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Maternal and children's outcomes for pregnant women with pre-existing multiple long-term conditions: a study protocol of an observational study in the United Kingdom

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61 **Keywords:** multimorbidity, multiple chronic conditions, multiple long-term conditions,
62 pregnancy, maternity, obstetric, outcome, children, offspring
63

64 **ABSTRACT**

65 **Introduction:** One in five pregnant women have multiple long-term conditions in the United
66 Kingdom (UK). Studies have shown that maternal multiple long-term conditions are
67 associated with adverse outcomes. This observational study aims to compare maternal and
68 children's outcome for pregnant women with multiple long-term to those without multiple
69 long-term conditions.

70 **Methods and analysis:** Pregnant women aged 15 to 49 years old with a conception date
71 between 2000 and 2019 in the UK will be included. The data source will be routine health
72 records from all four UK nations (Clinical Practice Research Datalink [CPRD, England],
73 Secure Anonymised Information Linkage [SAIL, Wales], Scotland routine health records and
74 Northern Ireland Maternity System [NIMATS]), and the Born in Bradford prospective birth
75 cohort.

76 The exposure of two or more pre-existing, long-term physical or mental health conditions
77 will be defined from a list of health conditions predetermined by women and clinicians. The
78 association of maternal multiple long-term conditions with (i) antenatal, (ii) peripartum, (iii)
79 postnatal and long-term, and (iv) mental health outcomes, for both women and their children
80 will be examined. Outcomes of interest will be guided by a core outcome set.

81 Comparisons will be made between pregnant women with and without multiple long-term
82 conditions using logistic and Cox regression. Generalised estimating equation will account
83 for the clustering effect of women who had more than one pregnancy episode. Where
84 appropriate, multiple imputation with chained equation will be used for missing data.

85 Federated analysis will be conducted for each dataset and results will be pooled using meta-
86 analysis.

87 **Ethics and dissemination:**

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88 Approval has been obtained from the respective data sources in each UK nation. Study
89 findings will be submitted for publications in peer reviewed journals and presented at key
90 conferences.

91 **282 words**

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For peer review only

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3 94 **ARTICLE SUMMARY**
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6 95 **Strengths and limitations of this study**
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- 9 96 • The study will utilise rich data sources from routine health records from all four UK
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11 97 nations and a birth cohort.
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13 98 • Beyond examining maternal outcomes, linked mother baby data and the birth cohort
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15 99 data will allow for the exploration of children's outcomes.
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17 100 • Key limitations include missing data, misclassification bias due to inaccurate clinical
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19 101 coding and residual confounding.
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102 INTRODUCTION

103 One in five pregnant women have two or more long-term physical or mental health
104 conditions prior to pregnancy in the United Kingdom (UK).¹ In the UK 2016-18 national
105 maternal mortality report, 90% of women who died during or up to a year after pregnancy
106 had multiple health or social problems.² Recent evidence has shown that maternal multiple
107 long-term conditions are associated with adverse outcomes for women and their children,
108 such as severe maternal morbidity and mortality, pre-eclampsia, emergency caesarean birth,
109 preterm birth, and low birth weight.³⁻⁵

110 Information on consequences for women with multiple long-term conditions and their
111 children is crucial for women and their health care professionals to make informed decisions
112 on pregnancy care planning. However, there remains a lack of evidence to guide care
113 pathways for pregnant women with multiple long-term conditions.^{5 6}

114 Healthcare is free in the UK and over 98% of the population are registered at a general
115 practice (akin to family practice in other countries).⁷ General practices not only provide
116 primary and community healthcare, but they also serve as the main point of contact for
117 referrals to specialist clinical services and provide the majority of prescribing outside of a
118 hospital setting.⁷ In the UK, pregnant women are recommended to have their booking
119 appointment before 10 weeks gestation.⁸ This is the pregnant woman's first midwife or
120 doctor appointment, where they undergo health and social care assessment of needs and risks
121 for her pregnancy.⁹ Over 97% of births occur in healthcare settings in England and Wales.¹⁰
122 Therefore, routine health records in primary and secondary care in the UK offer a rich data
123 source for observational studies of pregnant women and their children.

124 This observational study aims to compare outcomes for women with multiple long-term
125 conditions to those without multiple long-term conditions. Outcomes studied will include

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3 126 those for women and their children. Datasets from routine health records from all four UK
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5 127 nations (England, Wales, Scotland, and Northern Ireland) will be used. In addition, the Born
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7 128 in Bradford birth cohort from a deprived, ethnically diverse city in the UK, will also be
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10 129 used.¹¹
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13 130 The four research objectives are to examine the association between maternal pre-existing
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15 131 multiple long-term conditions with: (1) antenatal, (2) peripartum, (3) postnatal and long-term
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17 132 outcomes, and (4) mental health outcomes. The findings from each research objective will be
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20 133 published in a separate paper.
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26 135 **METHODS AND ANALYSIS**

29 136 **Study design**

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32 137 This is an observational study using data from routine healthcare records and a prospective
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34 138 birth cohort in the UK.
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40 140 **Study population and eligibility criteria**

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43 141 The study population will consist of women aged 15-49 years old at conception, with
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45 142 pregnancies beginning between 2000 and 2019 in the UK. Date of conception (pregnancy
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47 143 start date) will be defined as the first day of the last menstrual period or gestational day 0. To
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50 144 ensure sufficient quality data, eligible women must have health records that meet the standard
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52 145 data quality checks as defined by each data source and one year's worth of health records
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54 146 prior to index pregnancy.
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148 **Data sources**

149 Five population-based data sources (four routine health record datasets and one prospective
150 birth cohort) that will be used are described as follows.

151 *(1) Clinical Practice Research Datalink (CPRD), England*

152 CPRD contains anonymised, longitudinal medical records collected during provision of
153 routine healthcare, from participating general practices in the UK; currently 5% of UK
154 general practices contributes to the database.¹² It includes data on demographics, diagnoses,
155 symptoms, signs, tests and prescriptions.⁷ Linkage to area based deprivation index, Hospital
156 Episodes Statistics and Office for National Statistics death registration data is available for
157 patients whose general practices have consented to the CPRD linkage scheme.⁷

158 Within CPRD, the CPRD Pregnancy Register is an algorithm that takes information from
159 maternity, antenatal and birth health records from primary care to detect pregnancy episodes
160 and their outcomes.¹³ The Mother Baby Linked data, similarly links women and child records
161 using an algorithm,¹⁴ will allow for studying the outcomes of children born to mothers with
162 multiple long-term conditions.

163 CPRD has data for patients from all four UK nations, but analyses using CPRD data will only
164 include English general practices to avoid duplication of patients with datasets from the
165 devolved nations (Wales, Scotland and Northern Ireland).

166 *(2) Secure Anonymised Information Linkage (SAIL), Wales*

167 The SAIL databank is a whole population level database in Wales. It is a repository of
168 anonymised health and socio-economic administrative data and provides linkage at an
169 individual level.¹⁵ It holds data for 4.8 million people and covers 80% of Welsh general
170 practices.¹⁵ Within SAIL, the National Community Child Health Dataset will be used to

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3 171 detect births and linked to the Welsh Longitudinal General Practice dataset and the Welsh
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5 172 Demographic Service dataset for diagnoses, prescriptions and demographics data
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8 173 respectively.
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10 174 *(3) Scotland*

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13 175 A dataset will be created linking the Scottish Maternity Records (SMR02) to data from
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15 176 Hospital Admissions (SMR01), Mental Health Inpatients (SMR04), Accident and
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18 177 Emergency, and the Demography and Death registry. This will cover diagnoses and
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20 178 demographic data for all inpatient stays and day cases for residents in Scotland. The dataset
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23 179 will also be linked to the Prescribing Information System for data on all medications
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25 180 dispensed in the community. Pregnancies will be detected from maternity records or
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27 181 pregnancy-related hospital admissions.
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30 182 *(4) Northern Ireland Maternity System (NIMATS)*

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33 183 NIMATS holds demographic and clinical information on mothers and infants.¹⁶ It captures
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35 184 data relating to the current complete maternity process, and the women's past medical and
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37 185 obstetric history.¹⁶ It is a key source for data on birth numbers, interventions, maternal risk
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39 186 factors, birth weights, maternal smoking, body mass index and breastfeeding on discharge.¹⁶
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41
42 187 NIMATS covers all five Health and Social Care Trusts areas across Northern Ireland (11
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44 188 hospitals providing maternity services in total).¹⁶ Access to NIMATS is also available to
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46 189 midwives and clerical staff in various community clinics across NI to allow for booking
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48 190 appointments to be recorded.¹⁶ Pregnancies will be determined from maternity records
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50 191 derived from data recorded at booking appointments (the first antenatal appointment) and
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52 192 hospital admission for childbirth.
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3 194 *(5) Born in Bradford*
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6 195 This birth cohort follows over 13,500 children born from around 12,500 mothers at the
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8 196 Bradford Royal Infirmary between March 2007 and June 2011.¹⁷ Data is collected from
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10 197 pregnancy through childhood and into adult life.¹⁷ The database consists of over 13,500
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12 198 pregnancies with biological samples, sociodemographic data, offspring developmental,
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14 199 clinical and education data and is linked to health care records from maternity, primary care
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16 200 (mother and offspring) and hospital admissions.¹⁷
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23 202 **Exposure**
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26 203 The exposed group will consist of pregnant women with multiple long-term conditions. We
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28 204 shall define this as two or more long-term physical or mental health conditions that pre-
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30 205 existed before pregnancy. Pregnancy related complications will not be included as they will
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32 206 be studied as outcomes. Multiple long-term conditions will be defined from a list of health
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34 207 conditions previously described in our epidemiological work.¹ Sensitivity analysis will be
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36 208 performed defining maternal long-term conditions with a different list of health conditions by
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38 209 D'Arcy et al.¹⁸
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42 210 Exposure will be ascertained by the presence of diagnostic or prescriptions codes, including
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44 211 Read (to identify exposures in primary care data), International Classification of Disease 10th
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46 212 version (ICD-10, secondary care) and Operating Procedures Codes (OPCS) Classification of
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48 213 Interventions and Procedures.
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3 216 **Comparator**
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6 217 Pregnant women with no multiple long-term conditions (i.e. no or single long-term
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8 218 conditions) will be the comparator group. Comparisons will be made with the following
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10 219 exposure group:

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13 220 (i) pregnant women with multiple long-term conditions;

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16 221 (ii) pregnant women with increasing counts of long-term health conditions;

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19 222 (iii) pregnant women with different combinations of long-term health conditions.

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22 223 (iv) pregnant women in different health condition clusters (identified from ongoing clustering
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24 224 analyses); and

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28 225 In addition, we will also compare the outcomes for pregnant women who have mental health
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30 226 conditions as part of their multiple long-term conditions with pregnant women with multiple
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32 227 long-term conditions who do not have mental health conditions.
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38 229 **Outcomes**
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41 230 The outcomes will be grouped into the following four categories based on the research
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43 231 objectives: (1) antenatal, (2) peripartum, (3) postnatal and long-term outcomes, and (4)
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45 232 mental health outcomes. Examples of outcomes are provided as follows, based on existing
46
47 233 core outcome sets for pregnancy and childbirth.^{19 20} The definitive list of outcomes will be
48
49 234 confirmed once the development work for a core outcome set for studies of pregnant women
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51 235 with multiple long-term conditions is completed.²¹ Outcomes will be ascertained using Read,
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53 236 ICD-10 and OPCS codes.
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3 238 *(1) Antenatal*
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6 239 Antenatal outcomes occur from conception to before the onset of childbirth. Examples for
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8 240 women include miscarriage, gestational hypertension, pre-eclampsia, gestational diabetes,
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10 241 venous thromboembolism and placenta abruption. Examples for children include fetal growth
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13 242 restriction.
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16 243 *(2) Peripartum*
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19 244 Peripartum outcomes occur during and immediately after childbirth. This category will also
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21 245 include survival outcomes for women and children. Examples for women include mode of
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23 246 birth (spontaneous vaginal birth, birth with forceps/ventouse, caesarean birth), postpartum
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25 247 haemorrhage, severe maternal morbidity and maternal death. Examples for children include
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27 248 preterm birth, small for gestational age, stillbirth, perinatal death and neonatal death.
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31 249 *(3) Postnatal and long-term*
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34 250 Postnatal outcomes occur in the 42 days after birth.²² We will also include perinatal health
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36 251 care utilisation outcomes and long-term outcomes enduring beyond the peripartum and
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38 252 postpartum period. Examples for women include incontinence. Examples for children include
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40 253 congenital anomaly and neurodevelopmental disorders. Examples for health care utilisation
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42 254 include admission to intensive care.
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46 255 *(4) Mental health*
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49 256 Mental health outcomes cover the antenatal and postnatal period. Mental health outcomes
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51 257 will be considered up to 12 months after birth. This is to account for possible delay in women
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53 258 presenting to clinicians and reaching a formal diagnosis. Examples include postnatal
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55 259 depression, puerperal psychosis, post-traumatic stress disorder, self-harm and suicide
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57 260 attempts. Children's mental health and behavioural disorders will also be considered.
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261 **Covariates**

262 Analyses will adjust for the following covariates in a hierarchical manner to explore potential
263 mediating effects. Additional covariates may be added for individual outcomes based on the
264 literature. Where data for antenatal exposures are available (e.g. from NIMATS and Born in
265 Bradford's booking appointments), additional analyses may be conducted where appropriate.

266 *(i) Maternal age*

267 We shall explore whether the association between maternal age and the outcomes are linear.
268 Where this is not the case and to aid clinical interpretability, we will categorise maternal age
269 at conception into 5-yearly age bands.

270 *(ii) Parity/gravidity*

271 The variable used will depend on availability in study datasets. Where both variables are
272 available, both will be reported with preference given to *parity* (the number of times a woman
273 gave birth at gestation ≥ 24 weeks); and sensitivity analysis will be conducted using *gravidity*
274 (the number of times a woman has been pregnant).

275 *(iii) Ethnicity*

276 Maternal ethnicity will be categorised based on the variables available in the study datasets:
277 Asian, Black, Mixed, Other and White. Where numbers are too small and risk identifying
278 individuals, such as in NIMATS, we may collapse the categories to White and Non-white.

279 *(iv) Social deprivation*

280 The patient level Index of Multiple Deprivation specific to each nation will be used and
281 categorised into quintiles.

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3 283 *(v) Body mass index*
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6 284 We shall include the latest available pre-pregnancy body mass index (BMI) for the pregnant
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8 285 women. Where booking data is available before 16 weeks gestation, this will be used (e.g. in
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10 286 NIMATS). BMI will be considered a covariate instead of a health condition. The World
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12 287 Health Organisation's classification of obesity will be used to categorise BMI: <18.5 kg/m²,
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14 288 18.5 to 24.9 kg/m², 25.0 to 29.9 kg/m², 30.0 to 34.9 kg/m², 35.0 to 39.9 kg/m², and 40+
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16 289 kg/m².²³ Categories may be combined where numbers are too small.
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20 290 *(vi) Smoking*
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23 291 We shall include the latest available pre-pregnancy smoking status for the pregnant women.
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25 292 Smoking status will be categorised as: non-smoker, ex-smoker, and smoker.
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29 293 *(vii) Year (pregnancy start date)*
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32 294 Data quality and clinical guidelines may vary by year. Its effect on outcomes will be
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34 295 accounted for by adjusting for year of conception in the analysis.
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40 297 **Statistical analysis**
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43 298 Baseline characteristics of the study population and outcomes will be described with
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45 299 summary statistics. Multivariable logistic regression will be performed to estimate the odds
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47 300 ratios for selected study outcomes. Cox regression will be performed for longer-term
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49 301 outcomes. The unit of analysis will be the pregnancy episode.
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52 302 The covariates will be adjusted for in a hierarchical manner. This is because our prior
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54 303 epidemiological study observed that BMI and smoking may mediate the association between
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56 304 multiple long-term conditions with social deprivation.¹
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3 305 A federated analysis approach will be used, each dataset will be analysed separately within
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5 306 the approval of the data access. The effect sizes from the different datasets will then be
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8 307 included in a meta-analysis to produce a summary measure.
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11 308 Where rare combinations of health conditions and outcomes may lead to identification of an
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13 309 individual or at the prespecified minimum count allowed by each data source, we will
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15 310 suppress the output.
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20 21 312 **Pregnant women with more than one pregnancy episode**

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24 313 An individual may have more than one pregnancy over the study period. The pregnancy
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26 314 episodes of the same woman will not be independent of each other. The severity of the
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28 315 exposure variable (pre-existing multiple long-term conditions) may increase in later
29
30 316 pregnancy episodes as the pregnant woman accumulates more long-term health conditions. If
31
32 317 a woman had an adverse pregnancy outcome, she is more at risk of the same adverse outcome
33
34 318 in subsequent pregnancy episodes. We shall account for this clustering effect of women with
35
36 319 more than one pregnancy episode during the study period using the Generalised Estimating
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38 320 Equation in the regression analyses.
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45 46 322 **Multiple pregnancies**

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48
49 323 The main analysis will be limited to singleton pregnancies. Outcomes for pregnant women
50
51 324 with multiple long-term conditions and multiple pregnancies (i.e. twins and higher order
52
53 325 pregnancies) will be analysed as a separate cohort.
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328 **Missing data**

329 Where exposure and outcome conditions are identified based on diagnostic codes, the
330 absence of the code will be considered as an absence of the condition. The level and types of
331 missingness of covariates will be reviewed and where appropriate will be addressed with
332 representing missing data as a separate category or multiple imputation with chain equation
333 (MICE). For variables required to compute an outcome, missing values will be imputed using
334 MICE. Example of these variables include birthweight, gestational age and baby's sex to
335 determine preterm birth and small for gestational age. For each outcome, the statistical
336 analyses will be performed on the imputed datasets and the estimates will be pooled with
337 Rubin's rule.

338

339 **Sensitivity analysis**

340 We shall conduct sensitivity analysis using (i) complete case analysis and (ii) varying
341 definitions of maternal multiple long-term conditions exposure using D'Arcy et al's core
342 exposure set.¹⁸

343

344 **Patient and public involvement**

345 The research question was informed by discussions with our patient and public involvement
346 (PPI) advisory group and our PPI co-investigators NM and RP.

347 The selection of outcomes are guided by our ongoing work developing a core outcome set for
348 studies of pregnant women with multiple long-term conditions, where patients are key
349 stakeholders.²¹

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2
3 350 Our PPI advisory group and PPI co-investigators will be involved in interpreting the study
4
5 351 findings, producing lay summaries and infographics, and disseminating the study findings
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7
8 352 through their network.
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12 13 354 **Dissemination**

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15
16 355 Study findings will be submitted for publications in peer reviewed journals and presented at
17
18 356 key conferences for health and social care professionals involved in the care of pregnant
19
20 357 women with multiple long-term conditions and their children. We will also organise
21
22 358 dissemination events to share our findings with the public, service users, clinicians and
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24 359 researchers.
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30 31 361 **DISCUSSION**

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34 362 MuM-PreDiCT is a consortium across all four nations of the UK studying multiple long-term
35
36 363 conditions in pregnancy. As part of MuM-PreDiCT's program of work, we outlined the
37
38 364 protocol for an observational study of maternal and children's outcome for pregnant women
39
40 365 with multiple long-term conditions, using routine health records and a birth cohort in the UK.
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46 47 367 **Comparison with current literature**

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49
50 368 A recent systematic review found seven observational studies on the association of pre-
51
52 369 pregnancy multiple long-term conditions with adverse maternal outcomes.⁵ The review found
53
54 370 that pre-pregnancy multiple long-term conditions were associated with severe maternal
55
56 371 morbidity, hypertensive disorders of pregnancy, and acute health care use in the perinatal
57
58 372 period.⁵ Most studies were conducted in the United States.⁵ Authors of the review
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60

1
2
3 373 commented that many studies included conditions arising in pregnancy in defining multiple
4
5 374 long-term conditions, making it difficult to examine the impact of chronic conditions on
6
7
8 375 maternal health.⁵
9

10 376 This proposed study will be based in the UK and will use a broad range of long-term
11
12
13 377 conditions selected by women and clinicians to define multiple long-term conditions.
14
15 378 Pregnancy related conditions and complications will be treated as study outcomes and not
16
17 379 included in the exposure's definition. We will also study outcomes across all stages of
18
19
20 380 pregnancy and outcomes for both women and their children.
21
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23 381

24 25 26 382 **Strengths and limitations**

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28
29 383 This proposed study will utilise routine health records from all four nations of the UK
30
31 384 (England, Scotland, Wales and Northern Ireland). The available data sources consist of
32
33 385 anonymised patient records from primary and secondary care, community prescription data,
34
35 386 and maternity care data from routine booking appointments (first antenatal appointment
36
37 387 offered universally and as the gateway to access maternity care in the UK).
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39

40
41 388 Rich data will also be available from a prospective birth cohort from Bradford, an ethnically
42
43 389 diverse population in England. Beyond examining maternal outcomes, linked mother baby
44
45 390 data and the birth cohort data will allow for the exploration of children's outcomes. The key
46
47 391 strength of this proposed study therefore is the generalisability of study findings to the UK
48
49
50 392 population.
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52
53 393 As this is an observational study using anonymised routine health records, key limitations
54
55 394 include missing data, misclassification bias due to inaccurate clinical coding and residual
56
57 395 confounding.
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3 396 **Clinical implications**
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5 397 Current obstetric guidelines for pregnant women with medical conditions are focused on
6
7 398 specific and single health conditions.²⁴ There are currently no guidelines for the management
8
9 399 of pregnant women with multiple long-term conditions in the UK. As observed in the
10
11 400 systematic review, there is currently a lack of evidence on the consequences of pregnancy for
12
13 401 women with multiple long-term conditions.⁵ Our PPI advisory group and preliminary
14
15 402 findings from our core outcome set development work have highlighted how women valued
16
17 403 having information to help them mentally prepare to face potential adverse pregnancy
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19 404 outcomes.
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24 405 The output from this study will therefore provide valuable information for women to make
25
26 406 informed decision with their clinicians about family planning and their preconception,
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28 407 pregnancy and postpartum care. It will also provide valuable information to guide the future
29
30 408 design of care pathway for women with multiple long-term conditions.
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37 410 **Conclusion**
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40 411 This protocol outlines the study design of an observational study quantifying maternal and
41
42 412 children's outcomes for pregnant women with multiple long-term conditions. The outputs
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44 413 from this study will add to the current body of literature and provide valuable information to
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46 414 help women and their clinicians with their preconception, pregnancy and postpartum care
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48 415 planning.
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3 418 **ABBREVIATIONS**
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5 419 BMI Body mass index
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7 420 CPRD Clinical Practice Research Datalink
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9 421 ICD-10 International Classification of Disease 10th version
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11 422 MICE Multiple imputation with chain equation
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14 423 NICE National Institute for Health and Care Excellence
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16 424 NIMATS Northern Ireland Maternity System
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19 425 OPCS Operating Procedures Codes
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21 426 PPI Patient and public involvement
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23 427 SAIL Secure Anonymised Information Linkage
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26 428 UK United Kingdom
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3 **429 Ethics approval**
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6 **430 CPRD:** CPRD has broad National Research Ethics Service Committee ethics approval for
7
8 **431** purely observational research using the primary care data and established data linkages. The
9
10 **432** study has been reviewed and approved by CPRD's Independent Scientific Advisory
11
12
13 **433** Committee (reference: 20_181R).
14

15
16 **434 SAIL:** In accordance with UK Health Research Authority guidance, ethical approval is not
17
18 **435** mandatory for studies using only anonymised data. The study has been approved by SAIL
19
20
21 **436** Information Governance Review Panel.
22

23
24 **437 Scotland dataset:** The study has been approved by the National Health Service
25
26 **438** Scotland Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) and The
27
28 **439** University Teaching and Research Ethics Committee (UTREC) from the University of St
29
30 **440** Andrews.
31

32
33
34 **441 NIMATS:** The study has been approved by the Honest Broker Service Governance Board.
35

36
37 **442 Born in Bradford:** Ethics approval was granted by Bradford National Health Service
38
39 **443** Research Ethics Committee (ref 07/H1302/112) for the Born in Bradford cohort.
40

41
42 **444** The proposed study is purely observational and will use anonymised research data. The study
43
44 **445** will not involve participant recruitment. Therefore, consent to participate is not required.
45

46
47 **446 Consent for publication**
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49
50 **447** This is not applicable as the manuscript is a study protocol. In the proposed study, we will
51
52 **448** use de-identified study data, therefore consent for publication will not be required.
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55 **449**
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3 451 **Availability of data and materials**
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6 452 This is not applicable as the manuscript is a study protocol. In the proposed study, the data
7
8 453 that support the findings are available from CPRD, SAIL, Scotland National Health Service
9
10 454 Scotland Public Benefit and Privacy Panel for Health and Social Care, NIMATS and Born in
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13 455 Bradford, but restrictions apply to the availability of these data, which were used under
14
15 456 license for the current study, and so are not publicly available. Data are however available
16
17 457 from the authors upon reasonable request and with permission of CPRD, SAIL, Scotland
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19
20 458 National Health Service Scotland Public Benefit and Privacy Panel for Health and Social
21
22 459 Care, NIMATS and Born in Bradford.

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25 460 **Competing interests**
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27
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52

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54 472 preparation).
55
56 473 KN, MB, KAE, KMA, DOR - Conceptualisation, funding acquisition, methodology,
57 474 supervision, writing (review and editing)
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4 476 Conceptualisation, funding acquisition, methodology, writing (review and editing)
5
6 477 LK, KP, MS, MM, NC, SPBHS - Conceptualisation, methodology, writing (review and
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1 **Title: Maternal and child outcomes for pregnant women with pre-existing multiple**
 2 **long-term conditions: protocol for an observational study in the United Kingdom**

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63 **ABSTRACT**

64 **Introduction:** One in five pregnant women have multiple pre-existing long-term conditions
65 in the United Kingdom (UK). Studies have shown that maternal multiple long-term
66 conditions are associated with adverse outcomes. This observational study aims to compare
67 maternal and child outcomes for pregnant women with multiple long-term conditions to those
68 without multiple long-term conditions (0 or 1 long-term conditions).

69 **Methods and analysis:** Pregnant women aged 15 to 49 years old with a conception date
70 between 2000 and 2019 in the UK will be included with follow up till 2019. The data source
71 will be routine health records from all four UK nations (Clinical Practice Research Datalink
72 [CPRD, England], Secure Anonymised Information Linkage [SAIL, Wales], Scotland routine
73 health records and Northern Ireland Maternity System [NIMATS]); and the Born in Bradford
74 birth cohort. The exposure of two or more pre-existing, long-term physical or mental health
75 conditions will be defined from a list of health conditions predetermined by women and
76 clinicians. The association of maternal multiple long-term conditions with (i) antenatal, (ii)
77 peripartum, (iii) postnatal and long-term, and (iv) mental health outcomes, for both women
78 and their children will be examined. Outcomes of interest will be guided by a core outcome
79 set. Comparisons will be made between pregnant women with and without multiple long-
80 term conditions using modified Poisson and Cox regression. Generalised estimating equation
81 will account for the clustering effect of women who had more than one pregnancy episode.
82 Where appropriate, multiple imputation with chained equation will be used for missing data.
83 Federated analysis will be conducted for each dataset and results will be pooled using
84 random-effects meta-analyses.

85 **Ethics and dissemination:**

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86 Approval has been obtained from the respective data sources in each UK nation. Study
87 findings will be submitted for publications in peer reviewed journals and presented at key
88 conferences.

89 **295 words**

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For peer review only

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3 92 **ARTICLE SUMMARY**
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6 93 **Strengths and limitations of this study**
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- 9 94 • The study will utilise rich data sources from routine health records from all four UK
10 nations and a birth cohort.
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14 96 • Beyond examining maternal outcomes, linked mother baby data and the birth cohort
15 data will allow for the exploration of children's outcomes.
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19 98 • Key limitations include missing data, misclassification bias due to inaccurate clinical
20 coding and residual confounding.
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100 INTRODUCTION

101 Maternal single long-term conditions such as cardiac conditions, chronic kidney disease and
102 epilepsy are associated with adverse pregnancy outcomes.¹⁻⁴ This is likely to be compounded
103 when the pregnant woman has two or more long-term physical or mental health conditions
104 (multimorbidity). Some conditions may need different treatments from different health care
105 teams, thereby increasing the treatment burden and complexity of care.⁵ Recent evidence has
106 shown that maternal multiple long-term conditions are associated with adverse outcomes for
107 women and their children, such as severe maternal morbidity and mortality, pre-eclampsia,
108 emergency caesarean birth, preterm birth, and low birth weight.⁶⁻⁸ In the UK 2016-18
109 national maternal mortality report, 90% of women who died during or up to a year after
110 pregnancy had multiple health or social problems.⁹

111 Currently one in five pregnant women have multiple long-term conditions prior to pregnancy
112 in the United Kingdom (UK).¹⁰ The number of pregnant women with pre-existing multiple
113 long-term conditions is likely to increase as women are getting pregnant later in life and with
114 higher body weight.¹¹⁻¹⁴ As this becomes an increasingly important issue, information on
115 pregnancy, maternal and child outcomes is crucial for women and their health care
116 professionals to make informed decisions on preconception and pregnancy care planning.
117 However, there remains a lack of evidence to guide care pathways for pregnant women with
118 multiple long-term conditions.^{8 15}

119 Healthcare is free in the UK and over 98% of the population are registered at a general
120 practice (akin to family practice in other countries).¹⁶ General practices not only provide
121 primary and community healthcare, but they also serve as the main point of contact for
122 referrals to specialist clinical services and provide the majority of prescribing outside of a
123 hospital setting.¹⁶ In the UK, pregnant women are recommended to have their booking

1
2
3 124 appointment before 10 weeks gestation.¹⁷ This is the pregnant woman's first midwife or
4
5 125 doctor appointment, where they undergo health and social care assessment of needs and risks
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7 126 for her pregnancy.¹⁸ Over 97% of births occur in healthcare settings in England and Wales.¹⁹
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10 127 Therefore, routine health records in primary and secondary care in the UK offer a rich data
11
12 128 source for observational studies of pregnant women and their children.

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15 129 This observational study aims to compare outcomes for women with multiple long-term
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17 130 conditions to those without multiple long-term conditions. Outcomes studied will include
18
19 131 those for women and their children. Datasets from routine health records from all four UK
20
21 132 nations (England, Wales, Scotland, and Northern Ireland) will be used. In addition, the Born
22
23 133 in Bradford birth cohort from a deprived, ethnically diverse city in the UK, will also be
24
25 134 used.²⁰
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30 135 The four research objectives are to examine the association between maternal pre-existing
31
32 136 multiple long-term conditions with: (1) antenatal, (2) peripartum, (3) postnatal and long-term
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34 137 outcomes, and (4) mental health outcomes. The findings from each research objective will be
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36 138 published in a separate paper.
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141 **METHODS AND ANALYSIS**

142 **Study design**

143 This is a cohort observational study using data from routine healthcare records and a birth
144 cohort in the UK.

146 **Study population and eligibility criteria**

147 The study population will consist of women aged 15-49 years old at conception, with
148 pregnancies beginning between 1st January 2000 and 31st December 2019 in the UK. Date of
149 conception (pregnancy start date) will be defined as the first day of the last menstrual period
150 or gestational day 0. To ensure sufficient quality data, eligible women must have health
151 records that meet the standard data quality checks as defined by each data source and one
152 year's worth of health records prior to index pregnancy.

154 **Data sources**

155 Table 1 presents the five data sources that will be used. Each UK devolved nation is
156 represented by a population based routine health record dataset, with good national coverage
157 for Wales, Scotland and Northern Ireland and a representative sample for England.¹⁶ The
158 exposure status will be determined from primary care records for Clinical Practice Research
159 Datalink (CPRD) and Secure Anonymised Information Linkage (SAIL), with CPRD GOLD
160 representing 5% of UK general practices,²¹ and SAIL covering 80% of Welsh general
161 practices.²² For Scotland's linked routine records and Northern Ireland Maternity System
162 (NIMATS), the exposure status will be determined from hospital and prescribing records.

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3 163 CPRD and SAIL's primary care data offer the opportunity to study outcomes that may not be
4
5 164 captured in secondary care. For instance, vomiting in pregnancy, miscarriage and
6
7 165 neurodevelopmental conditions in children. The Scottish dataset provides detailed
8
9 166 information on the different types of hospital attendances, including psychiatric admissions
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11 167 and accident and emergency attendances. NIMATS's unique first antenatal visit dataset is a
12
13 168 good source of pre-pregnancy clinical data not available in other datasets.
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17 169 As routine health records were not collected for research purposes, it is prone to missing data.
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19 170 Therefore, we have also included Born in Bradford, a regional birth cohort (2007-2011)
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21 171 where data were collected systematically and longitudinally from pregnancy, childhood
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23 172 through to adult life.
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173 **Table 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) ¹⁶	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) ²²	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) ²³	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 ²⁴	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

175 **Exposure**

176 The exposed group will consist of pregnant women with multiple long-term conditions.

177 Measurements of multiple long-term conditions are variable in existing literature.^{25 26}

178 Currently only Bateman et al's Maternal Comorbidity Index has been developed specifically
179 for obstetric research.^{27 28} It consists of 20 health conditions and included conditions arising
180 in pregnancy such as gestational hypertension, pre-eclampsia and placenta praevia.²⁸ This
181 limits the ability to study the impact of pre-existing long-term conditions on maternal and
182 child health and the implication for long-term condition management preconception.⁸

183 In this study, we shall define multiple long-term conditions as two or more long-term
184 physical or mental health conditions that pre-existed before pregnancy. Pregnancy related
185 complications will not be included as they will be studied as outcomes. Multiple long-term
186 conditions will be defined from a list of 79 health conditions previously described in our
187 epidemiological work (Table 2) and will be measured with simple count.¹⁰ This list was
188 compiled from existing multimorbidity literature^{9 26 29} and a workshop with our
189 multidisciplinary research advisory group, including patient representatives and clinicians.¹⁰
190 Selection of health conditions were based on: (i) prevalence; (ii) potential to impact on
191 pregnancy outcomes; (iii) considered important by women; and (iv) recorded in the study
192 datasets.¹⁰ The phenome definitions for these health conditions have previously been
193 described in our epidemiological work.¹⁰ For health conditions that are transient and episodic
194 in nature (e.g. asthma, eczema, depression and anxiety), we will only include the condition if
195 it is active, which we have defined as requiring a doctors' consultation or medical
196 prescription in the 12 months preceding pregnancy.¹⁰ Sensitivity analysis will be performed
197 defining maternal multiple long-term conditions with a different list of health conditions by
198 D'Arcy et al.³⁰

199 Exposure will be ascertained by the presence of diagnostic or prescriptions codes, including
 200 Read (to identify exposures in primary care data) and International Classification of Disease
 201 10th version (ICD-10, secondary care).

202 **Table 2: List of 79 health conditions defining multiple long-term conditions in**
 203 **pregnancy**

<p>Cancers</p> <ol style="list-style-type: none"> 1. All cancers <ul style="list-style-type: none"> ○ Solid cancers ○ Haematological cancers ○ Metastatic cancers ○ Exclude basal cell carcinoma <p>Cardiovascular disease</p> <ol style="list-style-type: none"> 2. Hypertension 3. Ischemic heart disease & myocardial infarction 4. Heart failure 5. Stroke <ul style="list-style-type: none"> ○ 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 <p>Dermatology</p> <ol style="list-style-type: none"> 10. Eczema 11. Psoriasis 12. Autoimmune skin disease <ul style="list-style-type: none"> ○ Vitiligo ○ Alopecia areata 13. Other dermatological conditions <ul style="list-style-type: none"> ○ Seborrheic dermatitis ○ Rosacea ○ Hidradenitis suppurativa ○ Lichen planus <p>Ear, Nose, Throat</p> <ol style="list-style-type: none"> 14. Profound deafness 15. Allergic rhinitis & allergic conjunctivitis <p>Eye</p> <ol style="list-style-type: none"> 16. Inflammatory eye disease <ul style="list-style-type: none"> ○ Scleritis & episcleritis ○ Anterior uveitis ○ Posterior uveitis 17. Cataract 18. Diabetic eye disease 19. Severe blindness 20. Retinal detachment 	<p>Neurodevelopmental conditions</p> <ol style="list-style-type: none"> 43. Neurodevelopmental conditions <ul style="list-style-type: none"> ○ Learning disability ○ Attention deficit hyperactivity disorder ○ Autistic spectrum disorder <p>Rheumatology</p> <ol style="list-style-type: none"> 44. Systemic lupus erythematosus 45. Spondylarthritis <ul style="list-style-type: none"> ○ Psoriatic arthritis ○ Ankylosing spondylitis 46. Inflammatory arthritis <ul style="list-style-type: none"> ○ Rheumatoid arthritis ○ Sjogern's syndrome ○ Raynaud's syndrome ○ Systemic sclerosis ○ Primary systemic vasculitis 47. Ehler's Danlos Syndrome (EDS) Type 3 (Hypermobility EDS) <p>Orthopaedic</p> <ol style="list-style-type: none"> 48. Scoliosis 49. Vertebral disorder <ul style="list-style-type: none"> ○ Intervertebral disc disorder ○ Spondylosis ○ Spondylolisthesis ○ Collapsed vertebrae ○ Spinal stenosis 50. Chronic back pain 51. Osteoporosis 52. Osteoarthritis <p>Neurology</p> <ol style="list-style-type: none"> 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 <ul style="list-style-type: none"> ○ chronic fatigue syndrome / myalgic encephalomyelitis ○ fibromyalgia
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<p>Gastroenterology</p> <ol style="list-style-type: none"> 21. Irritable bowel syndrome 22. Inflammatory bowel disease <ul style="list-style-type: none"> ○ Ulcerative colitis ○ Crohn's disease 23. Coeliac disease 24. Chronic liver disease <ul style="list-style-type: none"> ○ Chronic hepatitis B & C ○ Alcoholic liver disease ○ Autoimmune liver disease ○ Cirrhosis ○ Non-alcoholic fatty liver disease 25. Peptic ulcer 26. Gall stones <p>Gynaecology</p> <ol style="list-style-type: none"> 27. Polycystic ovarian syndrome 28. Endometriosis 29. Fibroids 30. Infertility <p>Haematology</p> <ol style="list-style-type: none"> 31. History of venous thromboembolism <ul style="list-style-type: none"> ○ Deep vein thrombosis ○ Pulmonary embolism 32. Primary thrombocytopenia 33. Haemophilia 34. Sickle cell anaemia 35. Pernicious anaemia <p>Mental health</p> <ol style="list-style-type: none"> 36. Depression 37. Anxiety <ul style="list-style-type: none"> ○ Panic disorder ○ Phobia disorder ○ Post-traumatic stress disorder 38. Severe mental illness <ul style="list-style-type: none"> ○ Bipolar affective disorder ○ Schizophrenia ○ Psychosis 39. Eating disorder 40. History of alcohol use disorder (misuse / dependence) 41. History of substance misuse 42. Others <ul style="list-style-type: none"> ○ Obsessive compulsive disorder ○ Self-harm ○ Personality disorder ○ Dissociative disorder 	<ul style="list-style-type: none"> ○ chronic pain syndrome (includes chronic regional pain syndrome, myofascial pain syndrome) <p>Respiratory</p> <ol style="list-style-type: none"> 61. Asthma 62. Chronic obstructive pulmonary disease 63. Obstructive sleep apnoea 64. Pulmonary fibrosis, interstitial lung disease 65. Pulmonary hypertension 66. Bronchiectasis 67. Cystic fibrosis 68. Sarcoidosis <p>Renal</p> <ol style="list-style-type: none"> 69. Chronic kidney disease 70. Urinary tract stones <p>Endocrine</p> <ol style="list-style-type: none"> 71. Diabetes mellitus 72. Thyroid disorder 73. Pituitary disorder 74. Adrenal benign tumour 75. Hyperparathyroidism <p>Other</p> <ol style="list-style-type: none"> 76. Human immunodeficiency viral infection / Acquired immune deficiency syndrome 77. Turner's syndrome 78. Marfan's syndrome 79. Solid organ transplant
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205 **Comparator**206 *Multiple long-term conditions versus no multiple long-term conditions*

207 Comparisons will be made with the following exposure group:

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3 208 (i) pregnant women with multiple long-term conditions;
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6 209 (ii) pregnant women with increasing counts of long-term health conditions;
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9 210 (iii) pregnant women with different combinations of long-term health conditions; and
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12 211 (iv) pregnant women in different health condition clusters (identified from ongoing clustering
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14 212 analyses).

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17 213 The selection of which combinations and clusters of long-term conditions to study will be
18
19 214 based on how common they are and their clinical relevance, following consultation with
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21 215 patient representatives and clinicians in our research team. Pregnant women with no multiple
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23 216 long-term conditions (i.e. no or single long-term conditions) will be the common comparator
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26 217 group.

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29 218 *Multiple long-term conditions with and without mental illness*

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32 219 In addition, we will also compare the outcomes for pregnant women who have mental health
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34 220 conditions as part of their multiple long-term conditions against pregnant women with
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36 221 multiple long-term conditions who do not have mental health conditions.

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40 222 **Outcomes**

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43 223 The outcomes will be grouped into the following four categories based on the research
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45 224 objectives: (1) antenatal, (2) peripartum, (3) postnatal and long-term outcomes, and (4)
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47 225 mental health outcomes. Examples of outcomes are provided as follows, based on existing
48
49 226 core outcome sets for pregnancy and childbirth.^{31 32} The definitive list of outcomes will be
50
51 227 confirmed once the development work for a core outcome set for studies of pregnant women
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53 228 with multiple long-term conditions is completed.³³ Outcomes will be ascertained from the
54
55 229 study datasets (1st January 2000 to 31st December 2019) using clinical codes, such as Read,
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3 230 ICD-10 and Operating Procedures Codes (OPCS) Classification of Interventions and
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5 231 Procedures.

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8 232 *(1) Antenatal*

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11 233 Antenatal outcomes occur from conception to before the onset of childbirth. Examples for
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13 234 women include miscarriage, gestational hypertension, pre-eclampsia, gestational diabetes,
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15 235 venous thromboembolism, placenta abruption and antenatal hospital admissions. Examples
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17 236 for children include fetal growth restriction.

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21 237 *(2) Peripartum*

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24 238 Peripartum outcomes occur during and immediately after childbirth. This category will also
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26 239 include survival outcomes for women and children. Examples for women include mode of
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28 240 birth (spontaneous vaginal birth , birth with forceps/ ventouse, caesarean birth), postpartum
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30 241 haemorrhage, severe maternal morbidity, admission to intensive care and maternal death.
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32 242 Examples for children include preterm birth, small for gestational age, admission to neonatal
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34 243 unit, stillbirth, perinatal death and neonatal death.

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38 244 *(3) Postnatal and long-term*

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41 245 Postnatal outcomes occur in the 42 days after birth,³⁴ while long-term outcomes are beyond
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43 246 the peripartum and postpartum period. For women this would include functional outcomes
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45 247 such as incontinence. For children, we will use mother baby linked primary and secondary
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47 248 care data to study postnatal and long-term outcomes such as congenital anomalies,
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49 249 neurodevelopmental conditions (e.g. autism, attention deficit hyperactive disorder and
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51 250 learning difficulty), cerebral palsy, and chronic lung disease. The length of follow up will
52
53 251 depend on the availability of data in the routine health records. For example, CPRD has a
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55 252 median follow up of 5 years.¹⁶ We will also examine postpartum readmission for mother and
56
57 253 child.

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3 254 *(4) Mental health*
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6 255 Mental health outcomes cover the antenatal and postnatal period and will be considered up to
7
8 256 12 months after birth. This is to account for possible delay in women presenting to clinicians
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10 257 and reaching a formal diagnosis. We will consider both: (i) incident and (ii) recurrent mental
11
12 258 health outcomes, where incident means a woman enters the analysis with no prior record of
13
14 259 the specific mental health outcome. A perinatal mental health event is indicated by a primary
15
16 260 care visit or hospital admission and includes mental health outcomes of concern in the
17
18 261 antenatal and postnatal period (e.g. depression, psychosis, post-traumatic stress disorder, self-
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20 262 harm and suicide attempts). Comparing the mental health event rates of pregnant women who
21
22 263 have and have not got mental health conditions as part of their multiple long-term conditions
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24 264 will allow us to delineate the contribution of mental and physical morbidity to perinatal
25
26 265 mental health outcomes. Children's mental ill health will also be considered (e.g. depression
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28 266 and anxiety).
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34 267 **Covariates**
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37 268 Analyses will adjust for the following covariates. Additional covariates may be added for
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39 269 individual outcomes based on the literature. For example, in analyses of mental health
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41 270 outcomes there will be additional covariates. For the mother, we will include history of any
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43 271 mental illness, for the child we will include maternal history of any mental and/ or
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45 272 neurodevelopmental conditions.
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49 273 Where data for antenatal exposures are available (e.g. from NIMATS and Born in Bradford's
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51 274 booking appointments), additional analyses may be conducted where appropriate.
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54 275 *(i) Maternal age*
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3 276 We shall explore whether the association between maternal age and the outcomes are linear.

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5 277 Where this is not the case and to aid clinical interpretability, we will categorise maternal age

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8 278 at conception into 5-yearly age bands.

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11 279 *(ii) Parity/gravidity*

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14 280 The variable used will depend on availability in study datasets. Where both variables are

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16 281 available, both will be reported with preference given to *parity* (the number of times a woman

17
18 282 gave birth at gestation ≥ 24 weeks); and sensitivity analysis will be conducted using *gravidity*

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20 283 (the number of times a woman has been pregnant).

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23 284 *(iii) Ethnicity*

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26 285 Maternal ethnicity will be categorised based on the variables available and to allow for

27
28 286 harmonisation across the datasets: Asian, Black, Mixed, Other and White. Where data

29
30 287 permits, we may use more granular categories of ethnicity. Where numbers are too small and

31
32 288 risk identifying individuals, such as in NIMATS, we may collapse the categories to White

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34 289 and Non-white.

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37 290 *(iv) Social deprivation*

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40 291 The patient level Index of Multiple Deprivation specific to each nation will be used and

41
42 292 categorised into quintiles.

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45 293 *(v) Body mass index*

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48 294 We shall include the latest available pre-pregnancy body mass index for the pregnant women.

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50 295 Where booking data is available before 16 weeks gestation, this will be used (e.g. in

51
52 296 NIMATS). Body mass index will be considered a covariate instead of a health condition. The

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55 297 World Health Organisation's classification of obesity will be used to categorise body mass

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3 298 index: <18.5 kg/m², 18.5 to 24.9 kg/m², 25.0 to 29.9 kg/m², 30.0 to 34.9 kg/m², 35.0 to 39.9
4
5 299 kg/m², and 40+ kg/m².³⁵ Categories may be combined where numbers are too small.
6
7

8 300 *(vi) Smoking*
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11 301 We shall include the latest available pre-pregnancy smoking status for the pregnant women.
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13 302 Smoking status will be categorised as: non-smoker, ex-smoker, and smoker.
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16 303 *(vii) Year (pregnancy start date)*
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19 304 Data quality and clinical guidelines may vary by year. Its effect on outcomes will be
20
21 305 accounted for by adjusting for year of conception in the analysis.
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25 306 **Statistical analysis**
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28 307 We anticipate analyses will commence in June 2023 with study completion by June 2024.
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30 308 Baseline characteristics of the study population and outcomes will be described with
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32 309 summary statistics. Modified Poisson regression will be performed to estimate the relative
33
34 310 risks of study outcomes. Cox regression will be performed for longer-term outcomes. The
35
36 311 unit of analysis will be the pregnancy episode.
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40 312 A federated analysis approach will be used as data governance arrangements do not allow
41
42 313 pooling of the data across the four nations. Each dataset will be analysed separately following
43
44 314 a common study protocol. A common data model will be established and implemented across
45
46 315 the dataset, building on our previous work harmonising the phenome definitions for exposure
47
48 316 conditions.¹⁰ The effect sizes will be pooled using random-effects meta-analyses with inverse
49
50 317 variance weighting for the primary care and secondary care datasets respectively.³⁶
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54 318 Where rare combinations of health conditions and outcomes may lead to identification of an
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56 319 individual or at the prespecified minimum count allowed by each data source, we will
57
58 320 suppress the output.
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56 322 **Pregnant women with more than one pregnancy episode**
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9 323 An individual may have more than one pregnancy over the study period. The pregnancy
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11 324 episodes of the same woman will not be independent of each other. The severity of the
12
13 325 exposure variable (pre-existing multiple long-term conditions) may increase in later
14
15 326 pregnancy episodes as the pregnant women accumulates more long-term health conditions. If
16
17 327 a woman had an adverse pregnancy outcome, she is more at risk of the same adverse outcome
18
19 328 in subsequent pregnancy episodes. We shall account for this clustering effect of women with
20
21 329 more than one pregnancy episode during the study period using the Generalised Estimating
22
23 330 Equation in the regression analyses.
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28 331
2930 332 **Multiple pregnancies**
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34 333 The main analysis will be limited to singleton pregnancies. Outcomes for pregnant women
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36 334 with multiple long-term conditions and multiple pregnancies (i.e. twins and higher order
37
38 335 pregnancies) will be analysed as a separate cohort.
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43 337 **Missing data**
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45
46 338 Where exposure and outcome conditions are identified based on diagnostic codes, the
47
48 339 absence of the code will be considered as an absence of the condition. The level and types of
49
50 340 missingness of covariates will be reviewed and where appropriate will be addressed with
51
52 341 representing missing data as a separate category or multiple imputation with chain equation
53
54 342 (MICE). For variables required to compute an outcome, missing values will be imputed using
55
56 343 MICE. Example of these variables include birthweight, gestational age and baby's sex to
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3 344 determine preterm birth and small for gestational age. For each outcome, the statistical
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5 345 analyses will be performed on the imputed datasets and the estimates will be pooled with
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8 346 Rubin's rule.
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12 13 14 348 **Sensitivity analyses**

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17 349 We shall conduct sensitivity analyses using (i) complete case analysis, (ii) varying definitions
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19 350 of maternal multiple long-term conditions exposure using D'Arcy et al's core exposure set,³⁰
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21 351 and (iii) in primiparous women. The latter is to account for the fact that some long-term
22
23 352 conditions can arise from complications from a previous pregnancy.
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28 29 30 354 **Patient and public involvement**

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33 355 The research question was informed by discussions with our patient and public involvement
34
35 356 (PPI) advisory group and our PPI co-investigators NM and RP.

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38 357 The selection of outcomes are guided by our ongoing work developing a core outcome set for
39
40 358 studies of pregnant women with multiple long-term conditions, where patients are key
41
42 359 stakeholders.³³

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45 360 Our PPI advisory group and PPI co-investigators will be involved in interpreting the study
46
47 361 findings, producing lay summaries and infographics, and disseminating the study findings
48
49 362 through their network.
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54 55 56 364 **ETHICS AND DISSEMINATION**

57 58 59 365 **Ethics approval** 60

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3 366 **CPRD:** CPRD has broad National Research Ethics Service Committee ethics approval for
4
5 367 purely observational research using the primary care data and established data linkages. The
6
7 368 study has been reviewed and approved by CPRD's Independent Scientific Advisory
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10 369 Committee (reference: 20_181R).

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13 370 **SAIL:** In accordance with UK Health Research Authority guidance, ethical approval is not
14
15 371 mandatory for studies using only anonymised data. The study has been approved by SAIL
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18 372 Information Governance Review Panel.

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21 373 **Scotland dataset:** The study has been approved by the National Health Service
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23 374 Scotland Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) and The
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25 375 University Teaching and Research Ethics Committee (UTREC) from the University of St
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28 376 Andrews.

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31 377 **NIMATS:** The study has been approved by the Honest Broker Service Governance Board.

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34 378 **Born in Bradford:** Ethics approval was granted by Bradford National Health Service
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36 379 Research Ethics Committee (ref 07/H1302/112) for the Born in Bradford cohort.

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39 380 The proposed study is purely observational and will use anonymised research data. The study
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41 381 will not involve participant recruitment. Therefore, consent to participate is not required.

42 43 44 382 **Consent for publication**

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47 383 This is not applicable as the manuscript is a study protocol. In the proposed study, we will
48
49 384 use de-identified study data, therefore consent for publication will not be required.

50 51 52 385 **Dissemination**

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55 386 Study findings will be submitted for publications in peer reviewed journals and presented at
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57 387 key conferences for health and social care professionals involved in the care of pregnant
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59 388 women with multiple long-term conditions and their children. We will also organise

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3 389 dissemination events to share our findings with the public, service users, clinicians and
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5 390 researchers.
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11 392 **DISCUSSION**

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14 393 MuM-PreDiCT is a consortium across all four nations of the UK studying multiple long-term
15
16 394 conditions in pregnancy. As part of MuM-PreDiCT's program of work, we outlined the
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18 395 protocol for an observational study of maternal and child outcomes for pregnant women with
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20 396 multiple long-term conditions, using routine health records and a birth cohort in the UK.
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27 398 **Comparison with current literature**

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30 399 A recent systematic review found seven observational studies on the association of pre-
31
32 400 pregnancy multiple long-term conditions with adverse maternal outcomes.⁸ The review found
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34 401 that pre-pregnancy multiple long-term conditions were associated with severe maternal
35
36 402 morbidity, hypertensive disorders of pregnancy, and acute health care use in the perinatal
37
38 403 period.⁸ Most studies were conducted in the United States.⁸ Authors of the review
39
40 404 commented that many studies included conditions arising in pregnancy in defining multiple
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42 405 long-term conditions, making it difficult to examine the impact of chronic conditions on
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44 406 maternal health.⁸
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48
49 407 This proposed study will be based in the UK and will use a broad range of long-term
50
51 408 conditions selected by women and clinicians to define multiple long-term conditions.
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53 409 Pregnancy related conditions and complications will be treated as study outcomes and will
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55 410 not be included in the exposure's definition. We will also study outcomes across all stages of
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57 411 pregnancy and outcomes for both women and their children.
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412 **Strengths and limitations**

413 This proposed study will utilise routine health records from all four nations of the UK
414 (England, Scotland, Wales and Northern Ireland). The available data sources consist of
415 anonymised patient records from primary and secondary care, community prescription data,
416 and maternity care data from routine booking appointments (first antenatal appointment
417 offered universally and as the gateway to access maternity care in the UK).

418 Rich data will also be available from a birth cohort from Bradford, an ethnically diverse
419 population in England. Beyond examining maternal outcomes, linked mother baby data and
420 the birth cohort data will allow for the exploration of child outcomes. The key strength of this
421 proposed study therefore is the generalisability of study findings to the UK population.

422 Observing similar effect sizes across the different datasets will also increase the confidence in
423 the study findings. Conversely, discrepancy in findings will stimulate further exploration of
424 the datasets which may generate new knowledge.

425 As this is an observational study using anonymised routine health records, key limitations
426 include missing data, misclassification bias due to inaccurate clinical coding and residual
427 confounding.

428 Maternal multimorbidity will be quantified with simple counts. The severity of each health
429 conditions will not be captured and the dose-response relationship will only be reflected in
430 the total number of pre-existing long-term conditions. A systematic review of comorbidity
431 indices used in maternal health research found three indices: Maternal Comorbidity Index,
432 Charlson comorbidity index and Elixhauser comorbidity index.²⁷ Only the Maternal
433 Comorbidity Index was developed from pregnant and postpartum women.²⁷ It was developed
434 using hospital data with 20 maternal comorbidities but it included pregnancy related
435 complications and factors such as multiple gestation, gestational diabetes, and hypertension

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3 436 disorder of pregnancy.^{27 28} In contrast, the list of health conditions we will use to define
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5 437 maternal pre-existing multimorbidity is more comprehensive and included leading causes of
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7 438 indirect maternal death (e.g. epilepsy) and mental health conditions.
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10 439 Exposure and outcome events are only captured in routine health records when the pregnant
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12 440 women have presented to primary or secondary care and therefore the true prevalence and
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14 441 incidence may be underestimated. Health conditions that are managed conservatively in
15
16 442 primary care, such as depression, anxiety and miscarriage, may not be captured in secondary
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18 443 care datasets. Events such as termination of pregnancy that occurred outside of the traditional
19
20 444 health care settings may also be underestimated.³⁷ Similarly, antenatal hospital admission
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22 445 data may not reflect the full burden of additional antenatal appointments or acute care
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24 446 attendances, as care accessed through other routes may not be captured.
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30 447 Body mass index, which encompasses underweight and obese categories, will be studied as a
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32 448 covariate instead of being counted as part of multimorbidity. There is much debate around
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34 449 whether obesity should be considered a disease³⁸ or a risk factor for other long-term
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36 450 conditions such as cardiometabolic conditions and cancers.³⁹⁻⁴¹ What is clear is pre-
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38 451 pregnancy maternal obesity is associated with adverse pregnancy outcome and dedicated care
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40 452 guideline has been established to manage this risk.^{42 43} Studying body mass index as a
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42 453 separate variable will allow us to examine its independent effect and evidence may reaffirm
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44 454 its role as a modifiable risk factor for pregnant women with multiple long-term conditions.
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49 455 **Clinical implications**

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52 456 Current obstetric guidelines for pregnant women with medical conditions are focused on
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54 457 specific and single health conditions. There are currently no guidelines for the management
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56 458 of pregnant women with multiple long-term conditions in the UK. The heterogeneity of
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58 459 multiple long-term conditions means an all-encompassing guideline for every possible
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3 460 combination of long-term conditions would not be possible. Indeed the English national
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5 461 guideline for multimorbidity focuses on general approaches such as coordinated and holistic
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7 462 care, improving quality of life by reducing treatment burden and shared decision making
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9 463 between patients and clinicians.⁴⁴ A guideline for multiple long-term conditions
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11 464 (multimorbidity) in pregnancy is likely to follow the same principles but with additional
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13 465 focus on the maternity care aspect.
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18 466 The basis of shared decision making is the provision of evidence based information. As
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20 467 observed in the systematic review, there is currently a lack of evidence on the consequences
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22 468 of pregnancy for women with multiple long-term conditions.⁸ Our PPI advisory group and
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24 469 preliminary findings from our core outcome set development work have highlighted how
25
26 470 women valued having information to help them mentally prepare to face potential adverse
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28 471 pregnancy outcomes. The output from this study will therefore provide valuable information
29
30 472 for women to make informed decision with their clinicians about family planning and their
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32 473 preconception, pregnancy and postpartum care. It will also provide valuable information to
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34 474 guide the future design of care pathway for women with multiple long-term conditions.
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3 478 **ABBREVIATIONS**
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5 479 CPRD Clinical Practice Research Datalink
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7 480 ICD-10 International Classification of Disease 10th version
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9 481 MICE Multiple imputation with chain equation
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11 482 NICE National Institute for Health and Care Excellence
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14 483 NIMATS Northern Ireland Maternity System
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16 484 OPCS Operating Procedures Codes
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19 485 PPI Patient and public involvement
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21 486 SAIL Secure Anonymised Information Linkage
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24 487 UK United Kingdom
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3 488 **Data availability statement**
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6 489 This is not applicable as the manuscript is a study protocol. In the proposed study, the data
7
8 490 that support the findings are available from CPRD, SAIL, Scotland National Health Service
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10 491 Scotland Public Benefit and Privacy Panel for Health and Social Care, NIMATS and Born in
11
12 492 Bradford, but restrictions apply to the availability of these data, which were used under
13
14 493 license for the current study, and so are not publicly available. Data are however available
15
16 494 from the authors upon reasonable request and with permission of CPRD, SAIL, Scotland
17
18 495 National Health Service Scotland Public Benefit and Privacy Panel for Health and Social
19
20 496 Care, NIMATS and Born in Bradford.
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25 497 **Competing interests**
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27
28 498 The authors declare that they have no competing interests.
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30

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51 507 **Contributors**
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53 508 SIL – Conceptualisation, funding acquisition, methodology, writing (original draft
54 509 preparation).
55
56 510 KN, MB, KAE, KMA, DOR - Conceptualisation, funding acquisition, methodology,
57 511 supervision, writing (review and editing)
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512 HH, GS, AS, NM, AAL, AFF, CNP, CY, CMC, JIK, PB, RP, RR, ST, SB, UA, ZV-
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514 LK, KP, MS, MM, NC, SPBHS - Conceptualisation, methodology, writing (review and
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516 All authors read and approved the manuscript.
517

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BMJ Open

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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Primary Subject Heading :	Obstetrics and gynaecology
Secondary Subject Heading :	Epidemiology
Keywords :	Maternal medicine < OBSTETRICS, OBSTETRICS, EPIDEMIOLOGY

SCHOLARONE™
Manuscripts

1 **Maternal and child outcomes for pregnant women with pre-existing multiple long-term**
 2 **conditions: protocol for an observational study in the United Kingdom**

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3 66 **ABSTRACT**
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5 67 **Introduction:** One in five pregnant women have multiple pre-existing long-term conditions
6
7 68 in the United Kingdom (UK). Studies have shown that maternal multiple long-term
8
9 69 conditions are associated with adverse outcomes. This observational study aims to compare
10
11 70 maternal and child outcomes for pregnant women with multiple long-term conditions to those
12
13 71 without multiple long-term conditions (0 or 1 long-term conditions).
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16
17 72 **Methods and analysis:** Pregnant women aged 15 to 49 years old with a conception date
18
19 73 between 2000 and 2019 in the UK will be included with follow up till 2019. The data source
20
21 74 will be routine health records from all four UK nations (Clinical Practice Research Datalink
22
23 75 [CPRD, England], Secure Anonymised Information Linkage [SAIL, Wales], Scotland routine
24
25 76 health records and Northern Ireland Maternity System [NIMATS]); and the Born in Bradford
26
27 77 birth cohort. The exposure of two or more pre-existing, long-term physical or mental health
28
29 78 conditions will be defined from a list of health conditions predetermined by women and
30
31 79 clinicians. The association of maternal multiple long-term conditions with (i) antenatal, (ii)
32
33 80 peripartum, (iii) postnatal and long-term, and (iv) mental health outcomes, for both women
34
35 81 and their children will be examined. Outcomes of interest will be guided by a core outcome
36
37 82 set. Comparisons will be made between pregnant women with and without multiple long-
38
39 83 term conditions using modified Poisson and Cox regression. Generalised estimating equation
40
41 84 will account for the clustering effect of women who had more than one pregnancy episode.
42
43 85 Where appropriate, multiple imputation with chained equation will be used for missing data.
44
45 86 Federated analysis will be conducted for each dataset and results will be pooled using
46
47 87 random-effects meta-analyses.
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54 88 **Ethics and dissemination:** Approval has been obtained from the respective data sources in
55
56 89 each UK nation. Study findings will be submitted for publications in peer reviewed journals
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58 90 and presented at key conferences.
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45 92 **ARTICLE SUMMARY**
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78 93 **Strengths and limitations of this study**
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11 94 • The study will utilise rich data sources from routine health records from all four UK
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13 95 nations and a birth cohort.
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16 96 • Beyond examining maternal outcomes, linked mother baby data and the birth cohort
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18 97 data will allow for the exploration of children's outcomes.
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21 98 • Key limitations include missing data, misclassification bias due to inaccurate clinical
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23 99 coding and residual confounding.
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100 INTRODUCTION

101 Maternal single long-term conditions such as cardiac conditions, chronic kidney disease and
102 epilepsy are associated with adverse pregnancy outcomes.¹⁻⁴ This is likely to be compounded
103 when the pregnant woman has two or more long-term physical or mental health conditions
104 (multimorbidity). Some conditions may need different treatments from different health care
105 teams, thereby increasing the treatment burden and complexity of care.⁵ Recent evidence has
106 shown that maternal multiple long-term conditions are associated with adverse outcomes for
107 women and their children, such as severe maternal morbidity and mortality, pre-eclampsia,
108 emergency caesarean birth, preterm birth, and low birth weight.⁶⁻⁸ In the UK 2016-18
109 national maternal mortality report, 90% of women who died during or up to a year after
110 pregnancy had multiple health or social problems.⁹

111 Currently one in five pregnant women have multiple long-term conditions prior to pregnancy
112 in the United Kingdom (UK).¹⁰ The number of pregnant women with pre-existing multiple
113 long-term conditions is likely to increase as women are getting pregnant later in life and with
114 higher body weight.¹¹⁻¹⁴ As this becomes an increasingly important issue, information on
115 pregnancy, maternal and child outcomes is crucial for women and their health care
116 professionals to make informed decisions on preconception and pregnancy care planning.
117 However, there remains a lack of evidence to guide care pathways for pregnant women with
118 multiple long-term conditions.^{8 15}

119 Healthcare is free in the UK and over 98% of the population are registered at a general
120 practice (akin to family practice in other countries).¹⁶ General practices not only provide
121 primary and community healthcare, but they also serve as the main point of contact for
122 referrals to specialist clinical services and provide the majority of prescribing outside of a
123 hospital setting.¹⁶ In the UK, pregnant women are recommended to have their booking

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3 124 appointment before 10 weeks gestation.¹⁷ This is the pregnant woman's first midwife or
4
5 125 doctor appointment, where they undergo health and social care assessment of needs and risks
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8 126 for her pregnancy.¹⁸ Over 97% of births occur in healthcare settings in England and Wales.¹⁹
9
10 127 Therefore, routine health records in primary and secondary care in the UK offer a rich data
11
12 128 source for observational studies of pregnant women and their children.

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15 129 This observational study aims to compare outcomes for women with multiple long-term
16
17 130 conditions to those without multiple long-term conditions. Outcomes studied will include
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19 131 those for women and their children. Datasets from routine health records from all four UK
20
21 132 nations (England, Wales, Scotland, and Northern Ireland) will be used. In addition, the Born
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23 133 in Bradford birth cohort from a deprived, ethnically diverse city in the UK, will also be
24
25 134 used.²⁰
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30 135 The four research objectives are to examine the association between maternal pre-existing
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32 136 multiple long-term conditions with: (1) antenatal, (2) peripartum, (3) postnatal and long-term
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34 137 outcomes, and (4) mental health outcomes. The findings from each research objective will be
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36 138 published in a separate paper.
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141 **METHODS AND ANALYSIS**

142 **Study design**

143 This is a cohort observational study using data from routine healthcare records and a birth
144 cohort in the UK.

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146 **Study population and eligibility criteria**

147 The study population will consist of women aged 15-49 years old at conception, with
148 pregnancies beginning between 1st January 2000 and 31st December 2019 in the UK. Date of
149 conception (pregnancy start date) will be defined as the first day of the last menstrual period
150 or gestational day 0. To ensure sufficient quality data, eligible women must have health
151 records that meet the standard data quality checks as defined by each data source and one
152 year's worth of health records prior to index pregnancy.

153

154 **Data sources**

155 Table 1 presents the five data sources that will be used. Each UK devolved nation is
156 represented by a population based routine health record dataset, with good national coverage
157 for Wales, Scotland and Northern Ireland and a representative sample for England.¹⁶ The
158 exposure status will be determined from primary care records for Clinical Practice Research
159 Datalink (CPRD) and Secure Anonymised Information Linkage (SAIL), with CPRD GOLD
160 representing 5% of UK general practices,²¹ and SAIL covering 80% of Welsh general
161 practices.²² For Scotland's linked routine records and Northern Ireland Maternity System
162 (NIMATS), the exposure status will be determined from hospital and prescribing records.

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3 163 CPRD and SAIL's primary care data offer the opportunity to study outcomes that may not be
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5 164 captured in secondary care. For instance, vomiting in pregnancy, miscarriage and
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7 165 neurodevelopmental conditions in children. The Scottish dataset provides detailed
8
9 166 information on the different types of hospital attendances, including psychiatric admissions
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11 167 and accident and emergency attendances. NIMATS's unique first antenatal visit dataset is a
12
13 168 good source of pre-pregnancy clinical data not available in other datasets.
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17 169 As routine health records were not collected for research purposes, it is prone to missing data.
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19 170 Therefore, we have also included Born in Bradford, a regional birth cohort (2007-2011)
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21 171 where data were collected systematically and longitudinally from pregnancy, childhood
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23 172 through to adult life.
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173 **Table 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) ¹⁶	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) ²²	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) ²³	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 ²⁴	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

175 **Exposure**

176 The exposed group will consist of pregnant women with multiple long-term conditions.

177 Measurements of multiple long-term conditions are variable in existing literature.^{25 26}

178 Currently only Bateman et al's Maternal Comorbidity Index has been developed specifically
179 for obstetric research.^{27 28} It consists of 20 health conditions and included conditions arising
180 in pregnancy such as gestational hypertension, pre-eclampsia and placenta praevia.²⁸ This
181 limits the ability to study the impact of pre-existing long-term conditions on maternal and
182 child health and the implication for long-term condition management preconception.⁸

183 In this study, we shall define multiple long-term conditions as two or more long-term
184 physical or mental health conditions that pre-existed before pregnancy. Pregnancy related
185 complications will not be included as they will be studied as outcomes. Multiple long-term
186 conditions will be defined from a list of 79 health conditions previously described in our
187 epidemiological work (Table 2) and will be measured with simple count.¹⁰ This list was
188 compiled from existing multimorbidity literature^{9 26 29} and a workshop with our
189 multidisciplinary research advisory group, including patient representatives and clinicians.¹⁰
190 Selection of health conditions were based on: (i) prevalence; (ii) potential to impact on
191 pregnancy outcomes; (iii) considered important by women; and (iv) recorded in the study
192 datasets.¹⁰ The phenome definitions for these health conditions have previously been
193 described in our epidemiological work.¹⁰ For health conditions that are transient and episodic
194 in nature (e.g. asthma, eczema, depression and anxiety), we will only include the condition if
195 it is active, which we have defined as requiring a doctors' consultation or medical
196 prescription in the 12 months preceding pregnancy.¹⁰ Sensitivity analysis will be performed
197 defining maternal multiple long-term conditions with a different list of health conditions by
198 D'Arcy et al.³⁰

199 Exposure will be ascertained by the presence of diagnostic or prescriptions codes, including
 200 Read (to identify exposures in primary care data) and International Classification of Disease
 201 10th version (ICD-10, secondary care).

202 **Table 2. List of 79 health conditions defining multiple long-term conditions in**
 203 **pregnancy**

<p>Cancers</p> <ol style="list-style-type: none"> 1. All cancers <ul style="list-style-type: none"> ○ Solid cancers ○ Haematological cancers ○ Metastatic cancers ○ Exclude basal cell carcinoma <p>Cardiovascular disease</p> <ol style="list-style-type: none"> 2. Hypertension 3. Ischemic heart disease & myocardial infarction 4. Heart failure 5. Stroke <ul style="list-style-type: none"> ○ 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 <p>Dermatology</p> <ol style="list-style-type: none"> 10. Eczema 11. Psoriasis 12. Autoimmune skin disease <ul style="list-style-type: none"> ○ Vitiligo ○ Alopecia areata 13. Other dermatological conditions <ul style="list-style-type: none"> ○ Seborrheic dermatitis ○ Rosacea ○ Hidradenitis suppurativa ○ Lichen planus <p>Ear, Nose, Throat</p> <ol style="list-style-type: none"> 14. Profound deafness 15. Allergic rhinitis & allergic conjunctivitis <p>Eye</p> <ol style="list-style-type: none"> 16. Inflammatory eye disease <ul style="list-style-type: none"> ○ Scleritis & episcleritis ○ Anterior uveitis ○ Posterior uveitis 17. Cataract 18. Diabetic eye disease 19. Severe blindness 20. Retinal detachment 	<p>Neurodevelopmental conditions</p> <ol style="list-style-type: none"> 43. Neurodevelopmental conditions <ul style="list-style-type: none"> ○ Learning disability ○ Attention deficit hyperactivity disorder ○ Autistic spectrum disorder <p>Rheumatology</p> <ol style="list-style-type: none"> 44. Systemic lupus erythematosus 45. Spondylarthritis <ul style="list-style-type: none"> ○ Psoriatic arthritis ○ Ankylosing spondylitis 46. Inflammatory arthritis <ul style="list-style-type: none"> ○ Rheumatoid arthritis ○ Sjogern's syndrome ○ Raynaud's syndrome ○ Systemic sclerosis ○ Primary systemic vasculitis 47. Ehler's Danlos Syndrome (EDS) Type 3 (Hypermobility EDS) <p>Orthopaedic</p> <ol style="list-style-type: none"> 48. Scoliosis 49. Vertebral disorder <ul style="list-style-type: none"> ○ Intervertebral disc disorder ○ Spondylosis ○ Spondylolisthesis ○ Collapsed vertebrae ○ Spinal stenosis 50. Chronic back pain 51. Osteoporosis 52. Osteoarthritis <p>Neurology</p> <ol style="list-style-type: none"> 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 <ul style="list-style-type: none"> ○ chronic fatigue syndrome / myalgic encephalomyelitis ○ fibromyalgia
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<p>Gastroenterology</p> <ol style="list-style-type: none"> 21. Irritable bowel syndrome 22. Inflammatory bowel disease <ul style="list-style-type: none"> ○ Ulcerative colitis ○ Crohn's disease 23. Coeliac disease 24. Chronic liver disease <ul style="list-style-type: none"> ○ Chronic hepatitis B & C ○ Alcoholic liver disease ○ Autoimmune liver disease ○ Cirrhosis ○ Non-alcoholic fatty liver disease 25. Peptic ulcer 26. Gall stones <p>Gynaecology</p> <ol style="list-style-type: none"> 27. Polycystic ovarian syndrome 28. Endometriosis 29. Fibroids 30. Infertility <p>Haematology</p> <ol style="list-style-type: none"> 31. History of venous thromboembolism <ul style="list-style-type: none"> ○ Deep vein thrombosis ○ Pulmonary embolism 32. Primary thrombocytopenia 33. Haemophilia 34. Sickle cell anaemia 35. Pernicious anaemia <p>Mental health</p> <ol style="list-style-type: none"> 36. Depression 37. Anxiety <ul style="list-style-type: none"> ○ Panic disorder ○ Phobia disorder ○ Post-traumatic stress disorder 38. Severe mental illness <ul style="list-style-type: none"> ○ Bipolar affective disorder ○ Schizophrenia ○ Psychosis 39. Eating disorder 40. History of alcohol use disorder (misuse / dependence) 41. History of substance misuse 42. Others <ul style="list-style-type: none"> ○ Obsessive compulsive disorder ○ Self-harm ○ Personality disorder ○ Dissociative disorder 	<ul style="list-style-type: none"> ○ chronic pain syndrome (includes chronic regional pain syndrome, myofascial pain syndrome) <p>Respiratory</p> <ol style="list-style-type: none"> 61. Asthma 62. Chronic obstructive pulmonary disease 63. Obstructive sleep apnoea 64. Pulmonary fibrosis, interstitial lung disease 65. Pulmonary hypertension 66. Bronchiectasis 67. Cystic fibrosis 68. Sarcoidosis <p>Renal</p> <ol style="list-style-type: none"> 69. Chronic kidney disease 70. Urinary tract stones <p>Endocrine</p> <ol style="list-style-type: none"> 71. Diabetes mellitus 72. Thyroid disorder 73. Pituitary disorder 74. Adrenal benign tumour 75. Hyperparathyroidism <p>Other</p> <ol style="list-style-type: none"> 76. Human immunodeficiency viral infection / Acquired immune deficiency syndrome 77. Turner's syndrome 78. Marfan's syndrome 79. Solid organ transplant
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205 **Comparator**206 *Multiple long-term conditions versus no multiple long-term conditions*

207 Comparisons will be made with the following exposure group:

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3 208 (i) pregnant women with multiple long-term conditions;
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6 209 (ii) pregnant women with increasing counts of long-term health conditions;
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9 210 (iii) pregnant women with different combinations of long-term health conditions; and
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12 211 (iv) pregnant women in different health condition clusters (identified from ongoing clustering
13
14 212 analyses).

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17 213 The selection of which combinations and clusters of long-term conditions to study will be
18
19 214 based on how common they are and their clinical relevance, following consultation with
20
21 215 patient representatives and clinicians in our research team. Pregnant women with no multiple
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23 216 long-term conditions (i.e. no or single long-term conditions) will be the common comparator
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25 217 group.

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29 218 *Multiple long-term conditions with and without mental illness*

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32 219 In addition, we will also compare the outcomes for pregnant women who have mental health
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34 220 conditions as part of their multiple long-term conditions against pregnant women with
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36 221 multiple long-term conditions who do not have mental health conditions.

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40 222 **Outcomes**

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43 223 The outcomes will be grouped into the following four categories based on the research
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45 224 objectives: (1) antenatal, (2) peripartum, (3) postnatal and long-term outcomes, and (4)
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47 225 mental health outcomes. Examples of outcomes are provided as follows, based on existing
48
49 226 core outcome sets for pregnancy and childbirth.^{31 32} The definitive list of outcomes will be
50
51 227 confirmed once the development work for a core outcome set for studies of pregnant women
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53 228 with multiple long-term conditions is completed.³³ Outcomes will be ascertained from the
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55 229 study datasets (1st January 2000 to 31st December 2019) using clinical codes, such as Read,
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3 230 ICD-10 and Operating Procedures Codes (OPCS) Classification of Interventions and
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5 231 Procedures.

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8 232 *(1) Antenatal*

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11 233 Antenatal outcomes occur from conception to before the onset of childbirth. Examples for
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13 234 women include miscarriage, gestational hypertension, pre-eclampsia, gestational diabetes,
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15 235 venous thromboembolism, placenta abruption and antenatal hospital admissions. Examples
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17 236 for children include fetal growth restriction.

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21 237 *(2) Peripartum*

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24 238 Peripartum outcomes occur during and immediately after childbirth. This category will also
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26 239 include survival outcomes for women and children. Examples for women include mode of
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28 240 birth (spontaneous vaginal birth, birth with forceps/ventouse, caesarean birth), postpartum
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30 241 haemorrhage, severe maternal morbidity, admission to intensive care and maternal death.
31
32 242 Examples for children include preterm birth, small for gestational age, admission to neonatal
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34 243 unit, stillbirth, perinatal death and neonatal death.

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38 244 *(3) Postnatal and long-term*

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41 245 Postnatal outcomes occur in the 42 days after birth,³⁴ while long-term outcomes are beyond
42
43 246 the peripartum and postpartum period. For women this would include functional outcomes
44
45 247 such as incontinence. For children, we will use mother baby linked primary and secondary
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47 248 care data to study postnatal and long-term outcomes such as congenital anomalies,
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49 249 neurodevelopmental conditions (e.g. autism, attention deficit hyperactive disorder and
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51 250 learning difficulty), cerebral palsy, and chronic lung disease. The length of follow up will
52
53 251 depend on the availability of data in the routine health records. For example, CPRD has a
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55 252 median follow up of 5 years.¹⁶ We will also examine postpartum readmission for mother and
56
57 253 child.

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3 254 *(4) Mental health*
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6 255 Mental health outcomes cover the antenatal and postnatal period and will be considered up to
7
8 256 12 months after birth. This is to account for possible delay in women presenting to clinicians
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10 257 and reaching a formal diagnosis. We will consider both: (i) incident and (ii) recurrent mental
11
12 258 health outcomes, where incident means a woman enters the analysis with no prior record of
13
14 259 the specific mental health outcome. A perinatal mental health event is indicated by a primary
15
16 260 care visit or hospital admission and includes mental health outcomes of concern in the
17
18 261 antenatal and postnatal period (e.g. depression, psychosis, post-traumatic stress disorder, self-
19
20 262 harm and suicide attempts). Comparing the mental health event rates of pregnant women who
21
22 263 have and have not got mental health conditions as part of their multiple long-term conditions
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24 264 will allow us to delineate the contribution of mental and physical morbidity to perinatal
25
26 265 mental health outcomes. Children's mental ill health will also be considered (e.g. depression
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28 266 and anxiety).
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34 267 **Covariates**
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37 268 Analyses will adjust for the following covariates. Additional covariates may be added for
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39 269 individual outcomes based on the literature. For example, in analyses of mental health
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41 270 outcomes there will be additional covariates. For the mother, we will include history of any
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43 271 mental illness, for the child we will include maternal history of any mental and/ or
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45 272 neurodevelopmental conditions.
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49 273 Where data for antenatal exposures are available (e.g. from NIMATS and Born in Bradford's
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51 274 booking appointments), additional analyses may be conducted where appropriate.
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54 275 *(i) Maternal age*
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276 We shall explore whether the association between maternal age and the outcomes are linear.

277 Where this is not the case and to aid clinical interpretability, we will categorise maternal age
278 at conception into 5-yearly age bands.

279 *(ii) Parity/gravidity*

280 The variable used will depend on availability in study datasets. Where both variables are
281 available, both will be reported with preference given to *parity* (the number of times a woman
282 gave birth at gestation ≥ 24 weeks); and sensitivity analysis will be conducted using *gravidity*
283 (the number of times a woman has been pregnant).

284 *(iii) Ethnicity*

285 Maternal ethnicity will be categorised based on the variables available and to allow for
286 harmonisation across the datasets: Asian, Black, Mixed, Other and White. Where data
287 permits, we may use more granular categories of ethnicity. Where numbers are too small and
288 risk identifying individuals, such as in NIMATS, we may collapse the categories to White
289 and Non-white.

290 *(iv) Social deprivation*

291 The patient level Index of Multiple Deprivation specific to each nation will be used and
292 categorised into quintiles.

293 *(v) Body mass index*

294 We shall include the latest available pre-pregnancy body mass index for the pregnant women.
295 Where booking data is available before 16 weeks gestation, this will be used (e.g. in
296 NIMATS). Body mass index will be considered a covariate instead of a health condition. The
297 World Health Organisation's classification of obesity will be used to categorise body mass

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3 298 index: <18.5 kg/m², 18.5 to 24.9 kg/m², 25.0 to 29.9 kg/m², 30.0 to 34.9 kg/m², 35.0 to 39.9
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5 299 kg/m², and 40+ kg/m².³⁵ Categories may be combined where numbers are too small.
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8 300 *(vi) Smoking*
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11 301 We shall include the latest available pre-pregnancy smoking status for the pregnant women.
12
13 302 Smoking status will be categorised as: non-smoker, ex-smoker, and smoker.
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16 303 *(vii) Year (pregnancy start date)*
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19 304 Data quality and clinical guidelines may vary by year. Its effect on outcomes will be
20
21 305 accounted for by adjusting for year of conception in the analysis.
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25 306 **Statistical analysis**
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28 307 We anticipate analyses will commence in June 2023 with study completion by June 2024.
29
30 308 Baseline characteristics of the study population and outcomes will be described with
31
32 309 summary statistics. Modified Poisson regression will be performed to estimate the relative
33
34 310 risks of study outcomes. Cox regression will be performed for longer-term outcomes. The
35
36 311 unit of analysis will be the pregnancy episode.
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40 312 A federated analysis approach will be used as data governance arrangements do not allow
41
42 313 pooling of the data across the four nations. Each dataset will be analysed separately following
43
44 314 a common study protocol. A common data model will be established and implemented across
45
46 315 the dataset, building on our previous work harmonising the phenome definitions for exposure
47
48 316 conditions.¹⁰ The effect sizes will be pooled using random-effects meta-analyses with inverse
49
50 317 variance weighting for the primary care and secondary care datasets respectively.³⁶
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54 318 Where rare combinations of health conditions and outcomes may lead to identification of an
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56 319 individual or at the prespecified minimum count allowed by each data source, we will
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58 320 suppress the output.
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56 322 **Pregnant women with more than one pregnancy episode**
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9 323 An individual may have more than one pregnancy over the study period. The pregnancy
10
11 324 episodes of the same woman will not be independent of each other. The severity of the
12
13 325 exposure variable (pre-existing multiple long-term conditions) may increase in later
14
15 326 pregnancy episodes as the pregnant women accumulates more long-term health conditions. If
16
17 327 a woman had an adverse pregnancy outcome, she is more at risk of the same adverse outcome
18
19 328 in subsequent pregnancy episodes. We shall account for this clustering effect of women with
20
21 329 more than one pregnancy episode during the study period using the Generalised Estimating
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23 330 Equation in the regression analyses.
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3031 332 **Multiple pregnancies**
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34 333 The main analysis will be limited to singleton pregnancies. Outcomes for pregnant women
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36 334 with multiple long-term conditions and multiple pregnancies (i.e. twins and higher order
37
38 335 pregnancies) will be analysed as a separate cohort.
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42 336
4344 337 **Missing data**
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46 338 Where exposure and outcome conditions are identified based on diagnostic codes, the
47
48 339 absence of the code will be considered as an absence of the condition. The level and types of
49
50 340 missingness of covariates will be reviewed and where appropriate will be addressed with
51
52 341 representing missing data as a separate category or multiple imputation with chain equation
53
54 342 (MICE). For variables required to compute an outcome, missing values will be imputed using
55
56 343 MICE. Example of these variables include birthweight, gestational age and baby's sex to
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3 344 determine preterm birth and small for gestational age. For each outcome, the statistical
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5 345 analyses will be performed on the imputed datasets and the estimates will be pooled with
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8 346 Rubin's rule.
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12 13 14 348 **Sensitivity analyses**

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17 349 We shall conduct sensitivity analyses using (i) complete case analysis, (ii) varying definitions
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19 350 of maternal multiple long-term conditions exposure using D'Arcy et al's core exposure set,³⁰
20
21 351 and (iii) in primiparous women. The latter is to account for the fact that some long-term
22
23 352 conditions can arise from complications from a previous pregnancy.
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28 29 354 **Patient and public involvement**

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32 355 The research question was informed by discussions with our patient and public involvement
33
34 356 (PPI) advisory group and our PPI co-investigators (NM and RP).
35

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38 357 The selection of outcomes are guided by our ongoing work developing a core outcome set for
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40 358 studies of pregnant women with multiple long-term conditions, where patients are key
41
42 359 stakeholders.³³
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45 360 Our PPI advisory group and PPI co-investigators will be involved in interpreting the study
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47 361 findings, producing lay summaries and infographics, and disseminating the study findings
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49 362 through their network.
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54 55 56 364 **ETHICS AND DISSEMINATION**

57 58 59 365 **Ethics approval** 60

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3 366 **CPRD:** CPRD has broad National Research Ethics Service Committee ethics approval for
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5 367 purely observational research using the primary care data and established data linkages. The
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7 368 study has been reviewed and approved by CPRD's Independent Scientific Advisory
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10 369 Committee (reference: 20_181R).

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13 370 **SAIL:** In accordance with UK Health Research Authority guidance, ethical approval is not
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15 371 mandatory for studies using only anonymised data. The study has been approved by SAIL
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18 372 Information Governance Review Panel.

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21 373 **Scotland dataset:** The study has been approved by the National Health Service
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23 374 Scotland Public Benefit and Privacy Panel for Health and Social Care (HSC-PBPP) and The
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25 375 University Teaching and Research Ethics Committee (UTREC) from the University of St
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28 376 Andrews.

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31 377 **NIMATS:** The study has been approved by the Honest Broker Service Governance Board.

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33
34 378 **Born in Bradford:** Ethics approval was granted by Bradford National Health Service
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36 379 Research Ethics Committee (ref 07/H1302/112) for the Born in Bradford cohort.

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38
39 380 The proposed study is purely observational and will use anonymised research data. The study
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41 381 will not involve participant recruitment. Therefore, consent to participate is not required.

42 43 44 382 **Consent for publication**

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47 383 This is not applicable as the manuscript is a study protocol. In the proposed study, we will
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49 384 use de-identified study data, therefore consent for publication will not be required.

50 51 52 385 **Dissemination**

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55 386 Study findings will be submitted for publications in peer reviewed journals and presented at
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57 387 key conferences for health and social care professionals involved in the care of pregnant
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59 388 women with multiple long-term conditions and their children. We will also organise

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3 389 dissemination events to share our findings with the public, service users, clinicians and
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5 390 researchers.
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11 392 **DISCUSSION**

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14 393 MuM-PreDiCT is a consortium across all four nations of the UK studying multiple long-term
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16 394 conditions in pregnancy. As part of MuM-PreDiCT's program of work, we outlined the
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18 395 protocol for an observational study of maternal and child outcomes for pregnant women with
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20 396 multiple long-term conditions, using routine health records and a birth cohort in the UK.
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27 398 **Comparison with current literature**

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30 399 A recent systematic review found seven observational studies on the association of pre-
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32 400 pregnancy multiple long-term conditions with adverse maternal outcomes.⁸ The review found
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34 401 that pre-pregnancy multiple long-term conditions were associated with severe maternal
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36 402 morbidity, hypertensive disorders of pregnancy, and acute health care use in the perinatal
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38 403 period.⁸ Most studies were conducted in the United States.⁸ Authors of the review
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40 404 commented that many studies included conditions arising in pregnancy in defining multiple
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42 405 long-term conditions, making it difficult to examine the impact of chronic conditions on
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44 406 maternal health.⁸
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48
49 407 This proposed study will be based in the UK and will use a broad range of long-term

50 408 conditions selected by women and clinicians to define multiple long-term conditions.

51 409 Pregnancy related conditions and complications will be treated as study outcomes and will

52 410 not be included in the exposure's definition. We will also study outcomes across all stages of

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54 411 pregnancy and outcomes for both women and their children.
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412 **Strengths and limitations**

413 This proposed study will utilise routine health records from all four nations of the UK
414 (England, Scotland, Wales and Northern Ireland). The available data sources consist of
415 anonymised patient records from primary and secondary care, community prescription data,
416 and maternity care data from routine booking appointments (first antenatal appointment
417 offered universally and as the gateway to access maternity care in the UK).

418 Rich data will also be available from a birth cohort from Bradford, an ethnically diverse
419 population in England. Beyond examining maternal outcomes, linked mother baby data and
420 the birth cohort data will allow for the exploration of child outcomes. The key strength of this
421 proposed study therefore is the generalisability of study findings to the UK population.
422 Observing similar effect sizes across the different datasets will also increase the confidence in
423 the study findings. Conversely, discrepancy in findings will stimulate further exploration of
424 the datasets which may generate new knowledge.

425 As this is an observational study using anonymised routine health records, key limitations
426 include missing data, misclassification bias due to inaccurate clinical coding and residual
427 confounding.

428 Maternal multimorbidity will be quantified with simple counts. A systematic review of
429 comorbidity indices used in maternal health research found three indices: Maternal
430 Comorbidity Index, Charlson comorbidity index and Elixhauser comorbidity index.²⁷ Only
431 the Maternal Comorbidity Index was developed from pregnant and postpartum women.²⁷ It
432 was developed using hospital data with 20 maternal comorbidities but it included pregnancy
433 related complications and factors such as multiple gestation, gestational diabetes, and
434 hypertension disorder of pregnancy.^{27 28} In contrast, the list of health conditions we will use

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3 435 to define maternal pre-existing multimorbidity is more comprehensive and included leading
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5 436 causes of indirect maternal death (e.g. epilepsy) and mental health conditions.
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8 437 Nevertheless, when using simple counts to quantify multiple long-term conditions, the
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10 438 severity of each health conditions will not be captured. The dose-response relationship will
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12 439 only be reflected in the total number of pre-existing long-term conditions. For example, we
13
14 440 will not be able to distinguish the outcomes for a pregnant woman with diet controlled
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16 441 diabetes and mild asthma from a pregnant woman with insulin dependent diabetes and brittle
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18 442 asthma. However, pregnant women with severe conditions are more likely to receive intense
19
20 443 specialist care than pregnant women with mild conditions. As the number of pregnant women
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22 444 with greater disease severity is likely to be smaller than those with milder condition, adverse
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24 445 pregnancy outcomes may be underestimated.
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30 446 Exposure and outcome events are only captured in routine health records when the pregnant
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32 447 women have presented to primary or secondary care and therefore the true prevalence and
33
34 448 incidence may be underestimated. Health conditions that are managed conservatively in
35
36 449 primary care, such as depression, anxiety and miscarriage, may not be captured in secondary
37
38 450 care datasets. Events such as termination of pregnancy that occurred outside of the traditional
39
40 451 health care settings may also be underestimated.³⁷ Similarly, antenatal hospital admission
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42 452 data may not reflect the full burden of additional antenatal appointments or acute care
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44 453 attendances, as care accessed through other routes may not be captured.
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49 454 Body mass index, which encompasses underweight and obese categories, will be studied as a
50
51 455 covariate instead of being counted as part of multimorbidity. There is much debate around
52
53 456 whether obesity should be considered a disease³⁸ or a risk factor for other long-term
54
55 457 conditions such as cardiometabolic conditions and cancers.³⁹⁻⁴¹ What is clear is pre-
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3 458 pregnancy maternal obesity is associated with adverse pregnancy outcome and dedicated care
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5 459 guideline has been established to manage this risk.^{42 43}
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9 460 **Clinical implications**

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12 461 Current obstetric guidelines for pregnant women with medical conditions are focused on
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14 462 specific and single health conditions. There are currently no guidelines for the management
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16 463 of pregnant women with multiple long-term conditions in the UK. The heterogeneity of
17
18 464 multiple long-term conditions means an all-encompassing guideline for every possible
19
20 465 combination of long-term conditions would not be possible. Indeed the English national
21
22 466 guideline for multimorbidity focuses on general approaches such as coordinated and holistic
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24 467 care, improving quality of life by reducing treatment burden and shared decision making
25
26 468 between patients and clinicians.⁴⁴ A guideline for multiple long-term conditions
27
28 469 (multimorbidity) in pregnancy is likely to follow the same principles but with additional
29
30 470 focus on the maternity care aspect.
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36 471 The basis of shared decision making is the provision of evidence based information. As
37
38 472 observed in the systematic review, there is currently a lack of evidence on the consequences
39
40 473 of pregnancy for women with multiple long-term conditions.⁸ Our PPI advisory group and
41
42 474 preliminary findings from our core outcome set development work have highlighted how
43
44 475 women valued having information to help them mentally prepare to face potential adverse
45
46 476 pregnancy outcomes. The output from this study will therefore provide valuable information
47
48 477 for women to make informed decision with their clinicians about family planning and their
49
50 478 preconception, pregnancy and postpartum care. It will also provide valuable information to
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52 479 guide the future design of care pathway for women with multiple long-term conditions.
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3 483 **ABBREVIATIONS**
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5 484 CPRD Clinical Practice Research Datalink
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7 485 ICD-10 International Classification of Disease 10th version
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9 486 MICE Multiple imputation with chain equation
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11 487 NICE National Institute for Health and Care Excellence
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14 488 NIMATS Northern Ireland Maternity System
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16 489 OPCS Operating Procedures Codes
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19 490 PPI Patient and public involvement
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21 491 SAIL Secure Anonymised Information Linkage
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24 492 UK United Kingdom
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3 **493 Data availability statement**
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6 494 Not applicable for the present protocol manuscript. In the proposed study, the data that
7
8 495 support the findings are available from CPRD, SAIL, Scotland National Health Service
9
10 496 Scotland Public Benefit and Privacy Panel for Health and Social Care, NIMATS and Born in
11
12 497 Bradford, but restrictions apply to the availability of these data, which are used under license
13
14 498 for the current study, and so are not publicly available. However, data will be available from
15
16 499 the authors upon reasonable request and with permission of CPRD, SAIL, Scotland National
17
18 500 Health Service Scotland Public Benefit and Privacy Panel for Health and Social Care,
19
20 501 NIMATS and Born in Bradford.
21
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25 **502 Competing interests**
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27
28 503 The authors declare that they have no competing interests.
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30

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33
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43
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45
46 511 role in study design, decision to publish, or preparation of the manuscript.
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51 **512 Contributors**
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53 513 SIL: conceptualisation, funding acquisition, methodology, and writing (original draft
54 514 preparation). KN, MB, KAE, KMA, and DOR: conceptualisation, funding acquisition,
55 515 methodology, supervision, and writing (review and editing). HH, GS, AS, NM, AAL, AFF,
56 516 CNP, CY, CMC, JIK, PB, RP, RR, ST, SB, UA, and ZV: conceptualisation, funding
57 517 acquisition, methodology, and writing (review and editing). LK, KP, MS, MM, NC, and
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518 SPBHS: conceptualisation, methodology, and writing (review and editing). MuM-PreDiCT
519 group: conceptualisation, funding acquisition. All authors read and approved the manuscript.

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