoglycaemia (low blood sugar, child)	63.50%	63.79%	63.38%	200	58	142
62	General gross motor ability (child)	63.37%	51.67%	68.31%	202	60	142

63	Metabolic syndrome (child)	63.37%	62.71%	63.64%	202	59	143
64	Emotional & mental wellbeing (maternal)	62.98%	68.25%	60.69%	208	63	145
65	Hypothermia (low body temperature, child)	62.81%	57.63%	65.00%	199	59	140
66	Confidence in health / social care professionals	62.80%	73.02%	58.33%	207	63	144
67	Health related quality of life (maternal)	62.75%	68.85%	60.14%	204	61	143
68	General fine motor ability (child)	62.69%	51.67%	67.38%	201	60	141
69	Attitude of health / social care professionals	62.50%	71.43%	58.62%	208	63	145
70	Retained placenta	61.50%	63.33%	60.71%	200	60	140
71	Blood transfusion (child)	61.46%	64.52%	60.14%	205	62	143
72	Psychosocial support	61.35%	70.49%	57.53%	207	61	146
73	Blood transfusion (maternal)	60.87%	61.90%	60.42%	207	63	144
74	Types of birth (e.g., vaginal, caesarean)	60.19%	59.68%	60.42%	206	62	144
75	Physical functioning (maternal)	60.00%	66.67%	57.04%	205	63	142
76	Adherence with medication	59.71%	66.13%	56.94%	206	62	144
77	Pain / distress from test / treatment	59.71%	60.32%	59.44%	206	63	143
78	Involvement in decisions on infant feeding methods	59.62%	60.32%	59.31%	208	63	145
79	Treatment burden for the pregnant women	59.22%	61.29%	58.33%	206	62	144
80	Feeding difficulties (child)	59.02%	64.52%	56.64%	205	62	143
81	Parent-infant bonding	58.94%	68.25%	54.86%	207	63	144
82	Quality of care & experience of care	58.54%	64.52%	55.94%	205	62	143
83	Termination of pregnancy	58.42%	60.00%	57.75%	202	60	142
84	Chorioamnionitis	58.06%	66.67%	54.81%	186	51	135

85	Change in medication in pregnancy	57.89%	71.43%	52.05%	209	63	146
86	Education attainment (child)	57.43%	45.76%	62.24%	202	59	143
87	Continuity of care	56.73%	69.35%	51.37%	208	62	146
88	Incontinence	56.59%	55.00%	57.24%	205	60	145
89	Holistic & personalised care	55.34%	65.08%	51.05%	206	63	143
90	Preconception care	55.34%	54.10%	55.86%	206	61	145
91	Involvement in decisions on pain relief	55.34%	61.29%	52.78%	206	62	144
92	Birth experience	55.29%	60.32%	53.10%	208	63	145
93	Maternal guilt & pressure	55.07%	58.06%	53.79%	207	62	145
94	Neonatal jaundice	53.96%	48.39%	56.43%	202	62	140
95	Skin to skin with parents	53.88%	51.61%	54.86%	206	62	144
96	High utilisation of perinatal acute care services	53.69%	51.67%	54.55%	203	60	143
97	Involvement in decisions on types of birth	53.40%	63.49%	48.95%	206	63	143
98	Recovery time (maternal)	52.88%	68.25%	46.21%	208	63	145
99	Social participation (child)	52.22%	48.33%	53.85%	203	60	143
100	Types of labour onset (e.g., induced)	51.96%	52.46%	51.75%	204	61	143
101	Role as a mother	51.46%	50.79%	51.75%	206	63	143
102	Information provision to support preparation	51.22%	60.66%	47.22%	205	61	144
103	General social ability (child)	50.49%	40.98%	54.55%	204	61	143
104	Need for hospital transfer (maternal)	50.00%	52.46%	48.95%	204	61	143
105	Support for the family	49.51%	56.45%	46.53%	206	62	144
106	Hospital facilities / services	48.80%	60.32%	43.84%	209	63	146
107	Financial implications for family (child)	48.78%	50.82%	47.92%	205	61	144
108	Self-efficacy / self-management	48.06%	56.45%	44.44%	206	62	144

109	Methods of infant feeding	47.85%	46.03%	48.63%	209	63	146
110	Involvement in decisions on place of birth	47.32%	53.97%	44.37%	205	63	142
111	Birth without intervention	47.06%	48.39%	46.48%	204	62	142
112	Impact on family / carer / partner	46.57%	49.18%	45.45%	204	61	143
113	Obstetric cholestasis	45.74%	50.94%	43.70%	188	53	135
114	Health care cost (maternal)	44.61%	34.43%	48.95%	204	61	143
115	Number of appointments (child)	44.61%	37.10%	47.89%	204	62	142
116	Health care cost (child)	44.55%	34.43%	48.94%	202	61	141
117	Social functioning (maternal)	44.39%	50.82%	41.67%	205	61	144
118	Length of labour	43.69%	41.94%	44.44%	206	62	144
119	Hospital length of stay (maternal)	43.35%	45.90%	42.25%	203	61	142
120	Financial impact (e.g., time off work, maternal)	42.51%	43.55%	42.07%	207	62	145
121	Types of anaesthesia	40.59%	45.76%	38.46%	202	59	143
122	Labour augmentation	39.90%	46.55%	37.24%	203	58	145
123	Types of pain relief	37.93%	45.00%	34.97%	203	60	143
124	Mobility during labour (maternal)	37.50%	44.07%	34.75%	200	59	141
125	Number of appointments (maternal)	36.23%	42.86%	33.33%	207	63	144
126	Hyperemesis gravidarum	34.16%	40.98%	31.21%	202	61	141
127	Nausea & vomiting	21.57%	26.98%	19.15%	204	63	141

Second Delphi survey

		% of Participants that rated the outcome as *Critically Important (Consensus In)*			Number of participants that provided a rating for the outcome and included in the analysis		
No	**Outcomes**	**All**	**Women/Partner**	**Clinicians/Researchers**	**Denominator All**	**Denominator Women/Partner**	**Denominator Clinicians/Researchers**
1	Death after birth	99.13%	97.44%	100.00%	115	39	76
2	Death before birth (child)	99.13%	97.44%	100.00%	115	39	76
3	Maternal death	96.49%	89.74%	100.00%	114	39	75
4	Neonatal resuscitation required	93.86%	92.31%	94.67%	114	39	75
5	Requiring intubation / ventilation	93.81%	89.74%	95.95%	113	39	74
6	Pre-eclampsia, eclampsia, HELLP syndrome	90.00%	84.21%	93.06%	110	38	72
7	Severe maternal morbidity	88.99%	83.33%	91.78%	109	36	73
8	Admission to neonatal unit	88.79%	84.62%	90.91%	116	39	77
9	Neonatal birth injury	88.70%	87.18%	89.47%	115	39	76
11	Postpartum haemorrhage	88.50%	79.49%	93.24%	113	39	74
10	Neonatal sepsis	88.50%	84.62%	90.54%	113	39	74
12	Brain injury on imaging (child)	87.83%	81.58%	90.91%	115	38	77
13	Congenital anomaly (birth defect)	86.21%	84.62%	87.01%	116	39	77
14	Admission to intensive care (maternal)	86.09%	71.79%	93.42%	115	39	76
15	Cerebral palsy (child)	85.96%	74.36%	92.00%	114	39	75
16	Development of new long-term conditions	85.96%	87.18%	85.33%	114	39	75
17	Placental abruption	85.71%	84.21%	86.49%	112	38	74
18	Placental insufficiency	85.45%	78.95%	88.89%	110	38	72
19	Apgar score	82.61%	84.21%	81.82%	115	38	77
20	Chronic lung disease / bronchopulmonary dysplasia	82.30%	76.32%	85.33%	113	38	75
21	Suicide attempts (perinatal)	81.58%	71.79%	86.67%	114	39	75
22	Neonatal readmission to hospital	81.03%	79.49%	81.82%	116	39	77

23	Impact on long-term health conditions (maternal)	80.36%	78.95%	81.08%	112	38	74
24	Neonatal respiratory distress syndrome	80.00%	71.79%	84.21%	115	39	76
25	Post-traumatic stress disorder	80.00%	76.92%	81.58%	115	39	76
26	Gestational age at birth (preterm / post-term)	79.31%	58.97%	89.61%	116	39	77
27	Perinatal mental health	79.13%	69.23%	84.21%	115	39	76
28	Necrotizing enterocolitis	78.76%	68.42%	84.00%	113	38	75
29	Fetal growth restriction	78.45%	69.23%	83.12%	116	39	77
30	Retinopathy of prematurity	78.18%	76.32%	79.17%	110	38	72
31	Preterm premature rupture of membranes	78.07%	69.23%	82.67%	114	39	75
32	Venous thromboembolism	77.27%	67.57%	82.19%	110	37	73
33	Children's mental health & behavioural disorders	77.19%	69.23%	81.33%	114	39	75
34	Need for complex care (child)	76.72%	64.10%	83.12%	116	39	77
35	Neurodevelopmental disorder (child)	76.52%	76.92%	76.32%	115	39	76
36	Visual impairment / blindness	75.00%	74.36%	75.32%	116	39	77
37	Hysterectomy	74.77%	71.05%	76.71%	111	38	73
38	Self-harm (perinatal)	73.91%	61.54%	80.26%	115	39	76
39	Birth weight	73.68%	58.97%	81.33%	114	39	75
40	Neonatal abstinence syndrome	73.68%	71.79%	74.67%	114	39	75
41	Involvement in care decisions on overall care	73.28%	76.92%	71.43%	116	39	77
42	Perinatal mental health support	72.41%	69.23%	74.03%	116	39	77
43	Meconium aspiration syndrome (child)	72.17%	66.67%	75.00%	115	39	76
44	Maternal infection	70.80%	65.79%	73.33%	113	38	75
45	Postpartum admission / readmission (maternal)	70.43%	58.97%	76.32%	115	39	76

46	Quality of care & experience of care	69.83%	71.79%	68.83%	116	39	77
47	Gestational diabetes	69.64%	55.26%	77.03%	112	38	74
48	General cognitive ability (child)	69.57%	61.54%	73.68%	115	39	76
49	Gestational hypertension	69.37%	55.26%	76.71%	111	38	73
50	Care for long-term conditions (maternal)	68.97%	66.67%	70.13%	116	39	77
51	Quality of life (child)	68.70%	71.79%	67.11%	115	39	76
52	Fetal / neonatal anaemia	68.42%	68.42%	68.42%	114	38	76
53	Shoulder dystocia	68.18%	55.56%	74.32%	110	36	74
54	Miscarriage	68.14%	73.68%	65.33%	113	38	75
55	General gross motor ability (child)	67.54%	56.41%	73.33%	114	39	75
56	Blood transfusion (child)	67.24%	74.36%	63.64%	116	39	77
57	General fine motor ability (child)	66.67%	60.53%	69.74%	114	38	76
58	Hypoglycaemia (low blood sugar, child)	66.38%	61.54%	68.83%	116	39	77
60	Separation of mother from newborn baby	66.38%	74.36%	62.34%	116	39	77
59	Inheritance of mother's health conditions (child)	66.38%	79.49%	59.74%	116	39	77
61	Retained placenta	65.18%	65.79%	64.86%	112	38	74
62	Hypothermia (low body temperature, child)	64.66%	64.10%	64.94%	116	39	77
63	Hearing impairment / deafness (child)	64.35%	61.54%	65.79%	115	39	76
64	Postpartum and long-term support	64.35%	61.54%	65.79%	115	39	76
65	Birth injury (e.g., 3rd /4th degree tear, obstetric fistula)	64.29%	60.53%	66.22%	112	38	74
66	Emotional & mental wellbeing (maternal)	63.79%	61.54%	64.94%	116	39	77
67	Involvement in decisions on pain relief	63.79%	71.79%	59.74%	116	39	77

68	Faltering growth	63.48%	58.97%	65.79%	115	39	76
69	Termination of pregnancy	63.39%	71.05%	59.46%	112	38	74
70	Types of birth (e.g., vaginal, caesarean)	62.83%	53.85%	67.57%	113	39	74
71	Involvement in decisions on types of birth	62.07%	71.79%	57.14%	116	39	77
72	Metabolic syndrome (child)	61.40%	69.23%	57.33%	114	39	75
73	Involvement in decisions on infant feeding methods	61.21%	64.10%	59.74%	116	39	77
74	Psychosocial support	61.21%	64.10%	59.74%	116	39	77
75	Quality of life (mother)	59.48%	64.10%	57.14%	116	39	77
76	Confidence in health / social care professionals	59.13%	57.89%	59.74%	115	38	77
77	Education attainment (child)	58.62%	46.15%	64.94%	116	39	77
78	Blood transfusion (maternal)	58.56%	65.79%	54.79%	111	38	73
79	Physical functioning (maternal)	57.76%	56.41%	58.44%	116	39	77
80	Chorioamnionitis	57.55%	57.14%	57.75%	106	35	71
81	Utilisation of antenatal / perinatal acute care services	57.39%	50.00%	61.04%	115	38	77
82	Feeding difficulties (child)	56.90%	46.15%	62.34%	116	39	77
83	Multidisciplinary coordination of care	56.90%	53.85%	58.44%	116	39	77
84	Involvement in decisions on place of birth	56.90%	61.54%	54.55%	116	39	77
85	Preconception care	56.52%	50.00%	59.74%	115	38	77
86	Accessibility of services	56.03%	48.72%	59.74%	116	39	77
87	Attitude of health / social care professionals	56.03%	56.41%	55.84%	116	39	77
88	Incontinence	55.65%	41.03%	63.16%	115	39	76
89	Birth experience	54.78%	64.10%	50.00%	115	39	76
93	Need for hospital transfer (maternal)	54.31%	41.03%	61.04%	116	39	77

90	Adherence with medication	54.31%	53.85%	54.55%	116	39	77
91	Change in medication in pregnancy	54.31%	53.85%	54.55%	116	39	77
94	Parent infant interaction, bonding, attachment	54.31%	53.85%	54.55%	116	39	77
92	Continuity of care	54.31%	56.41%	53.25%	116	39	77
95	Pain / distress from test / treatment	52.59%	56.41%	50.65%	116	39	77
96	Treatment burden for the pregnant women	52.17%	60.53%	48.05%	115	38	77
97	Holistic & personalised care	51.72%	51.28%	51.95%	116	39	77
98	Neonatal jaundice	51.30%	48.72%	52.63%	115	39	76
99	Recovery time (maternal)	50.00%	64.10%	42.67%	114	39	75
100	Skin to skin with parents	48.70%	51.28%	47.37%	115	39	76
101	Childhood vaccination	48.28%	51.28%	46.75%	116	39	77
102	Types of labour onset (e.g., induced)	48.25%	48.72%	48.00%	114	39	75
103	Cephalopelvic disproportion	47.17%	52.78%	44.29%	106	36	70
104	Social participation (child)	46.96%	48.72%	46.05%	115	39	76
105	Financial implications for family (child)	46.55%	38.46%	50.65%	116	39	77
106	Maternal guilt & pressure	46.55%	43.59%	48.05%	116	39	77
107	Support for the family	46.55%	46.15%	46.75%	116	39	77
108	Health care cost (child)	45.69%	41.03%	48.05%	116	39	77
109	Hyperemesis gravidarum	45.54%	52.63%	41.89%	112	38	74
110	Role as a mother	45.22%	48.72%	43.42%	115	39	76
111	Obstetric cholestasis	44.95%	51.35%	41.67%	109	37	72
113	Hospital length of stay (maternal)	44.83%	35.90%	49.35%	116	39	77
112	General social ability (child)	44.83%	51.28%	41.56%	116	39	77
114	Information provision to support preparation	44.35%	46.15%	43.42%	115	39	76
115	Methods of infant feeding	43.48%	41.03%	44.74%	115	39	76

116	Labour augmentation	40.91%	47.37%	37.50%	110	38	72
117	Hospital facilities / services	40.52%	48.72%	36.36%	116	39	77
118	Types of pain relief	40.35%	48.72%	36.00%	114	39	75
120	Health care cost (maternal)	39.13%	28.95%	44.16%	115	38	77
119	Feeding support	39.13%	46.15%	35.53%	115	39	76
121	Self-efficacy / self-management	38.26%	36.84%	38.96%	115	38	77
122	Types of anaesthesia	36.84%	41.03%	34.67%	114	39	75
123	Social functioning (maternal)	35.09%	35.14%	35.06%	114	37	77
124	Length of labour	34.51%	31.58%	36.00%	113	38	75
125	Impact on family / carer / partner	34.48%	33.33%	35.06%	116	39	77
126	Birth without intervention	33.93%	36.84%	32.43%	112	38	74
127	Number of appointments (child)	33.62%	33.33%	33.77%	116	39	77
128	Mobility during labour (maternal)	30.97%	34.21%	29.33%	113	38	75
129	Financial impact (maternal)	26.09%	30.77%	23.68%	115	39	76
130	Nausea & vomiting	20.35%	18.42%	21.33%	113	38	75
131	Number of appointments (maternal)	20.00%	23.68%	18.18%	115	38	77

Outcomes suggested in the first Delphi survey

No	Outcomes suggested by participants in the 1st Delphi survey	Comments / Changes made to 2nd Delphi
1	Antepartum hospitalization on Obstetric unit	Change 'High utilisation of perinatal acute services' to 'Utilisation of antenatal & perinatal acute services'
2	Antepartum hospitalization on Psychiatric unit	Change 'High utilisation of perinatal acute services' to 'Utilisation of antenatal & perinatal acute services'
3	Number of antenatal emergency department attendances	Change 'High utilisation of perinatal acute services' to 'Utilisation of antenatal & perinatal acute services'
4	Involvement of the general practitioner as the coordinator of care in UK	
5	Primary care - unable to access the required treatment because primary care services do not want to prescribe	
6	There should also be information about the father's health and its role in pregnancy complications and care for the baby and child, such as addiction	Risk factor for pregnancy outcome
7	single mom vs good partner relationship vs bad partner relationship	Risk factor for pregnancy outcome
8	Effect on non-birthing partner	Captured in 'Impact on family / carer / partner'
9	Outcomes in fathers / partners	Captured in 'Impact on family / carer / partner'
10	Father and relatives support during pregnancy and after delivery.	Captured in 'Support for the family'
11	The effects of domestic violence	Risk factor for pregnancy outcome
12	obstetric violence/abuse	
13	Abuse and neglect in both parent and child	
14	Babies having withdrawal symptoms from medication (that is deemed completely safe) the mother was taking during pregnancy.	Add 'Neonatal abstinence syndrome'
15	Mothers' medication effect on baby during pregnancy and after they are born.	Add 'Neonatal abstinence syndrome'
16	Medication in pregnancy	
17	Medication in the newborn	
18	To have correct info at the right time about what medication for pregnant women's conditions that are suitable for conception/pregnancy/breastfeeding	Captured by 'information provision for preparation'

19	Maternal obesity / body mass index	
20	Gestational weight gain	
21	Immunization of Mother and Baby.	Add 'Childhood vaccination'
22	Immunization of the newborn	Add 'Childhood vaccination'
23	Adherence to vaccinations during the first year of life	Add 'Childhood vaccination'
24	Obstructed labour, cephalopelvic disproportion	Add 'Cephalopelvic disproportion'
25	Cephalopelvic disproportion in labour	Add 'Cephalopelvic disproportion'
26	Maternal autonomy	Captured by 'Involvement in care decisions'
27	Respect of mother's consent	
28	Feeding support at hospital as well as community level	Add 'Feeding support'
29	Need for extra services e.g., breastfeeding support, perinatal mental health team.	Add 'Feeding support'
30	Establishment of breast feeding (where preferred by mothers)	
31	Respect of mother	Captured by 'Attitude of health / social care professionals'
32	Discrimination and stigma from health professionals related to chronic conditions (e.g., attitudes towards obesity)	Captured by 'Attitude of health / social care professionals'
33	Infertility - challenges with conception due to chronic condition or treatment	Study population is women who are already pregnant so not in scope
34	Spontaneous pregnancy vs ARTs	Study population is women who are already pregnant so not in scope
35	Prenatal screening to enhance early detection of this abnormalities among women of child bearing age.	Captured in 'Preconception care'
36	Pre- pregnancy counselling	Captured in 'Preconception care'
37	Preconception interventions to improve management of long-term conditions	Captured in 'Preconception care'
38	Preconception intervention to reduce risks of concomitant medications	Captured in 'Preconception care'
39	Parent infant interaction not just bonding	Change 'Parent-infant bonding' to 'Parent infant interaction, bonding, attachment'
40	Quality of mother-infant interaction	Change 'Parent-infant bonding' to 'Parent infant interaction, bonding, attachment'
41	Infant socio-emotional development (attachment)	Change 'Parent-infant bonding' to 'Parent infant interaction, bonding, attachment'

42	Attachment status of parent and child (i.e., transmission of not, link to trauma or not etc)	Change 'Parent-infant bonding' to 'Parent infant interaction, bonding, attachment'
43	Child emotional development before age 5 (DC 0 to 5)	
44	Child psychiatric disorder during childhood and adolescence, i.e., for example depression and suicidal ideation if information is available.	Captured by 'Children's mental health & behavioural disorder'
45	Access to postnatal contraception	
46	Impact upon future family plans	
47	Management of emergencies	
48	Vertical transmission risk to fetus	
49	Routine early new born care in day-to-day life	
50	Regular specialist check-ups of children up to 10 years	
51	Psychotic, manic or severe depressive episode	Captured in 'Perinatal mental health'
52	Recurrent UTIs in pregnancy	
53	Ongoing engagement with health services, i.e., has there been improvement or break down of trust with health care professionals due to birth and pregnancy experiences.	
54	Contact with family/friends while an inpatient	
55	Wellbeing of the care providers.	
56	Hypocalcaemia in pregnancy	
57	Patients' feelings about pregnancy	
58	Social judicial status	
59	Adoption, foster care	
60	Environmental insults and adverse events	
61	Uterine artery first trimester	
62	The term "failure to thrive" is out of date - "faltering growth" is used in current NICE/NHS guidelines.	Change 'Failure to thrive' to 'Faltering growth'
63	Joint MDT care where applicable	Captured in 'Multidisciplinary coordination of care'
64	Delivery place- home or hospital	Captured in 'Involvement in care decisions for overall care'
65	Support to parents with long term health conditions once released home.	Captured in 'postpartum and long-term support'
66	Support systems in place for the individual need considering. Family, Friends not just the medical side.	Captured in 'Psychosocial support'

67	How parents experienced pregnancy, birth, postnatal time, did they feel supported?	Captured in 'Birth experience' and 'Quality & experience of care'
68	Postpartum haemorrhage	Captured in 'Postpartum haemorrhage'
69	Continually updating the caregivers	Captured in 'Information Provision for Preparation'
70	Considerations of Pre-eclampsia and Eclampsia.	Captured in 'Pre-eclampsia, eclampsia, HELLP syndrome'
71	New onset maternal medical disease	Captured in 'Development of new long-term conditions'
72	Recurrence risk of condition	Captured in 'Impact on long-term condition'
73	Accuracy of information provided to the mother by health care staff	Captured in 'Information provision for preparation'
74	Maternal parity	Risk factor for pregnancy outcomes
75	Tobacco use	Risk factor for pregnancy outcomes
76	Substance use disorder	This is part of the pre-existing multimorbidity of the pregnant women, would regard it as an exposure
77	Consideration of women with cardiac and kidney disorders.	This is part of the pre-existing multimorbidity of the pregnant women, would regard it as an exposure
78	Mother previous birth history	Risk factor for pregnancy outcomes
79	Family history of any congenital abnormalities	Risk factor for pregnancy outcomes

Attrition analysis

Mann Whitney test

Compared the average scores of each outcome in the 1st Delphi survey. Comparison made between participants who completed the 1st survey only and participants who completed both surveys.

Outcome	**Median (interquartile range) score in 1st Delphi**		**% of Participants that rated the outcome as *Critically Important* (Consensus In) in the 1st Delphi, n (%)**			**P value**
	Participants who only participated in the 1st Delphi	Participants who participated in the 1st and 2nd Delphi	Participants who only participated in the 1st Delphi	Participants who participated in the 1st and 2nd Delphi	All participants	
Admission to intensive care (maternal)	7.5 (7 to 9)	8.5 (7 to 9)	74 / 90 (82.22%)	98 / 114 (85.96%)	172 / 204 (84.31%)	0.0226
Obstetric cholestasis	6 (5 to 7)	6 (6 to 8)	34 / 83 (40.96)	52 / 105 (49.52)	86 / 188 (45.74%)	0.0227
Financial implications for family (child)	7 (6 to 8)	6 (5 to 8)	54 / 91 (59.34%)	46 / 114 (40.35%)	100 / 205 (48.78%)	0.0308

Chi squared test

Compared the proportion of participants who voted to include / exclude each outcome (collapsed into binary categories). Comparison made between participants who completed the 1st survey only and participants who completed both surveys.

Outcomes	**% of Participants that rated the outcome as Critically Important (Consensus In) in the 1st Delphi, n (%)**			**P value**
	Participants who only participated in the 1st Delphi	Participants who participated in the 1st and 2nd Delphi	All participants	
General social ability (child)	61.80	41.74	50.49	0.004487
Financial implications for family (child)	59.34	40.35	48.78	0.006881
Role as a mother	60.44	44.35	51.46	0.021742
Skin to skin with parents	61.96	47.37	53.88	0.036787
Social participation (child)	60.23	46.09	52.22	0.045635
Neonatal birth injury	85.56	93.86	90.20	0.047656

Bonferroni correction of the p value for level of significance: 0.05 / 127 outcomes = 0.0004. None would have been significant.

Supplementary Material 7.4: First consensus meeting report

First consensus meeting: Core outcome set for studies of pregnant women with multiple long-term conditions (multimorbidity)

Date: 12th Sept 2022

Time: 1130am to 1330pm UK time

Aim of the meeting

To determine whether outcomes for *Further discussion* should be included for discussion in the second consensus meeting, in addition to those that have already reached *Consensus in* in the Delphi surveys. Outcomes were eligible for *Further discussion* if in the second survey: (i) ≥70% of all participants rated the outcome as *Important but not critical,* or (ii) when ≥70% of participants in one stakeholder group rated an outcome as *Critically important* but *Consensus in* was not reached.

Premeeting task

Participants were sent the list of *Borderline* outcomes with plain English explanation in advance. They were asked to consider whether these outcomes should be included ahead of the meeting.

Summary of round robin and group discussions for the 15 outcomes for *Further discussion*

1. Maternal outcomes: Miscarriage
Women with multiple long-term conditions and on medications may be at higher risk of miscarriage and have taken a lot of preconception preparation such as medication adjustment. This is the only marker for fertility. The outcome has huge psychological impact, intervention may improve this outcome. Potentially covered by *Death before birth* already. Need to be able to clearly distinguish whether the miscarriage is attributable to the women's condition.

2. Maternal outcomes: Termination of pregnancy
Potentially covered by *Death before birth* already. Needs to be more specific as there is a wide range of reasons for termination of pregnancy (TOP). Important to distinguish between TOP because of medical reasons where the survival of mother and child is at risk, social reasons, lack of support, and whether women were being coerced. More important to measure whether women or couples received the right kind of care around the decision.

3. Maternal outcomes: Gestational diabetes
For: This outcome is important in certain long-term conditions. For women with multiple long-term conditions, having a new condition to manage in pregnancy, new set of treatments and appointments can be challenging.

Against: In low middle income countries, women with these conditions tend to progress to chronic conditions. Many agreed that there are already a lot of studies covering these outcomes and hence should not be in the core outcome set. Discussed whether these outcomes would already be included in multimorbidity (exposure state, but currently this is limited to pre-existing health conditions), or

already included in the outcome *Development of new long-term conditions* as women with these conditions should receive lifelong monitoring.

4. Maternal outcomes: Gestational hypertension
This outcome was discussed together with *gestational diabetes*, so please see above.

5. Maternal outcomes: Involvement in care decisions for types of birth
Birth experience can have long-term impact. Women with multiple long-term conditions may need different types of birth. Discussed about the possibility of combining this outcome with *Involvement with care decision in overall care*, and list specific decisions as subdomains of the outcome. Women spoke about concerns that combining this outcome with *Overcall care* would make the outcome too broad and very subjective. Important to monitor the two aspects of involvement in care decisions (types of birth and pain relief), whether pregnant women with multiple long-term conditions were abused, discriminated against, or consented properly, as these outcomes can lead to post-traumatic stress disorder and postpartum mental illness. Highlighted evidence that appalling treatment of women is still a problem now based on a recent United Nation report and the Ockendon report.

6. Maternal outcomes: Involvement in care decisions for pain relief
Types of pain relief is already a major focus in antenatal care provision and there is a lot of information provision. Discussed about not being able to access the care or pain relief due to circumstances, despite women being involved in the care decisions and agreeing on a pain relief care plan antenatally. Hence it is important to consider *Experience of care*, not just *Involvement in care decisions*, and to consider whether *Involvement in care decisions* can be aligned with *Experience of care.* Pain management is important for women with chronic pain even before labour. People with mental illness or other health conditions may be discriminated against and denied pain relief even in non-labour context.

7. Maternal outcomes: Shoulder dystocia
Discussed whether should exclude given this outcome is rare and obstetric teams are usually very well prepared to manage it. However, when it happens, the consequences for mother and baby can be serious. If women with multiple long-term conditions are usually advised to have a caesarean birth for medical reasons, then this risk may not be relevant.

8. Maternal outcomes: Quality & experience of care
Prioritised by clinicians as want women and babies to be safe, well and have a positive experience. If negative experiences are not addressed, women may develop fear of childbirth in the future. Very few outcomes in the current core outcome set cover subjective experiences, many are hard clinical outcomes. There are ways to collect subjective experiences nowadays. The experiences will differ based on the women's long-term conditions.

To consider whether this outcome can be combined with *Involvement in care*, as being involved in care planning does not mean the care delivered was what was agreed on, and those who were not involved in their care decisions would usually not report a good experience of care.

9. Maternal outcomes: Care for long-term conditions
Women get good care for some long-term conditions, such as diabetes and lupus, but not for their other conditions, care is fragmented, so putting it all together is very important.

10. Children's outcomes: Separation of mother from newborn baby

Potentially have impact on other areas such as feeding, bonding, longer term mental health and psychological outcomes if separated for long periods of time. However, this outcome is also well covered by the outcome *Admission to neonatal unit*.

11. Children's outcomes: Blood transfusion
Key reasons for blood transfusion in the neonatal period are baby's conditions at birth (related to problems at birth) and prematurity. There are already other outcomes that would cover baby's condition at birth and prematurity: gestational age at birth, birthweight, APGAR score. Therefore, even though this outcome is important, would not include in the core outcome set.

12. Children's outcomes: Inheritance of mothers' condition
This outcome needs to be more specific in terms of inheritance of what types of health conditions, e.g., genetic conditions such as Down syndrome, haemophilia, sickle cell. Need to differentiate from environmental factors. Need to consider if individual long-term conditions may already have good evidence available for inheritability and not duplicate the work.

For: Knowing the risk, mothers can then watch out for early signs of the condition in their children and take mitigating actions.

Against: Some conditions may manifest later in life. Risk of inheritance of health conditions already discussed quite a lot before conception, unsure if care can impact on whether baby inherits the condition.

13. Children's outcomes: Quality of life
Currently there is no good measure for babies' quality of life but including it in the core outcome set may encourage researchers to strive to do so in the future. Important as a long-term outcome for children. Can also impact on mother's quality of life and mother's perceived well-being.

14. Children's outcomes: General cognitive ability
For: It is problematic to combine a wide range of different functions (general gross motor ability, general fine motor ability, general cognitive ability etc) with different severity into one binary outcome under *Neurodevelopmental conditions*. *General cognitive ability* is how children will do in school in terms of their thinking. It is not well covered by the broad heading *Neurodevelopmental conditions*. There was strong feedback from parents in the neonatal units that they want to know the impact of things that happened on the neonatal unit and during pregnancy on the development of the child, so they can make decisions on treatments for the baby and care the mother receives during pregnancy. Women would want to know the impact of medication during pregnancy on children's cognitive ability.

Against: Already covered by some other outcomes, e.g., *Brain injury* that is directly related to something going wrong within birth or pregnancy. Concerned about this outcome being misused and lead to ableism and eugenics.

15. Children's outcomes: General gross motor ability
Already covered by some other outcomes such as *Cerebral Palsy*.

Other general comments

Comments	Response
(1) Mother's quality of life is not included in the core outcome set.	This outcome did not reach *Consensus in* in the second Delphi survey. Percentage of participants that rated this outcome as *Critically important:* - All participants 59.48% - Women / partner 64.10% - Health professionals / researchers 57.14%
(2) There was more health professionals / researchers stakeholders compared to women stakeholders at the consensus meeting. Women's point of view should be prioritised.	We made a post hoc decision to address this by also including outcomes that were voted in by women stakeholders in the consensus meeting. This would add *Termination of pregnancy.*
(3) Social determinants of health are not included in the core outcome set, e.g., homelessness, child sexual abuse, adverse childhood events, although acknowledged these are not illnesses.	We have considered social determinants as risk factors for developing the outcomes.
(4) Concerns that there are no long-term outcomes for children.	Some of the children's core outcomes apply in the longer term, such as *Cerebral Palsy, Visual impairment, Needing complex care, Children's mental health & behavioural disorder.* Other longer-term outcomes that would manifest when the child is older, such as *Education attainment* and *Social participation* did not reach *Consensus in* in the Delphi surveys.
(5) Combining specific components of *Involvement in care decisions* (overall care, types of birth, pain relief), and perhaps with *quality & experience of care*.	Based on the group discussions, we will keep these outcomes separate.
(6) Concerns for including *Neurodevelopmental condition* in the core outcome set. Including it in the core outcome set will encourage unethical studies that blame mother's choices (pain relief, caesarean section, breastfeeding) and lead to mothers being denied certain mode of birth. This outcome is ableist and eugenics.	*Neurodevelopmental condition (children's outcome)* reached *Consensus in* in the Delphi surveys. There is representation of women with neurodevelopmental condition in the Delphi surveys, consensus meeting and our Patient and Public Involvement advisory group. Percentage of participants that rated this outcome as *Critically important* in the second Delphi*:*

	- All participants 76.52% - Women 76.92% - Health professionals / researchers 76.32% We will highlight the concerns in the manuscript.
(7) Concerns that there are very few experiences-based outcomes in the core outcome set.	Experience based outcomes, such as *Birth experience* were included in the Delphi surveys, but did not reach *Consensus in.* Percentage of participants that rated *Birth experience* as *Critically important* in the second Delphi*:* - All participants 54.78% - Women 64.10% - Health professionals / researchers 50.00% This does not mean this outcome is not important. We have discussed the importance of experience-based outcomes in our focus group study that informed the design of our Delphi surveys.

First consensus meeting live poll for the 15 outcomes that were for *Further discussion*

Criteria for inclusion: ≥70% of all participants, or ≥70% of women stakeholders voting in favour of the outcome. These outcomes will be included in addition to the 45 outcomes that reached *Consensus in* in the second Delphi survey.

No	Outcome	2nd Delphi survey Yes, %			Consensus meeting final vote Yes, n (%)			Included
		All, n=116	Women / Partner, n=39	Clinicians / researchers, n=77	All, n=13	Women, n=6	Clinician/ researchers, n=7	
	Maternal outcomes							
1	Miscarriage	68.14	73.68	65.33	12 (92.31)	6 (100)	6 (85.71)	Y
2	Termination of pregnancy	63.39	71.05	59.46	8 (61.54)	5 (83.33)	3 (42.86)	Y
3	Gestational diabetes	69.64	55.26	77.03	3 (23.08)	0 (0)	3 (42.86)	N
4	Gestational hypertension	69.37	55.26	76.71	5 (38.46)	1 (16.67)	4 (57.14)	N
5	Involvement in care decisions for types of birth	62.07	71.79	57.14	10 (76.92)	3 (50.00)	7 (100)	Y
6	Involvement in care decisions for pain relief	63.79	71.79	59.74	7 (53.85)	3 (50.00)	4 (57.14)	N
7	Shoulder dystocia	68.18	55.56	74.32	2 (15.38)	0 (0)	2 (28.57)	N
8	Quality & experience of care	69.83	71.79	68.83	11 (84.62)	4 (66.67)	7 (100)	Y
9	Care for long-term conditions	68.97	66.67	70.13	11 (84.62)	6 (100)	5 (71.43)	Y
	Children's outcomes							
10	Separation of mother from baby	66.38	74.36	62.34	10 (76.92)	3 (50.00)	7 (100)	Y
11	Blood transfusion (child)	67.24	74.36	63.64	0 (0)	0 (0)	0 (0)	N
12	Inheritance of mother's condition	66.38	79.49	59.74	7 (53.85)	4 (66.67)	3 (42.86)	N
13	Quality of life (child)	68.70	71.79	67.11	11 (84.62)	4 (66.67)	7 (100)	Y
14	General cognitive ability	69.57	61.54	73.68	9 (69.23)	3 (50.00)	6 (85.71)	N
15	General gross motor ability	67.54	56.41	73.33	4 (30.77)	3 (50.00)	1 (14.29)	N

Supplementary Material 7.5: Second consensus meeting report

Second virtual consensus meeting: Core outcome set for studies of pregnant women with multiple long-term conditions (multimorbidity)

Date: 24th February 2023 **Time:** 1200pm to 1600pm UK time

Aim of the meeting: To reduce the 52 outcomes that have been included in the process so far (Delphi surveys and first consensus meeting) to a shorter list for the core outcome set.

Premeeting preparation

Premeeting was arranged with study participants to explain the aim of the meeting, explain what a core outcome set is, and explain the premeeting task. We provisionally aimed for 10 to 12 outcomes in the final core outcome set. We emphasised that just because an outcome is not included does not mean it is not important. Researchers studying specific research questions can still measure more specific and in-depth outcomes related to the question.

Premeeting task

The premeeting task aims to help prepare participants for the discussion in the consensus meeting. Participants were invited to review the list of 52 outcomes, consider any overlaps in the outcomes and based on this which outcomes can be combined or removed from the core outcome set. Participants were also asked to consider which 5-8 outcomes they would choose to include. Participants were provided with plain English explanation of the outcomes, the results from the Delphi surveys and voting from the first consensus meeting; the overall results were presented, as well as stratified by stakeholder groups.

Meeting structure

One hour was dedicated to a **group discussion** on which outcomes can be combined or removed from the core outcome set, changes were made subsequently when there are no objections. Outcomes where decisions on combining or removing could not be made were kept for the next stage (voting). Participants were also asked if there were any outcomes that were removed from the discussion that they would like to add back to the voting stage.

This was followed by a **formal voting** for the remaining outcomes. Forty-five minutes were allocated for maternal outcomes and forty-five minutes for child outcomes. Participants were asked to do a binary vote for each of the remaining outcomes. The overall results and results stratified by stakeholder groups (people with lived experience, clinicians) were reviewed together. Any key areas where no outcomes were included, or outcomes where there was discrepancy between stakeholders (especially if an outcome was voted in by ≥80% women representative) would then be rediscussed and revoted (additional votes).

We also clarified that the meeting is to decide which outcomes to include. Decisions on how to define or measure the outcomes is beyond the scope of this meeting and current study and would require a separate piece of work to reach consensus on.

Criteria for inclusion in the second consensus meeting

Outcomes that were voted in by ≥80% of all participants will be included in the final core outcome set. This was prespecified to all participants in the premeeting.

Voting results

First vote for maternal outcomes

Three maternal outcomes were included in this round of voting:

1. Maternal death
2. Severe maternal morbidity
3. Change in existing long-term conditions

There was no discrepancy (an outcome not reaching the overall threshold, but one group voted ≥80% to include it) between stakeholder groups.

The voting results were reviewed when responses from 17 participants were received. Nine participants indicated they were clinicians and eight participants indicated they were women representatives. This mean one woman representative may have mistakenly voted as a clinician stakeholder (as there were nine women representatives and eight clinicians). No one identified themselves as voting twice. As the votes were anonymous, we were not able to rectify the error and presented the vote results as it is. This did not affect the overall score but would affect the stakeholder breakdowns slightly.

First vote for maternal outcomes

No	Outcome	Percentage voting to include the outcome, n (%)		
		All, n=17	Women, n=8	Clinician, n=9
1	Maternal death	17 / 17 (100)	8 / 8 (100)	9 / 9 (100)
2	Termination of pregnancy*	8 / 16 (50)	4 / 8 (50)	4 / 8 (50)
3	Preterm premature rupture of membrane	3 / 17 (18)	2 / 8 (25)	1 / 9 (11)
4	Severe maternal morbidity	17 / 17 (100)	8 / 8 (100)	9 / 9 (100)
5	Hysterectomy	4 / 17 (24)	3 / 8 (38)	1 / 9 (11)
6	Maternal infection	7 / 17 (41)	4 / 8 (50)	3 / 9 (33)
7	Development of new long-term conditions	12 / 17 (71)	5 / 8 (63)	7 / 9 (78)
8	Change in existing long-term conditions	15 / 17 (88)	7 / 8 (88)	8 / 9 (89)
9	Involvement in care decisions (overall care)	5 / 17 (29)	4 / 8 (50)	1 / 9 (11)
10	Involvement in care decision (types of birth)	1 / 17 (6)	1 / 8 (13)	0 / 9 (0)
11	Postpartum admission / readmission	8 / 17 (47)	4 / 8 (50)	4 / 9 (44)
12	Quality and experience of care	10 / 17 (59)	4 / 8 (50)	6 / 9 (67)
13	Severe mental illness	11 / 17 (65)	5 / 8 (63)	6 / 9 (67)
14	Development of new mental health conditions	12 / 17 (71)	6 / 8 (75)	6 / 9 (67)

*One participant did not vote for this outcome

First vote for child outcomes

Three child outcomes were included in this round of voting:

1. Survival of baby
2. Gestational age at birth
3. Neurodevelopmental conditions / impairment

There was discrepancy for 'Separation of baby from mother', with ≥80% women representative voting to include it.

First vote for child outcomes

No	Outcome	Percentage voting to include the outcome, n (%)		
		All, n=17	Women, n=9	Clinician, n=8
1	Survival of baby	17 / 17 (100)	9 / 9 (100)	8 / 8 (100)
2	Gestational age at birth	17 / 17 (100)	9 / 9 (100)	8 / 8 (100)
3	Birth weight	13 / 17 (77)	7 / 9 (78)	6 / 8 (75)
4	Neonatal birth injury	6 / 17 (35)	5 / 9 (56)	1 / 8 (13)
5	Neonatal sepsis	8 / 17 (47)	5 / 9 (56)	3 / 8 (38)
6	Brain injury on imaging*	6 / 16 (38)	4 / 9 (44)	2 / 7 (25)
7	Separation of baby from mother	12 / 17 (71)	8 / 9 (89)	4 / 8 (50)
8	Congenital anomaly	12 / 17 (71)	6 / 9 (67)	6 / 8 (75)
9	Neurodevelopmental conditions / impairment	15 / 17 (88)	8 / 9 (89)	7 / 8 (88)
10	Children mental health & behavioural disorders	7 / 17 (41)	4 / 9 (44)	3 / 8 (38)
11	Need for complex care	10 / 17 (59)	7 / 9 (78)	3 / 8 (38)
12	Visual impairment / blindness	4 / 17 (24)	3 / 9 (33)	1 / 8 (13)
13	Quality of life (child)	13 / 17 (77)	7 / 9 (78)	6 / 8 (75)
14	Admission to neonatal unit (including intensive care)	12 / 17 (71)	7 / 9 (78)	5 / 8 (63)
15	Neonatal readmission to hospital	1 / 17 (6)	1 / 9 (11)	0 / 8 (0)

*One participant did not vote for this outcome

First revote (maternal outcomes)

There were concerns that votes for the following outcomes were split due to the overlapping concepts, leading to none being included.

1. ‘Quality and experience of care’, ‘involvement in care decisions’
2. ‘Severe mental health conditions’ and ‘development of new mental health conditions’

There was no objection for combining the first set of outcomes as ‘quality and experience of care’ for the revote. There was no consensus on how to combine the second set of outcomes, so both were included for the revote.

Results: ‘Severe mental health conditions’ was voted through. The remaining two outcomes did not reach the inclusion threshold overall but was voted in by ≥80% of women representative. There was no objection to include ‘quality and experience of care’ in the core outcome set. ‘Development of new mental health conditions’ was put forward for the third revote.

Second revote (child outcomes)

Although not voted in overall, ‘separation of baby from mother’ was voted in by ≥80% of women representative in the first vote. There were concerns that votes for the following outcomes were split due to the overlapping concepts, leading to none being included.

‘Separation of baby from mother’ and ‘admission to neonatal unit’

However, no consensus was reached on how to combine these outcomes. Both were put forward for the second revote. Chair has asked that people vote for both if they felt both are important to avoid the splitting effect.

In the first vote, ‘quality of life (child)’ and ‘birth weight’ both received an overall 77% vote for inclusion, close to the inclusion threshold. Many outcomes (e.g., fetal growth restriction, placenta insufficiency) were removed with the understanding that they can be derived from gestational age and birth weight. ‘Quality of life (child)’ and ‘birth weight’ were put forward for revoting.

Results: ‘Quality of life (child)’ and ‘birth weight’ were both voted through. ‘Separation of baby from mother’ and ‘admission to neonatal unit’ both did not meet the inclusion threshold.

Third revote

‘Development of new mental health conditions’ did not meet the threshold for inclusion in the first revote but was voted in by ≥80% of women representative. ‘Separation of baby from mother’ and ‘admission to neonatal unit’ were combined and renamed as ‘separation of baby from mother for health care needs’ for the third revote.

Results: ‘Development of new mental health conditions’ and ‘separation of baby from mother for health care needs’ were voted through.

Fourth revote

The core outcome set was reviewed by the wider research team, and it was noted that the development of new or worsening of existing 'severe mental health conditions' overlapped with 'change in existing long-term conditions (physical and mental)' and 'development of new mental health conditions'. This was also raised by a woman participant. Therefore, all participants were contacted to vote on whether they agreed with removing 'severe mental health conditions' from the core outcome set.

Results: 'Severe mental health conditions' was removed from the core outcome set, we emphasised that 'change in existing long-term conditions' should include both physical and mental health conditions.

Revotes

No	Outcome	Percentage voting to include the outcome, n (%)		
		All	**Women**	**Clinician**
First revote (maternal outcomes)				
1	Quality and experience of care	12 / 16 (75)	7 / 8 (88)	5 / 8 (63)
2	Severe mental health conditions	13 / 16 (81)	6 / 8 (75)	7 / 8 (88)
3	Development of new mental health conditions	11 / 16 (69)	7 / 8 (88)	4 / 8 (50)
Second revote (child outcomes)				
1	Separation of baby from mother	12 / 17 (71)	7 / 9 (78)	5 / 8 (63)
2	Admission to neonatal unit (including intensive care)	13 / 17 (76)	7 / 9 (78)	6 / 8 (75)
3	Quality of life (child)	14 / 17 (82)	7 / 9 (78)	7 / 8 (88)
4	Birth weight	15 / 17 (88)	8 / 9 (89)	7 / 8 (88)
Third revote				
1	Development of new mental health conditions	14 / 17 (82)	8 / 9 (89)	6 / 8 (75)
2	Separation of baby from mother for health care needs	15 / 17 (88)	9 / 9 (100)	6 / 8 (75)
Fourth revote				
1	Remove *severe mental health condition* as overlaps with *change in existing long-term conditions (physical and mental)* and *development of new mental health conditions*	16 / 17 (94)	8 / 9 (89)	8 / 8 (100)

Summary of group discussions

General consideration for core outcome sets

As we cannot have too many core outcomes, the core outcomes cannot be too specific.

Some outcomes have varying definitions (e.g., stillbirth, preterm birth) or have international variation (e.g., special baby care unit, different admission criteria). However, 'gestational age at birth', 'birthweight', can be easily measured by anyone in the world, and additional study specific outcomes can be derived from these. To consider hard outcomes if we are requiring everyone to measure the core outcomes.

Suggestion that we need to choose outcomes that can be identified universally by international classification of disease codes and to consider their availability in medical records as the aim is to make future studies homogenous and comparable in different countries.

There should be more outcomes for mothers, and child outcomes that are most important to the mother. Most research focuses on the baby, pregnant women may be counselled to accept certain intervention that health professionals felt to be in the best interest for the baby at the cost of the women's quality of life.

Concerns on unethical research

Women representative expressed concerns the core outcome set may be misused in unethical research, suggest we should make the effort when choosing and phrasing outcomes to avoid this. Clinical academic representatives suggest this could be a separate discussion focusing on research ethics, use and misuse of outcomes.

Maternal death

For: As there is a lot of heterogeneity with multiple long-term conditions, maternal death would be a core outcome. Researchers would then be obliged to follow up study participants to check for survival at specific time points. Cause of death should then be captured with International Classification of Disease which can include any type of health conditions.

Decision: Kept for voting.

Suicide

For: Unsure if should be merged with 'maternal death' as it is the top cause of maternal death alongside cardiovascular disease. Could consider merging with 'self-harm'.

Against: Captured by 'maternal death'. Studies where the specific research question is perinatal mental health may measure suicide specifically and other perinatal mental health outcomes in detail. But should we require studies that are not related to perinatal mental health to always report suicide as an outcome?

Decision: Removed from core outcome set.

Perinatal mental health

Agreement to reduce the 5 perinatal mental health outcomes. The key is to capture whether there were perinatal mental health issues or not. To consider having proportionate number of perinatal mental health outcomes in the core outcome set as there are many other long-term conditions.

Suggestion of reducing this to 2 outcomes: severe mental illness and anther outcome for mental health conditions that are not severe mental illness, e.g., postnatal depression, anxiety, and other mild-moderate mental health conditions managed in primary care.

Suggestion: To use 'perinatal mental health' as an umbrella outcome.

For: Includes both development of new mental health conditions and relapse of existing mental health conditions.

Against: Important to differentiate between severity as 'perinatal mental health conditions' may be too broad and include a large number of women.

Important to distinguish the perinatal mental health conditions (new or aggravation of existing ones) attributable to the pregnancy, the multiple long-term conditions, or interventions from those attributable to unrelated circumstantial events. Concerns that identifying mental health outcomes through diagnosis codes in medical records cannot distinguish this.

Discussed about addressing this by phrasing it as 'new mental health conditions'. However, new mental health conditions that coincide with pregnancy does not mean pregnancy is the cause. This issue is addressed through study designs by having a comparator group, as this will take into account background events that happen by chance.

Decision: 'Severe mental health conditions' and 'development of new mental health conditions' were put through for the first vote.

Severe mental health conditions, severe mental illness

Two different approaches to 'severe mental health conditions'
There are two approaches to defining severe mental health conditions.

First approach: only includes a number of specific mental health conditions (e.g., bipolar disorder, schizophrenia), and is currently used in the UK and UK primary care records coding system.

Second approach: includes all possible mental health condition, and within each condition, only include those that are severe, measuring it on a severity scale using patient reported outcome tools (e.g., like rating pain on a scale of one to ten).

Some mental health researchers, especially those in perinatal psychiatry, do not want severe mental illness to only include long-term conditions that occur outside of the

peripartum period. This is because this approach would not include acute but severe issues, such as acute trauma, which may or may not become post-traumatic stress disorder, according to how you are taken care of. If the second approach is taken, then severe trauma, complex trauma is a major outcome, and it would be included in 'severe mental health conditions' as it is a mental illness and is included in the Diagnostic and Statistical Manual of Mental Disorders (DSM). Clinician representative suggests that we advocate for this definition in this current core outcome set work.

For: Recognised term, recognised composite outcome. Severe mental illness carries its own sets of risk and adverse outcomes. That does not mean other mental health outcomes are not important, the core outcome set would not stop other mental health outcomes being measured in studies where perinatal mental health is the focus of the research question.

Against: Concerns that in observational studies, confounding factors can lead to biases, socioeconomic factors may lead to different diagnosis rates in different groups. However, this is a limitation with the study design, not with the choice of outcomes.

Concerns of study methodological limitations if diagnosis recorded in routine health records (primary care records or hospital records) are used to detect mental health outcomes. Limitations including misdiagnosis and subsequent misclassification of severity; does not provide information on the cause / triggers / associated significant life events; existing mental health conditions may be newly diagnosed around the time of pregnancy / birth due to the increased contact with health professionals. Concerns of stigma associated with severe mental illness.

Concerns that birth trauma / post-traumatic stress disorder will not be captured in 'severe mental health conditions', and researchers will continue to use the first definition, especially since there is variation of definitions used in different countries. Birth trauma / post-traumatic stress disorder also may not be reflected in 'quality & experience of care' (if good care was received) or 'severe maternal morbidity' (only capture physical trauma). This is an important outcome as it is common even in the general population as a result of difficult birth or negative care experience.

Suggestions for revotes: Initial suggestion for only this outcome to be revoted in the first revote, with the understanding that this includes both worsening of existing condition or a new condition.

Decision: As no maternal mental health outcome was voted in in the first vote, and no consensus was reached on how to combine the outcomes, both 'severe mental health conditions' and 'development of new mental health condition' was entered in the first revote. 'Severe mental health conditions' was voted in in the first revote, 'development of new mental health conditions' was voted in in the third revote.

However, in the final core outcome set, there was overlap between 'severe mental health condition' with 'change in long-term condition' (which includes mental health conditions) and 'development of new mental health conditions'. Participants were contacted individually to ask if they agree with removing this outcome because of the duplication.

Development of new mental health conditions

For: This outcome was proposed because 'change in long-term condition' and 'development of new long-term conditions' would not cover new mental health conditions that are short-term, e.g., post-traumatic stress disorder that was managed in a timely manner. Could include the development of a new severe mental health condition.

Suggestions for revotes: To keep this in the revote option, as women representative wanted to be able to count minor mental health conditions. Concerned that birth trauma / post-traumatic stress disorder would not be captured by 'severe mental health conditions' if the definition with limited scope is being used. Birth trauma / post-traumatic stress disorder is common and seriously important for women, especially if they are as a result of care they received, or their physical conditions causing complication during birth.

Decision: Put forward for the first vote. As no maternal mental health outcome was voted in, this outcome was entered in the first revote. In the first revote, this outcome did not reach the 80% threshold, but was voted for inclusion by ≥80% women representative. Therefore, it was entered in the third revote (second revote for this outcome) and was subsequently voted in.

Maternal: miscarriage, termination of pregnancy
Child: death before birth, death after birth

Suggestions: Combine 'miscarriage', 'termination of pregnancy', 'death of baby before and after birth' as 'loss of baby'. Alternatively, combine as 'pregnancy loss' and to include 'death before birth', and keep 'death after birth' (perinatal / neonatal / infant) as a separate outcome. Reframe baby death / loss to 'survival' of child as that is what we really want to be looking at, there can be different definitions, e.g., survival at to a certain time frame, survival at 28 days (as opposed to neonatal death).

For: In all these circumstances the baby died, important to ensure the timing of when the death occurred is captured. Although miscarriage and termination of pregnancy is very different, both are pregnancy loss that may need additional support and postpartum care.

Against: Early pregnancy loss and losing baby at term feels different, the latter does not involve any decision making from the women, where else women may have been told to think about terminating their pregnancy because of their health. To keep 'termination of pregnancy' separate because in the first consensus meeting, there were discussions on the different reasons behind women choosing to have a termination of pregnancy, including reasons other than their health conditions, and whether they have been coerced by clinicians e.g., when the baby may have genetic conditions. The language 'loss of baby' may not be suitable to include 'termination of pregnancy'.

Decision: Combined 'miscarriage', 'death before and after birth' (child) as 'survival of baby' and kept 'termination of pregnancy' separate for the vote.

Pre-eclampsia, eclampsia, HELLP syndrome
Placenta abruption
Placenta insufficiency
Postpartum haemorrhage

Admission to intensive care unit (maternal)
Severe maternal morbidity

Suggestions: Remove some of the antenatal and peripartum complications that are already represented by 'severe maternal morbidity' (SMM).

For: SMM does not have a fixed definition, but the recognised definitions include the most severe manifestation of many pregnancy complications, e.g., heart stopping, blood clotting, or kidneys failing, which can happen in pre-eclampsia. Some of the antenatal complications (placenta abruption, placenta insufficiency, pre-eclampsia) are more specific to certain long-term conditions, and if we are looking for outcomes that are generically applicable to all types of long-term conditions, then the severe risk associated are captured by SMM.

Decision: Removed 'pre-eclampsia, eclampsia, HELLP syndrome', 'placenta abruption', 'placenta insufficiency', 'postpartum haemorrhage', 'admission to intensive care unit' (maternal).

Hysterectomy

Extremely rare, between 1 in 1000 to 1 in 1500 in the whole population. Peripartum hysterectomy is 0.3-0.4/1,000 births in UK. Women with multiple long-term conditions may be more at risk because they are more likely to have caesarean section and may subsequently have a morbidly adherent placenta in a future pregnancy.

For: Should be a standalone outcomes as it is life changing

Decision: Kept in for voting.

Preterm premature rupture of membrane

Against: Covered by gestational age at birth (preterm birth). Currently listed under maternal outcomes, but potentially has a larger impact on the baby, as baby is then at risk of being born early or much higher risk of infection. Is it the process that matters or is it the actual outcome and impact on the baby? It is clearly distressing to have your water break early, but is one of the reason that it is distressing is because you know the impact this might have on your baby coming early and the problems that might entail?

Decision: Did not manage to confirm consensus for removing during the pre-vote group discussion, so this was kept in for voting.

Quality and experience of care
Involvement in care decisions (overall care)
Involvement in care decisions (types of birth)

Suggestions: To combine 'involvement in care decisions' under the umbrella 'quality and experience of care'. 'Involvement in care decisions (types of birth)' is a subset of 'involvement in care decisions (overall care)'.

For: If someone was very involved in their care decision, would that be broad enough to represent quality of care? Quality of care has so many aspect to it with involvement in care being one. Involvement in care decisions would influence experience of care. Quality of care can be measured with many scales, and usually includes involvement in care. Because there is a recognised framework for what is quality of care in maternity services, and that includes involvement in decision making, so we can confidently say the 2 involvement in care outcomes are included within quality of care. Mode of birth is an important care decisions but there are other important care decisions too.

Against: 'Quality and experience of care' is too vague, more meaningful to keep involvement in care.

Decision: All three outcomes will be kept for the voting stage. In the revote stage, 'involvement in care decisions' were combined under 'quality and experience of care'.

Care for long-term conditions

Against: This is a process measure, the way care is delivered, something that leads to an outcome. For instance, if the care for long-term condition is poor (process measure), it may lead to a change of status in the long-term condition or mental health (outcome).

Decision: Removed from core outcome set.

Impact on long-term conditions
Development of new long-term conditions

The wording for 'impact on long-term conditions' was not clear, whether this meant pathophysiological changes to the existing long-term conditions or the global holistic impact on the pregnant women and her care.

Suggestion: Combine these two outcomes. Rename as 'change in long-term conditions' to encompass worsening / improvement of existing conditions or an addition of new conditions.

Against: These two outcomes are very important but also are distinct entities.

Decision: These two outcomes were kept separate, and both entered into the voting stage. 'Impact on long-term conditions' renamed as 'change in long-term conditions', and to mean worsening / improvement of existing physical or mental health conditions.

Hospitalisation
Suggestion: A proxy for severe / acute conditions that is either new onset or relapse of existing conditions.

Against: Some long-term conditions don't lead to hospitalisation.

Decision: Not used as a replacement outcome for other outcomes.

Gestational age at birth

For: Keep this wording instead of changing to 'preterm birth' so it would include 'post-term births'. 'Gestation age at birth' and 'birth weight' can be used to derived other outcomes.

Decision: Kept the wording unchanged and kept for the voting stage.

Birth weight

For: Important for deriving other outcomes such as fetal growth restriction, which can be derived from birth weight and gestational age. Also reflects the impact of maternal factors on baby, such as placenta insufficiency and hypertension in pregnancy. Acknowledge it is not perfect, but it is a good measure of how well the placenta has been able to support the developing fetus and to understand how well the baby has grown.

Decision: Kept in for the first vote and for the second revote.

Fetal growth restriction

Against: Can be captured by 'birthweight' and 'gestational age at birth'.

Decision: Removed from core outcome set.

Neonatal abstinence syndrome

Against: Important to mothers who require specific medications during pregnancy, important in specific trials, e.g., trials looking at opiates, but may not be applicable to all trials and all long-term conditions.

Decision: Removed from core outcome set.

Meconium aspiration syndrome

Against: Very specific outcome. Would require resuscitation so could be combined with other conditions that requires resuscitation.

Decision: Removed from core outcome set.

Necrotising enterocolitis
Retinopathy of prematurity
Neonatal respiratory distress syndrome
Chronic lung disease

Against: These only apply to preterm babies and are also rare even in premature babies. 'Gestational age at birth' which covers preterm birth can be a proxy for these outcomes. They may also be overly specific.

Decision: Removed from core outcome set.

Neonatal resuscitation required
Requiring intubation / ventilation

Against: Is it the care / intervention that the baby receives that is important, or is it what happens to the baby in the end, i.e., the outcome of those intervention (e.g., admission to neonatal unit) that is important? Does it matter if there is no longer term impact on the baby, no neonatal unit admission, no separation from the mother?

Decision: Removed from core outcome set.

Apgar score

Against: Not particularly useful in premature babies. It is a snapshot of how the baby is at the particular point of time after birth. What is important is whether they go on to develop longer term problems like cerebral palsy or other conditions later on in life, or whether they are admitted to a neonatal unit or are separated from their mother. Significant difference in how babies are scored in different countries.

Decision: Removed from core outcome set.

Congenital anomaly

Against: This is an outcome of interest for specific maternal diseases or to specific drugs that may be teratogenic. For most studies on maternal chronic diseases, it could be dropped. Discussed whether this outcome can be combined with neurodevelopmental conditions if the impairment is not large.

For: There is a range of severity, for example lip defect can be very severe but can also be minor. Severity is subjective, how much a condition affects a child, or a family cannot be easily judged often by the measures that we use. Mild congenital anomaly can still have long running consequences, such as relapse of the condition, needing surgical intervention when the child is older. Some women representative want to know whether taking medication during pregnancy can have an impact so this outcome is important.

Decision: Kept in for the voting stage.

Children's mental health and behavioural disorder

For: Includes mental health conditions that occur in adulthood for the child. If risk of mental health conditions and behavioural disorder is higher in children born to mothers with multiple long-term conditions, then additional support may be needed.

Against: Questions on whether these are caused by the medications, the pregnancy, or the environment the child is raised in, and these may not be life-long impairment, are short term or context specific. Concerns that there is high risk of conflation.

Women representative raised that it is not the behavioural disorder or a child that is agitated that is the actual issue or impacting on the quality of life. It is a societal issue of parents or doctors wanting the child to behave the same (as the social norm). However, clinician representative says societal intolerance of children with behavioural disorder is

beyond our control, and this can significantly impact on the way the child is taken care of, therefore it is an important outcome.

Decision: Kept in for the voting stage.

Cerebral palsy

Suggestion: Combine with 'neurodevelopmental conditions'.

Clarified that 'cerebral palsy' was voted in in the Delphi surveys and was not discussed in the first consensus meeting (where outcomes that were borderline were discussed). At the survey design stage, this outcome was considered important enough to be a standalone outcome. Clarified that it is not specifically linked to any particular condition. It is often included as part of neurodevelopmental conditions (gross motor, fine motor, speech, vision, hearing etc).

For: Neurodevelopmental conditions, cerebral palsy, mental health, and behavioural disorder makes a massive difference to patients and families as the children grow up. Patients and parents are less worried about the labels but more the impact on the family.

Decision: Combined with neurodevelopmental conditions.

Neurodevelopmental conditions

Against:
Concerns of underdiagnosis and misdiagnosis of autistic spectrum disorder
Women representative noted that autistic spectrum disorder is not always diagnosed in childhood and diagnosis in women is often missed, therefore suggested to consider adding autistic spectrum disorder traits and behaviours to 'Neurodevelopmental outcomes'.

Concerns that autistic spectrum disorder is often misdiagnosed as other behavioural or mental health conditions, concerns of the diagnosis being country and culture sensitive, rather than a clear criteria for more severe learning disability, genetic conditions, and physical impairment.

Concerns that undiagnosed autistic spectrum disorder in the mother may lead to misattribution of mother's medication to children's neurodevelopmental conditions, instead of attributing to genetic causes.

Concerns of unethical research, stigma, eugenics, ableism
The issue for autism is not the child's behaviour, but society is not tolerant of the child's behaviour. Concerns that researchers are conducting studies to proof certain interventions cause autistic spectrum disorder, which limit pregnant women's access to certain interventions.

Response: Beyond the scope of the core outcome set work to fix the problems with all research and would not be solved by not recording the outcome.

Suggestion for renaming as 'impairment'

Could these outcomes be combined and be renamed as ‘impairment’ instead of listing it as neurodevelopmental conditions or mental health conditions, and researchers can specify which actual impairment is it impacting, e.g., visual impairment, speech impairment, learning disability, noise sensitivity. This would have more value, be less stigmatising and guard against eugenics, unethical research, and misuse of the core outcome set, e.g., studies to link vaccine with autism. Discussed about challenges of protecting the core outcome set from being misused, difficulty with relying on researchers’ good intention when studying outcomes such as children mental health and learning disability.

On the spectrum of impairment, it is the severe end of ‘intellectual disability’ that is more important when considering the need for care, services, and quality of life. Truly impairing learning disability is what should be kept instead of general conditions like autistic spectrum disorder or attention deficit hyperactive disorder that don’t always cause learning disability or significant impairment.

Response: How a condition impairs the child is quite subjective and difficult to measure, it depends on lots of factors, including the environmental the child lives in. A ‘disorder’ or ‘impairment’ may be too broad and may need more narrowing down. Important point on threshold on when some things become problematic and some things don’t, this has to be considered at a later stage in a separate work defining the outcomes.

There is a clear question of whether we have neurodevelopmental impairment as an overarching outcome, or we separate that down into the individual domains: such as motor impairment (e.g., cerebral palsy), hearing impairment, vision impairment, social and communication impairment (e.g., autism) and cognitive impairment. For example, in the neonatal core outcome set study, the research team break it down into the individual components, some were important enough to go through to the core outcome set, some were not. For this core outcome set, we could split these up too, but we are also trying not to lead to more outcomes. But for an area where this is so important, we could do that.

Response: Not asking for the impairment domains to be listed separately, but putting everything under the same umbrella, but change the wording of the outcome so it is not focusing on specific conditions but on the actual impairment.

For:

Importance of studying neurodevelopmental conditions

The whole context of this work is multiple long-tern conditions in pregnancy. Many of these women take medicines that they cannot stop because of managing their multiple long-term conditions in pregnancy.

For example, for studies of women with epilepsy in pregnancy, if we had not included the concept of autistic spectrum disorder and attention deficit hyperactive disorder, we would never have discovered the problems associated with valproate and being able to relieve women of any anxiety for some of the newer anti-seizure medications that are not associated with these outcomes. Eugenics is a completely separate discussion to what we are having here.

We are not making value judgement on the outcome conditions that we are measuring. However, if a medication would lead to more people having an outcome conditions, we

would want to know that. People would want to have that information when they are making decisions for their own care, so recording it in research is a way of providing information to people who are faced with that decision in the future.

Need to capture developmental outcomes long-term up till adulthood of children whose mother have taken medication such as valproate for epilepsy or bipolar disorder. We need clear definition of what we mean by neurodevelopmental conditions, including intellectual disabilities, which is the major negative impact associated with or without autistic spectrum disorder, attention deficit hyperactive disorder, and other conditions.

Decision: Kept in for the voting stage. Important to include the ethics and importance of this outcome not being misused in the discussion in the manuscript. Clearly a lot of controversy, challenges in diagnosing these and variation between groups in society, different countries, different settings, which are all important factors to be considered in the next stage when determining how outcomes are defined. But the concept of neurodevelopmental outcomes is very important.

Physical impairment (child)

Question: Concerns there is no outcome for physical impairment for children.

Response: Difficult to understand how we would measure that. There is no good composite outcome like there is for maternal morbidity. A lot of the key physical impairment, such as cerebral palsy, are included in neurodevelopmental outcomes and these are often related to birth issues. So some of the child outcomes for physical impairment has been captured. Acknowledged that some other physical health conditions that might affect the child, for example asthma, are not included within neurodevelopmental outcomes, but birth factors are less commonly related to those outcomes, and they had not come through from previous phases of the core outcome set process, which makes it difficult to bring them in at this stage.

Composite outcomes for babies

Question: Is there an equivalent of 'severe maternal morbidity' for children?

Response: There is no equivalent of 'severe maternal morbidity' for children or accepted common list of severe neonatal morbidity. There are various different combinations of complications that can occur in very premature babies but that is not really applicable to the wider population.

Quality of life (child)

For: An important child outcome, often separate from the condition / illness.

Need to consider measurability, very subjective. Should be a self-account of the child and where not possible, accounts of the parent. Research is getting better at measuring this outcome. It is still a challenge to measure it in very small babies, but that is not to say it is not important and doesn't mean we should not use the core outcome set to push forward the agenda for people to develop a tool to measure it.

Quality of life (maternal) is raised as important too, but this did not make it through in the Delphi surveys.

Decision: Kept in for the voting stage. This outcome was put forward for a repeat vote as it was close to the inclusion threshold in the first vote for child outcomes.

Birth injury

Further explanation: An injury from the birth itself, commonly used to talk about conditions when the baby gets stuck and they have to be pulled out or delivered quite rapidly and often with quite a lot of force. They can get fractures of their arm or their shoulders and can have injuries to their nerve in their arms. It could also include injuries related to babies being cut from a caesarean section. All these outcomes are rare.

Neonatal sepsis

Further explanation: A severe form of infection that is common in the neonatal period. Neonatologists spend a lot of time giving babies antibiotics to prevent this from happening. Affects preterm babies more but also affects term babies.

Brain injury on imaging

Further explanation: Imaging is something that most babies would not get routinely. Babies that were born preterm or go to neonatal unit will often, in a high-income setting, get ultrasound scan/s of their brain. So this outcome is important to babies that go to the neonatal unit, but it is not so relevant to the wider group of babies that are not born preterm. Injury on imaging is only a proxy marker of the effect that it would have on the baby in the longer term, such as neurodevelopmental problems, blindness or need for complex care.

Neonatal readmission to hospital

Further explanation: 'Neonatal readmission to hospital' is when the baby has to come back into hospital in the first month after birth, after they have gone home or left the hospital. In contrast, 'admission to neonatal unit' would cover instances where a baby was admitted shortly after birth or in the next day or so when the mother is still in hospital or being admitted during the initial stay.

'Neonatal readmission to hospital' is not a universally accepted outcome and there are slight challenges with it. Where they go on readmission is very setting / country specific (e.g., paediatric ward, postnatal ward, neonatal unit).

Postpartum admission / readmission (maternal)

Suggestion: Combine with 'admission to neonatal unit' as 'separation of baby from mother' as women are stressed about not being able to look after their baby when these two situation occurs.

Against: Postpartum admission / readmission may not always mean separation of baby from the mother.

Decision: Kept in for the voting stage.

Admission to neonatal unit

In lots of settings around the world, there may not be access to neonatal units. Challenges with international variation on the wording used to describe babies who receive extra care. E.g., in the UK, some hospitals have a unit that covers both Intensive and Special care (different levels), and it is not easy to differentiate which they have received.

To consider whether it is the admission to neonatal unit that is important or is it the separation from mother to receive care somewhere else that is important, and whether it can be rephrased to incorporate that and be reflective of the wider world.

To consider putting a timeframe e.g., neonatal unit admission / additional medical care for more than 24 hours or 48 hours to account for variation in doctor's experience and threshold for admission.

Suggestion: Combine as 'separation of baby from mother'.

Against: Although this outcome overlaps with separation of baby from mother, women representative feel it is more than the separation. It comes with separate stress and aggravation related to the neonatal unit admission. Mothers are worried about the long-term consequences for the baby and the mother.

Separation of baby from mother may not capture the need for additional care for newborn baby in circumstances where kangaroo care (skin-to-skin care) is provided, e.g., for preterm and low birth weight baby in resource limited settings / lower middle-income countries as an alternative. However, this would be captured by 'gestational age at birth / preterm birth.'

Decision: Kept in for the voting stage. Definition of this outcome (time frame, setting) is for discussion in a separate piece of work.

Separation of baby from mother

Current wording is vague as it includes both hospitalisation of the mother and hospitalisation of the baby. Discussed the need for defining the types of separation, for instance, differentiating between separation for a few minutes for a blood test as opposed to separation for a few weeks for admission to neonatal unit. The definitions and threshold setting are beyond the scope of this consensus meeting and would need to be addressed in a separate piece of work. Clarified the decision now is whether the idea that your baby is taken away or separated from you for medical reasons, should be included as a core outcome.

For: Very strong support from women representatives to keep this in, it comes with associated stress and anxiety. Both women and clinician felt the separation, the taking my baby away from me, regardless of the cause, is the issue.

Impact on feeding and bonding
Women will be worried about whether they will be able to breastfeed or bond with the baby. Clinician representative felt this is an important proxy for infant feeding which was not voted in from the Delphi survey.

Impact on maternal mental health
Women representative shared the anxiety they felt when their child was at risk of / has been admitted to neonatal unit, and how this was influenced by previous pregnancy events or influences whether they experience anxiety in future pregnancies. These examples illustrate the impact of the separation on maternal mental health.

Suggestions for renaming:

- 'Separation of baby from mother in order to receive neonatal care' if this was going to replace the neonatal admission outcome.
- 'Separation of baby from mother for health issues' to rule out the temporary, less scary separation and keep the one where mother is more scared for the baby or her own health issues.
- 'Separation for infant or neonatal issues'
- 'Separation of baby from mother for care / location of care delivery', but is the latter the same as admission to neonatal unit? Neonatal unit may not be universal globally.
- 'Separation for baby reasons? For delivery of neonatal care?' But these would not cover if mother was admitted to intensive care, which was covered with the broad separation of baby from mother
- Women representative suggested 'separation of baby from mother for health care needs' so it would cover both the health needs for baby and mother.

Decision: Kept in for the first child outcomes voting, and for the revote. In the final revote, this was combined with 'admission to neonatal unit' and renamed as 'separation of baby from mother for health care needs'.

Chapter 8

Supplementary Material 8.1: Protocol for an observational study: Maternal and child outcomes for pregnant women with pre-existing multiple long-term conditions

Published manuscript

Lee SI, Hope H, O'Reilly D, et al. Maternal and child outcomes for pregnant women with pre-existing multiple long-term conditions: protocol for an observational study in the United Kingdom. *BMJ Open. https://dx.doi.org/10.1136/bmjopen-2022-068718*

Personal contribution

- Study design
- Applied for data access approval
- Led the discussion with the study team on what outcomes to study
- Led the core outcome set work that will guide what outcomes to study
- Drafted and submitted the manuscript for publication, addressed reviewers' comments

Title: Maternal and child outcomes for pregnant women with pre-existing multiple long-term conditions: protocol for an observational study in the United Kingdom

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Abstract

Introduction: One in five pregnant women have multiple pre-existing long-term conditions in the United Kingdom (UK). Studies have shown that maternal multiple long-term conditions are associated with adverse outcomes. This observational study aims to compare maternal and child outcomes for pregnant women with multiple long-term conditions to those without multiple long-term conditions (0 or 1 long-term conditions).

Methods and analysis: Pregnant women aged 15 to 49 years old with a conception date between 2000 and 2019 in the UK will be included with follow up till 2019. The data source will be routine health records from all four UK nations (Clinical Practice Research Datalink [CPRD, England], Secure Anonymised Information Linkage [SAIL, Wales], Scotland routine health records and Northern Ireland Maternity System [NIMATS]); and the Born in Bradford birth cohort. The exposure of two or more pre-existing, long-term physical or mental health conditions will be defined from a list of health conditions predetermined by women and clinicians. The association of maternal multiple long-term conditions with (i) antenatal, (ii) peripartum, (iii) postnatal and long-term, and (iv) mental health outcomes, for both women and their children will be examined. Outcomes of interest will be guided by a core outcome set. Comparisons will be made between pregnant women with and without multiple long-term conditions using modified Poisson and Cox regression. Generalised estimating equation will account for the clustering effect of women who had more than one pregnancy episode. Where appropriate, multiple imputation with chained equation will be used for missing data. Federated analysis will be conducted for each dataset and results will be pooled using random-effects meta-analyses.

Ethics and dissemination:

Approval has been obtained from the respective data sources in each UK nation. Study findings will be submitted for publications in peer reviewed journals and presented at key conferences.

ARTICLE SUMMARY

Strengths and limitations of this study

- The study will utilise rich data sources from routine health records from all four UK nations and a birth cohort.
- Beyond examining maternal outcomes, linked mother baby data and the birth cohort data will allow for the exploration of children's outcomes.
- Key limitations include missing data, misclassification bias due to inaccurate clinical coding and residual confounding.

Background

Maternal single long-term conditions such as cardiac conditions, chronic kidney disease and epilepsy are associated with adverse pregnancy outcomes.[34 67 71 74] This is likely to be compounded when the pregnant woman has two or more long-term physical or mental health conditions (multimorbidity). Some conditions may need different treatments from different health care teams, thereby increasing the treatment burden and complexity of care.[5] Recent evidence has shown that maternal multiple long-term conditions are associated with adverse outcomes for women and their children, such as severe maternal morbidity and mortality, pre-eclampsia, emergency caesarean birth, preterm birth, and low birth weight.[44 47 66] In the UK 2016-18 national maternal mortality report, 90% of women who died during or up to a year after pregnancy had multiple health or social risk factors.[173]

Currently one in five pregnant women have multiple long-term conditions prior to pregnancy in the United Kingdom (UK).[172] The number of pregnant women with pre-existing multiple long-term conditions is likely to increase as women are getting pregnant later in life and with higher body weight.[35-38] As this becomes an increasingly important issue, information on pregnancy, maternal and child outcomes is crucial for women and their health care professionals to make informed decisions on preconception and pregnancy care planning. However, there remains a lack of evidence to guide care pathways for pregnant women with multiple long-term conditions.[66 178]

Healthcare is free in the UK and over 98% of the population are registered at a general practice (akin to family practice in other countries).[153] General practices not only provide primary and community healthcare, but they also serve as the main point of contact for referrals to specialist clinical services and provide the majority of prescribing outside of a hospital setting.[153] In the UK, pregnant women are recommended to have their booking appointment before 10 weeks gestation.[383] This is the pregnant woman's first midwife or doctor appointment, where they

undergo health and social care assessment of needs and risks for her pregnancy.[384] Over 97% of births occur in healthcare settings in England and Wales.[385] Therefore, routine health records in primary and secondary care in the UK offer a rich data source for observational studies of pregnant women and their children.

This observational study aims to compare outcomes for women with multiple long-term conditions to those without multiple long-term conditions. Outcomes studied will include those for women and their children. Datasets from routine health records from all four UK nations (England, Wales, Scotland, and Northern Ireland) will be used. In addition, the Born in Bradford birth cohort from a deprived, ethnically diverse city in the UK, will also be used.[351]

The four research objectives are to examine the association between maternal pre-existing multiple long-term conditions with: (1) antenatal, (2) peripartum, (3) postnatal and long-term outcomes, and (4) mental health outcomes. The findings from each research objective will be published in a separate paper.

Methods and analysis

Study design

This is a cohort observational study using data from routine healthcare records and a birth cohort in the UK.

Study population and eligibility criteria

The study population will consist of women aged 15-49 years old at conception, with pregnancies beginning between 1st January 2000 and 31st December 2019 in the UK. Date of conception (pregnancy start date) will be defined as the first day of the last menstrual period or gestational day 0. To ensure sufficient quality data, eligible women must have health records

that meet the standard data quality checks as defined by each data source and one year's worth of health records prior to index pregnancy.

Data sources

Supplementary Material Table 8.1 presents the five data sources that will be used. Each UK devolved nation is represented by a population based routine health record dataset, with good national coverage for Wales, Scotland and Northern Ireland and a representative sample for England.[153] The exposure status will be determined from primary care records for Clinical Practice Research Datalink (CPRD) and Secure Anonymised Information Linkage (SAIL), with CPRD GOLD representing 5% of UK general practices,[386] and SAIL covering 80% of Welsh general practices.[154] For Scotland's linked routine records and Northern Ireland Maternity System (NIMATS), the exposure status will be determined from hospital and prescribing records.

CPRD and 'AIL's primary care data offer the opportunity to study outcomes that may not be captured in secondary care. For instance, vomiting in pregnancy, miscarriage, and neurodevelopmental conditions in children. The Scottish dataset provides detailed information on the different types of hospital attendances, including psychiatric admissions and accident and emergency attendances. NIMATS's unique first antenatal visit dataset is a good source of pre-pregnancy clinical data not available in other datasets.

As routine health records were not collected for research purposes, it is prone to missing data. Therefore, we have also included Born in Bradford, a regional birth cohort (2007-2011) where data were collected systematically and longitudinally from pregnancy, childhood through to adult life.

Exposure

The exposed group will consist of pregnant women with multiple long-term conditions. Measurements of multiple long-term conditions are variable in existing literature.[9 55] Currently only Bateman et al's Maternal Comorbidity Index has been developed specifically for obstetric research.[63 64] It consists of 20 health conditions and included conditions arising in pregnancy such as gestational hypertension, pre-eclampsia and placenta praevia.[64] This limits the ability to study the impact of pre-existing long-term conditions on maternal and child health and the implication for long-term condition management preconception.[66]

In this study, we shall define multiple long-term conditions as two or more long-term physical or mental health conditions that pre-existed before pregnancy. Pregnancy related complications will not be included as they will be studied as outcomes. Multiple long-term conditions will be defined from a list of 79 health conditions previously described in our epidemiological work (Supplementary Material Table 8.2) and will be measured with simple count.[172] This list was compiled from existing multimorbidity literature[55 65 173] and a workshop with our multidisciplinary research advisory group, including patient representatives and clinicians.[172] Selection of health conditions were based on: (i) prevalence; (ii) potential to impact on pregnancy outcomes; (iii) considered important by women; and (iv) recorded in the study datasets.[172] The phenome definitions for these health conditions have previously been described in our epidemiological work.[172] For health conditions that are transient and episodic in nature (e.g. asthma, eczema, depression and anxiety), we will only include the condition if it is active, which we have defined as requiring a doctors' consultation or medical prescription in the 12 months preceding pregnancy.[172] Sensitivity analysis will be performed defining maternal multiple long-term conditions with a different list of health conditions by D'Arcy et al.[387]

Exposure will be ascertained by the presence of diagnostic or prescriptions codes, including Read (to identify exposures in primary care data) and International Classification of Disease 10th version (ICD-10, secondary care).

Comparator

Multiple long-term conditions versus no multiple long-term conditions

Comparisons will be made with the following exposure group:

(i) pregnant women with multiple long-term conditions;

(ii) pregnant women with increasing counts of long-term health conditions;

(iii) pregnant women with different combinations of long-term health conditions; and

(iv) pregnant women in different health condition clusters (identified from ongoing clustering analyses).

The selection of which combinations and clusters of long-term conditions to study will be based on how common they are and their clinical relevance, following consultation with patient representatives and clinicians in our research team. Pregnant women with no multiple long-term conditions (i.e., no or single long-term conditions) will be the common comparator group.

Multiple long-term conditions with and without mental illness

In addition, we will also compare the outcomes for pregnant women who have mental health conditions as part of their multiple long-term conditions against pregnant women with multiple long-term conditions who do not have mental health conditions.

Outcomes

The outcomes will be grouped into the following four categories based on the research objectives: (1) antenatal, (2) peripartum, (3) postnatal and long-term outcomes, and (4) mental health outcomes. Examples of outcomes are provided as follows, based on existing core outcome sets for pregnancy and childbirth.[133] [134] The definitive list of outcomes will be confirmed once the development work for a core outcome set for studies of pregnant women with multiple long-term conditions is completed.[211] Outcomes will be ascertained from the study datasets (1st January 2000 to 31st December 2019) using clinical codes, such as Read, ICD-10 and Operating Procedures Codes (OPCS) Classification of Interventions and Procedures.

(1) Antenatal

Antenatal outcomes occur from conception to before the onset of childbirth. Examples for women include miscarriage, gestational hypertension, pre-eclampsia, gestational diabetes, venous thromboembolism, placenta abruption and antenatal hospital admissions. Examples for children include fetal growth restriction.

(2) Peripartum

Peripartum outcomes occur during and immediately after childbirth. This category will also include survival outcomes for women and children. Examples for women include mode of birth (spontaneous vaginal birth , birth with forceps/ ventouse, caesarean birth), postpartum haemorrhage, severe maternal morbidity, admission to intensive care and maternal death. Examples for children include preterm birth, small for gestational age, admission to neonatal unit, stillbirth, perinatal death, and neonatal death.

(3) Postnatal and long-term

Postnatal outcomes occur in the 42 days after birth,[388] while long-term outcomes are beyond the peripartum and postpartum period. For women this would include functional outcomes such as incontinence. For children, we will use mother baby linked primary and secondary care data to study postnatal and long-term outcomes such as congenital anomalies, neurodevelopmental conditions (e.g., autism, attention deficit hyperactive disorder and learning difficulty), cerebral palsy, and chronic lung disease. The length of follow up will depend on the availability of data in the routine health records. For example, CPRD has a median follow up of 5 years.[153] We will also examine postpartum readmission for mother and child.

(4) Mental health

Mental health outcomes cover the antenatal and postnatal period and will be considered up to 12 months after birth. This is to account for possible delay in women presenting to clinicians and reaching a formal diagnosis. We will consider both: (i) incident and (ii) recurrent mental health outcomes, where incident means a woman enters the analysis with no prior record of the specific mental health outcome. A perinatal mental health event is indicated by a primary care visit or hospital admission and includes mental health outcomes of concern in the antenatal and postnatal period (e.g., depression, psychosis, post-traumatic stress disorder, self-harm, and suicide attempts). Comparing the mental health event rates of pregnant women who have and have not got mental health conditions as part of their multiple long-term conditions will allow us to delineate the contribution of mental and physical morbidity to perinatal mental health outcomes. Children's mental ill health will also be considered (e.g., depression and anxiety).

Covariates

Analyses will adjust for the following covariates. Additional covariates may be added for individual outcomes based on the literature. For example, in analyses of mental health outcomes there will be additional covariates. For the mother, we will include history of any mental illness, for the child we will include maternal history of any mental and/ or neurodevelopmental conditions.

Where data for antenatal exposures are available (e.g., from NIMATS and Born in Bradford's booking appointments), additional analyses may be conducted where appropriate.

(i) Maternal age

We shall explore whether the association between maternal age and the outcomes are linear. Where this is not the case and to aid clinical interpretability, we will categorise maternal age at conception into 5-yearly age bands.

(ii) Parity/gravidity

The variable used will depend on availability in study datasets. Where both variables are available, both will be reported with preference given to *parity (*the number of times a woman gave birth at gestation ≥24 weeks); and sensitivity analysis will be conducted using *gravidity* (the number of times a woman has been pregnant).

(iii) Ethnicity

Maternal ethnicity will be categorised based on the variables available and to allow for harmonisation across the datasets: Asian, Black, Mixed, Other and White. Where data permits, we may use more granular categories of ethnicity. Where numbers are too small and risk identifying individuals, such as in NIMATS, we may collapse the categories to White and Non-white.

(iv) Social deprivation

The patient level Index of Multiple Deprivation specific to each nation will be used and categorised into quintiles.

(v) Body mass index

We shall include the latest available pre-pregnancy body mass index for the pregnant women. Where booking data is available before 16 weeks gestation, this will be used (e.g., in NIMATS). Body mass index will be considered a covariate instead of a health condition. The World Health Organisation's classification of obesity will be used to categorise body mass index: <18.5 kg/m^2, 18.5 to 24.9 kg/m^2, 25.0 to 29.9 kg/m^2, 30.0 to 34.9 kg/m^2, 35.0 to 39.9 kg/m^2, and 40+ kg/m^2.[389] Categories may be combined where numbers are too small.

(vi) Smoking

We shall include the latest available pre-pregnancy smoking status for the pregnant women. Smoking status will be categorised as: non-smoker, ex-smoker, and smoker.

(vii) Year (pregnancy start date)

Data quality and clinical guidelines may vary by year. Its effect on outcomes will be accounted for by adjusting for year of conception in the analysis.

Statistical analysis

We anticipate analyses will commence in June 2023 with study completion by June 2024. Baseline characteristics of the study population and outcomes will be described with summary statistics. Modified Poisson regression will be performed to estimate the relative risks of study outcomes. Cox regression will be performed for longer-term outcomes. The unit of analysis will be the pregnancy episode.

A federated analysis approach will be used as data governance arrangements do not allow pooling of the data across the four nations. Each dataset will be analysed separately following a common study protocol. A common data model will be established and implemented across the dataset, building on our previous work harmonising the phenome definitions for exposure conditions.[172] The effect sizes will be pooled using random-effects meta-analyses with inverse variance weighting for the primary care and secondary care datasets respectively.[390]

Where rare combinations of health conditions and outcomes may lead to identification of an individual or at the prespecified minimum count allowed by each data source, we will suppress the output.

Pregnant women with more than one pregnancy episode

An individual may have more than one pregnancy over the study period. The pregnancy episodes of the same woman will not be independent of each other. The severity of the exposure variable (pre-existing multiple long-term conditions) may increase in later pregnancy episodes as the pregnant women accumulates more long-term health conditions. If a woman had an adverse pregnancy outcome, she is more at risk of the same adverse outcome in subsequent pregnancy episodes. We shall account for this clustering effect of women with more than one pregnancy episode during the study period using the Generalised Estimating Equation in the regression analyses.

Multiple pregnancies

The main analysis will be limited to singleton pregnancies. Outcomes for pregnant women with multiple long-term conditions and multiple pregnancies (i.e., twins and higher order pregnancies) will be analysed as a separate cohort.

Missing data

Where exposure and outcome conditions are identified based on diagnostic codes, the absence of the code will be considered as an absence of the condition. The level and types of missingness of covariates will be reviewed and where appropriate will be addressed with representing missing data as a separate category or multiple imputation with chain equation (MICE). For variables required to compute an outcome, missing values will be imputed using MICE. Example of these variables include birthweight, gestational age, and baby's sex to determine preterm birth and small for gestational age. For each outcome, the statistical analyses will be performed on the imputed datasets and the estimates will be pooled with Rubin's rule.

Sensitivity analyses

We shall conduct sensitivity analyses using (i) complete case analysis, (ii) varying definitions of maternal multiple long-term conditions exposure using D'Arcy et al's core exposure set,[387] and (iii) in primiparous women. The latter is to account for the fact that some long-term conditions can arise from complications from a previous pregnancy.

Patient and public involvement

The research question was informed by discussions with our patient and public involvement (PPI) advisory group and our PPI co-investigators NM and RP.

The selection of outcomes are guided by our ongoing work developing a core outcome set for studies of pregnant women with multiple long-term conditions, where patients are key stakeholders.[211]

Our PPI advisory group and PPI co-investigators will be involved in interpreting the study findings, producing lay summaries and infographics, and disseminating the study findings through their network.

Ethics and dissemination

Ethics approval

CPRD: CPRD has broad National Research Ethics Service Committee ethics approval for purely observational research using the primary care data and established data linkages. The study has been reviewed and approved by CPRD's Independent Scientific Advisory Committee (reference: 20_181R).

SAIL: In accordance with UK Health Research Authority guidance, ethical approval is not mandatory for studies using only anonymised data. The study has been approved by SAIL Information Governance Review Panel.

Scotland dataset: The study has been approved by the National Health Service Scotland Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) and The University Teaching and Research Ethics Committee (UTREC) from the University of St Andrews.

NIMATS: The study has been approved by the Honest Broker Service Governance Board.

Born in Bradford: Ethics approval was granted by Bradford National Health Service Research Ethics Committee (ref 07/H1302/112) for the Born in Bradford cohort.

The proposed study is purely observational and will use anonymised research data. The study will not involve participant recruitment. Therefore, consent to participate is not required.

Consent for publication

This is not applicable as the manuscript is a study protocol. In the proposed study, we will use de-identified study data, therefore consent for publication will not be required.

Dissemination

Study findings will be submitted for publications in peer reviewed journals and presented at key conferences for health and social care professionals involved in the care of pregnant women with multiple long-term conditions and their children. We will also organise dissemination events to share our findings with the public, service users, clinicians, and researchers.

Discussion

MuM-PreDiCT is a consortium across all four nations of the UK studying multiple long-term conditions in pregnancy. As part of MuM-PreDiCT's program of work, we outlined the protocol for an observational study of maternal and child outcomes for pregnant women with multiple long-term conditions, using routine health records and a birth cohort in the UK.

Comparison with current literature

A recent systematic review found seven observational studies on the association of pre-pregnancy multiple long-term conditions with adverse maternal outcomes.[66] The review found that pre-pregnancy multiple long-term conditions were associated with severe maternal morbidity, hypertensive disorders of pregnancy, and acute health care use in the perinatal period.[66] Most studies were conducted in the United States.[66] Authors of the review commented that many studies included conditions arising in pregnancy in defining multiple long-term conditions, making it difficult to examine the impact of chronic conditions on maternal health.[66]

This proposed study will be based in the UK and will use a broad range of long-term conditions selected by women and clinicians to define multiple long-term conditions. Pregnancy related conditions and complications will be treated as study outcomes and will not be included in the

exposure's definition. We will also study outcomes across all stages of pregnancy and outcomes for both women and their children.

Strengths and limitations

This proposed study will utilise routine health records from all four nations of the UK (England, Scotland, Wales, and Northern Ireland). The available data sources consist of anonymised patient records from primary and secondary care, community prescription data, and maternity care data from routine booking appointments (first antenatal appointment offered universally and as the gateway to access maternity care in the UK).

Rich data will also be available from a birth cohort from Bradford, an ethnically diverse population in England. Beyond examining maternal outcomes, linked mother baby data and the birth cohort data will allow for the exploration of child outcomes. The key strength of this proposed study therefore is the generalisability of study findings to the UK population. Observing similar effect sizes across the different datasets will also increase the confidence in the study findings. Conversely, discrepancy in findings will stimulate further exploration of the datasets which may generate new knowledge.

As this is an observational study using anonymised routine health records, key limitations include missing data, misclassification bias due to inaccurate clinical coding and residual confounding.

Maternal multimorbidity will be quantified with simple counts. A systematic review of comorbidity indices used in maternal health research found three indices: Maternal Comorbidity Index, Charlson comorbidity index and Elixhauser comorbidity index.[63] Only the Maternal Comorbidity Index was developed from pregnant and postpartum women.[63] It was developed using hospital data with 20 maternal comorbidities but it included pregnancy related complications and factors such as multiple gestation, gestational diabetes, and hypertension

disorder of pregnancy.[63 64] In contrast, the list of health conditions we will use to define maternal pre-existing multimorbidity is more comprehensive and included leading causes of indirect maternal death (e.g. epilepsy) and mental health conditions.

Nevertheless, when using simple counts to quantify multiple long-term conditions, the severity of each health conditions will not be captured. The dose-response relationship will only be reflected in the total number of pre-existing long-term conditions. For example, we will not be able to distinguish the outcomes for a pregnant woman with diet-controlled diabetes and mild asthma from a pregnant woman with insulin dependent diabetes and brittle asthma. However, pregnant women with severe conditions are more likely to receive intense specialist care than pregnant women with mild conditions. As the number of pregnant women with greater disease severity is likely to be smaller than those with milder condition, adverse pregnancy outcomes may be underestimated.

Exposure and outcome events are only captured in routine health records when the pregnant women have presented to primary or secondary care and therefore the true prevalence and incidence may be underestimated. Health conditions that are managed conservatively in primary care, such as depression, anxiety, and miscarriage, may not be captured in secondary care datasets. Events such as termination of pregnancy that occurred outside of the traditional health care settings may also be underestimated.[391] Similarly, antenatal hospital admission data may not reflect the full burden of additional antenatal appointments or acute care attendances, as care accessed through other routes may not be captured.

Body mass index, which encompasses underweight and obese categories, will be studied as a covariate instead of being counted as part of multimorbidity. There is much debate around whether obesity should be considered a disease[392] or a risk factor for other long-term conditions such as cardiometabolic conditions and cancers.[393-395] What is clear is pre-pregnancy maternal

obesity is associated with adverse pregnancy outcome and dedicated care guideline has been established to manage this risk.[396 397]

Clinical implications

Current obstetric guidelines for pregnant women with medical conditions are focused on specific and single health conditions. There are currently no guidelines for the management of pregnant women with multiple long-term conditions in the UK. The heterogeneity of multiple long-term conditions means an all-encompassing guideline for every possible combination of long-term conditions would not be possible. Indeed the English national guideline for multimorbidity focuses on general approaches such as coordinated and holistic care, improving quality of life by reducing treatment burden and shared decision making between patients and clinicians.[21] A guideline for multiple long-term conditions (multimorbidity) in pregnancy is likely to follow the same principles but with additional focus on the maternity care aspect.

The basis of shared decision making is the provision of evidence-based information. As observed in the systematic review, there is currently a lack of evidence on the consequences of pregnancy for women with multiple long-term conditions.[66] Our PPI advisory group and preliminary findings from our core outcome set development work have highlighted how women valued having information to help them mentally prepare to face potential adverse pregnancy outcomes. The output from this study will therefore provide valuable information for women to make informed decision with their clinicians about family planning and their preconception, pregnancy, and postpartum care. It will also provide valuable information to guide the future design of care pathway for women with multiple long-term conditions.

Data availability statement

This is not applicable as the manuscript is a study protocol. In the proposed study, the data that support the findings are available from CPRD, SAIL, Scotland National Health Service Scotland Public Benefit and Privacy Panel for Health and Social Care, NIMATS and Born in Bradford, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of CPRD, SAIL, Scotland National Health Service Scotland Public Benefit and Privacy Panel for Health and Social Care, NIMATS and Born in Bradford.

Competing interests

The authors declare that they have no competing interests.

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Contributors

SIL – Conceptualisation, funding acquisition, methodology, writing (original draft preparation).

KN, MB, KAE, KMA, –OR - Conceptualisation, funding acquisition, methodology, supervision, writing (review and editing)

HH, GS, AS, NM, AAL, AFF, CNP, CY, CMC, JIK, PB, RP, RR, ST, SB, UA, ZV- Conceptualisation, funding acquisition, methodology, writing (review and editing)

LK, KP, MS, MM, NC, SPBHS - Conceptualisation, methodology, writing (review and editing)

MuM-PreDiCT group – Conceptualisation, funding acquisition

All authors read and approved the manuscript.

Supplementary Material Table 8.1: Summary of data sources

Name of data source	Country	Population: pregnant women	Exposure: maternal multiple long-term conditions status	Outcomes: pregnant women	Outcomes: children
Clinical Practice Research Datalink (CPRD)[153]	England	Pregnancy register (primary care)	Primary care routine health records	Primary care records, hospital admissions, death registration	Mother-baby linked data: primary care records, hospital admissions, death registration
Secure Anonymised Information Linkage (SAIL)[154]	Wales	Births from National Community Child Health Dataset	Primary care routine health records	Primary care records, hospital admissions, death registration	Mother-baby linked data: primary care records, hospital admissions, death registration
Scotland routine health records	Scotland	Scottish Maternity Records, pregnancy-related hospital admissions	Hospital admissions, psychiatric admissions, accident and emergency attendances, prescriptions	Hospital admissions, psychiatric admissions, accident and emergency attendances, death registration	Mother-baby linked data: hospital admissions, psychiatric admissions, accident and emergency attendances, death registration
Northern Ireland Maternity System (NIMATS)[398]	Northern Ireland	Maternity booking (first antenatal) appointment records, birth related hospital admissions	Maternity booking (first antenatal) appointment records, birth related hospital admissions, prescriptions	Hospital admissions	Mother-baby linked data: hospital admissions
Born in Bradford[399]	Bradford, England	Birth cohort of over 13,500 children born from around 12,500 mothers at the Bradford Royal Infirmary between March 2007 and June 2011	Primary care routine health records	Data from birth cohort: clinical data Data from linked health records: maternity, primary care, hospital admissions	Data from birth cohort: offspring developmental, clinical and education data Data from linked health records: primary care, hospital admissions

Supplementary Material Table 8.2: List of 79 health conditions defining multiple long-term conditions in pregnancy

Cancers

1. All cancers
    - Solid cancers
    - Haematological cancers
    - Metastatic cancers
    - Exclude basal cell carcinoma

Cardiovascular disease

2. Hypertension
3. Ischemic heart disease & myocardial infarction
4. Heart failure
5. Stroke
    - Transient ischemic attack
    - Ischemic stroke
    - Haemorrhagic stroke
    - Unspecified stroke
6. Atrial fibrillation
7. Congenital heart disease
8. Valvular heart disease (mitral, aortic, mixed)
9. Cardiomyopathy

Dermatology

10. Eczema
11. Psoriasis
12. Autoimmune skin disease
    - Vitiligo
    - Alopecia areata
13. Other dermatological conditions
    - Seborrheic dermatitis
    - Rosacea
    - Hidradenitis suppurativa
    - Lichen planus

Ear, Nose, Throat

14. Profound deafness
15. Allergic rhinitis & allergic conjunctivitis

Eye

16. Inflammatory eye disease
    - Scleritis & episcleritis
    - Anterior uveitis
    - Posterior uveitis
17. Cataract
18. Diabetic eye disease
19. Severe blindness
20. Retinal detachment

Gastroenterology

21. Irritable bowel syndrome
22. Inflammatory bowel disease
    - Ulcerative colitis
    - Crohn's disease
23. Coeliac disease
24. Chronic liver disease
    - Chronic hepatitis B & C
    - Alcoholic liver disease
    - Autoimmune liver disease

Neurodevelopmental conditions

43. Neurodevelopmental conditions
    - Learning disability
    - Attention deficit hyperactivity disorder
    - Autistic spectrum disorder

Rheumatology

44. Systemic lupus erythematosus
45. Spondylarthritis
    - Psoriatic arthritis
    - Ankylosing spondylitis
46. Inflammatory arthritis
    - Rheumatoid arthritis
    - Sjogern's syndrome
    - Raynaud's syndrome
    - Systemic sclerosis
    - Primary systemic vasculitis
47. Ehlers Danlos Syndrome (EDS) Type 3 (Hypermobile EDS)

Orthopaedic

48. Scoliosis
49. Vertebral disorder
    - Intervertebral disc disorder
    - Spondylosis
    - Spondylolisthesis
    - Collapsed vertebrae
    - Spinal stenosis
50. Chronic back pain
51. Osteoporosis
52. Osteoarthritis

Neurology

53. Migraine
54. Other chronic headache (including cluster headache, tension headache)
55. Epilepsy
56. Multiple sclerosis
57. Spina bifida
58. Idiopathic intracranial hypertension
59. Peripheral neuropathy
60. Other neurological conditions / musculoskeletal disorders
    - chronic fatigue syndrome / myalgic encephalomyelitis
    - fibromyalgia
    - chronic pain syndrome (includes chronic regional pain syndrome, myofascial pain syndrome)

Respiratory

61. Asthma
62. Chronic obstructive pulmonary disease
63. Obstructive sleep apnoea

- Cirrhosis
- Non-alcoholic fatty liver disease

25. Peptic ulcer
26. Gall stones

Gynaecology

27. Polycystic ovarian syndrome
28. Endometriosis
29. Fibroids
30. Infertility

Haematology

31. History of venous thromboembolism
    - Deep vein thrombosis
    - Pulmonary embolism
32. Primary thrombocytopenia
33. Haemophilia
34. Sickle cell anaemia
35. Pernicious anaemia

Mental health

36. Depression
37. Anxiety
    - Panic disorder
    - Phobia disorder
    - Post-traumatic stress disorder
38. Severe mental illness
    - Bipolar affective disorder
    - Schizophrenia
    - Psychosis
39. Eating disorder
40. History of alcohol use disorder (misuse / dependence)
41. History of substance misuse
42. Others
    - Obsessive compulsive disorder
    - Self-harm
    - Personality disorder
    - Dissociative disorder

64. Pulmonary fibrosis, interstitial lung disease
65. Pulmonary hypertension
66. Bronchiectasis
67. Cystic fibrosis
68. Sarcoidosis

Renal

69. Chronic kidney disease
70. Urinary tract stones

Endocrine

71. Diabetes mellitus
72. Thyroid disorder
73. Pituitary disorder
74. Adrenal benign tumour
75. Hyperparathyroidism

Other

76. Human immunodeficiency viral infection / Acquired immune deficiency syndrome
77. Turner's syndrome
78. Marfan's syndrome
79. Solid organ transplant