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Factors associated with maternal death from direct pregnancy complications: a UK national case–control study

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Objective To investigate the factors associated with maternal death from direct pregnancy complications in the UK.

Design Unmatched case–control analysis.

Setting All hospitals caring for pregnant women in the UK.

Population A total of 135 women who died (cases) between 2009 and 2012 from eclampsia, pulmonary embolism, severe sepsis, amniotic fluid embolism, and peripartum haemorrhage, using data from the Confidential Enquiry into Maternal Death, and another 1661 women who survived severe complications (controls) caused by these conditions (2005–2013), using data from the UK Obstetric Surveillance System.

Methods Multivariable regression analyses were undertaken to identify the factors that were associated with maternal deaths and to estimate the additive odds associated with the presence of one or more of these factors.

Main outcome measures Odds ratios associated with maternal death and population-attributable fractions, with 95% confidence intervals. Incremental risk of death associated with the factors using a 'risk factors' score.

Results Six factors were independently associated with maternal death: inadequate use of antenatal care (adjusted odds ratio, aOR 15.87, 95% CI 6.73–37.41); substance misuse (aOR 10.16, 95% CI 1.81–57.04); medical comorbidities (aOR 4.82, 95% CI 3.14–7.40); previous pregnancy problems (aOR 2.21, 95% CI 1.34–3.62); hypertensive disorders of pregnancy (aOR 2.44, 95% CI 1.31–4.52); and Indian ethnicity (aOR 2.70, 95% CI 1.14–6.43). Of the increased risk associated with maternal death, 70% (95% CI 66–73%) could be attributed to these factors. Odds associated with maternal death increased by three and a half times per unit increase in the 'risk factor' score (aOR 3.59, 95% CI 2.83–4.56).

Conclusions This study shows that medical comorbidities are importantly associated with direct (obstetric) deaths. Further studies are required to understand whether specific aspects of care could be improved to reduce maternal deaths among women with medical comorbidities in the UK.

Keywords Maternal mortality, risk factors, severe maternal morbidity, UK.

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Introduction

Timely identification and appropriate management of factors that increase the risk of progression from severe maternal morbidity to mortality have the potential to improve pregnancy care and to prevent deaths. Several previous studies have identified a number of factors that are thought to contribute to an increased risk of progression from severe maternal morbidity to death, such as delay in the identification of high-risk status and inappropriate management and referral, inadequate antenatal care, and suboptimal clinical care during delivery and postpartum.[1–4]

A previous study in the UK identified four characteristics that were more frequent amongst women who died, compared with women who had specific severe maternal morbidities: older maternal age (>35 years); obesity; belonging to unemployed or manual socio-economic groups; and black Caribbean and African ethnic backgrounds.[5] The data

available for women who died limited the detailed investigation of factors potentially underlying these associations, however, in particular medical comorbidities, substance misuse, inadequate antenatal care, and problems during the current and previous pregnancies. The aim of the current study was to further investigate the potential role of these factors in the progression from severe morbidity to direct maternal death among pregnant women in the UK, by undertaking a case–control study to investigate their association with maternal death using new and more detailed data on maternal deaths.

Methods

We performed an unmatched case–control analysis using data on maternal deaths from 2009–12 reported through the Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) Confidential Enquiry into Maternal Deaths,[6] and data on women who survived severe life-threatening complications during pregnancy and childbirth between 2005 and 2013 from the UK Obstetric Surveillance System (UKOSS).[7] Five major causes of direct maternal deaths in the UK for which data were available from both databases were included in this analysis: eclampsia, pulmonary embolism, severe sepsis, amniotic fluid embolism (AFE), and peripartum haemorrhage.

Morbidity data for pulmonary embolism and eclampsia were collected through UKOSS between 2007 and 2009,[8,9] and data for severe sepsis were collected between 2012 and 2013.[10] Data on survivors of peripartum haemorrhage (defined as severe haemorrhage requiring surgical interventions, including uterine compression sutures and hysterectomy) were obtained from studies conducted between 2009 and 2013.[11,12] Morbidity data for AFE was accrued between 2005 and 2013.[13] We identified 135 women who died from these causes and a control group of 1661 who survived. Data on a subset of the women with three of these conditions (eclampsia, pulmonary embolism, and AFE) were included in a previous study by Kayem et al.[5] Conditions were defined using standard case definitions.[11,14]

Details of the UKOSS methodology are described elsewhere.[7,15] Briefly, UKOSS is a research platform enabling the investigation of uncommon disorders of pregnancy.[7] Case notification cards are sent to nominated reporting doctors and midwives in all consultant-led obstetric units in the UK every month, with a 'nil-reporting' approach. Details are collected on a data-collection form for each case reported by the clinician responsible for managing the case. Rigorous follow-up of non-responders ensures the completeness of the data set.[7]

Surveillance of maternal deaths in the UK is undertaken through the MBRRACE-UK collaboration.[6] Deaths of women during or after pregnancy are identified through a variety of sources, the majority being notified to the MBRRACE-UK office directly from the unit in which the maternal death occurred. Other sources include coroners/procurators fiscal or pathologists, local supervising authority midwifery officers, members of the public, and inquest reports from the media. In addition, case ascertainment is cross-checked with routine birth and death vital statistics records from the Office for National Statistics and the National Records of Scotland. For every death reported, basic demographic and clinical details are collected.

Fourteen known risk factors for severe maternal morbidity and mortality were included as independent variables: gestational diabetes; hypertensive disorders of pregnancy during the current pregnancy; anaemia; multiple pregnancy; inadequate use of antenatal care services; smoking; substance misuse; previous pregnancy problems; pre-existing medical conditions; parity; body mass index (BMI); employment status; maternal age; and ethnicity.[13,14,16–18] Women were categorised as having gestational diabetes, hypertensive disorders of pregnancy, and anaemia during the current pregnancy, based on clinician-recorded conditions in the medical records. The variable 'ethnicity' refers to the racial origin of women and not their culture, and was categorised according to the UK national census classification.[19] Maternal age, BMI, and parity were each categorised into three groups.[14,17,20,21] In order to compare the findings with that of the previous UK study,[5] we also categorised parity and BMI into binary variables and re-categorised age and tested these in a separate regression model. Medical comorbidities were grouped initially as a single variable, and subsequently into 18 categories (Box 1).

With 135 cases (deaths) and 1661 controls (survivors), our analysis had a power of 80% to detect an odds ratio of 1.6 or greater associated with fatality at a significance level of $P < 0.05$ (two-tailed) for the risk factor that had the highest prevalence among the controls (42% for nulliparity), and an odds ratio of 9.6 or greater for substance misuse (0.2%), which had the lowest prevalence.

Statistical analysis

We conducted an initial descriptive analysis of cases and controls to identify potential associated factors. A core logistic regression model (model 1) was then built including all 14 variables that were identified from previous literature to be associated with maternal death. None of the independent variables were found to be highly correlated with one another. We tested for plausible interactions (between substance misuse and employment status, smoking and employment status, pre-existing mental health problems and use of antenatal care, and substance misuse and use of antenatal care) by adding interaction terms, one at a time, and subsequent likelihood ratio testing (LR-test,

Box 1. Pre-existing medical conditions

Asthma	Mental health problems
Autoimmune diseases (e.g. systemic lupus erythematosus)	Haematological disorders (e.g. thalassemia, sickle-cell anaemia, iron deficiency anaemia, and pro-coagulant states)
Known malignancies	Epilepsy
Cardiac problems (congenital and acquired)	Inflammatory disorders and allergic/atopic conditions (e.g. eczema and ulcerative colitis)
Diabetes mellitus (types I or II)	Essential hypertension
Diseases caused by blood-borne viruses (e.g. HIV, hepatitis B and C)	Thrombotic events
Endocrine disorders, excluding diabetes mellitus (e.g. hypothyroidism and hyperthyroidism)	Musculoskeletal disorders (e.g. osteoarthritis and hip replacement)
Renal problems (e.g. pyelonephritis, nephrectomy, and recurrent urinary tract infection)	Other infections, excluding blood-borne viruses (e.g. sexually transmitted infections, tuberculosis, and group–B *Streptococcus* infection)
Neurological disorders (e.g. migraine)	Treated for infertility

$P < 0.05$). As no significant interactions were observed, we did not fit the interaction terms in the final multivariable model in order to improve parsimony.

We tested the continuous variables maternal age and BMI for deviations from linearity by fitting functional polynomials in the univariable logistic regression models with multiple transformations of the continuous variables.[22] This suggested presence of nonlinear associations of the continuous variables with the outcome, thus the variables were included as categorical variables in the logistic regression model. To compare the results with the previous study we re-ran the logistic regression analysis incorporating the re-categorised variables for parity, maternal age, and BMI.[5] This did not substantively change the results. In addition, we conducted separate sensitivity analyses including only the three conditions included in the previous paper (AFE, pulmonary embolism, and eclampsia) or the two new conditions (severe sepsis and haemorrhage). We also examined a restricted model that included only data collected between 2009 and 2012.

The proportion of missing data for most variables was <0.8%, except BMI (8.2%), smoking (2.4%), and employment status (16%). On the basis of previous studies, we assumed that the data were not missing at random and included a proxy variable for the missing group.[14,23] In addition, a series of sensitivity analyses were performed by assuming extreme scenarios and accordingly redistributing the missing observations into the extreme groups; this did not materially alter the results.

We further investigated the role of medical comorbidities by examining different subgroups of comorbidity. We conducted univariable analyses to assess the association of the 18 specific pre-existing medical comorbidities with the outcome. Thirteen variables found to be associated with the outcome at $P < 0.05$ (two-tailed) and those identified as important factors associated with maternal morbidity and mortality in previous literature were included in a second multivariable logistic regression model (model 2). This was followed by an additional exploratory regression analysis to examine the factors that were associated with medical comorbidities in the study population.

A 'risk factors' score was generated to understand the additive odds associated with the presence of one or more factors that were found to be statistically significantly associated with maternal death. Using the method employed by Kayem et al.,[5] we assigned a score of one to each factor. We also calculated the population attributable fraction (PAF) for the 'risk factors' score and the individual factors using standard methods for calculating PAF in case–control studies.[24] All analyses were performed using STATA 13 (StataCorp, College Station, TX, USA).

Results

Six factors were independently associated with maternal death after controlling for other independent variables (Table 1). The odds ratio of inadequate use of antenatal care was 15 times higher among women who died compared with women who survived (adjusted odds ratio, aOR 15.87; 95% confidence interval, 95% CI 6.73–37.41), and the odds of substance misuse was ten-fold higher among cases compared with controls (aOR 10.16; 95% CI 1.81–57.04). Women who died were also found to have a four-fold higher odds of having any medical comorbidity, and had more than two-fold higher odds of problems during previous pregnancies and hypertensive disorders of pregnancy during the current pregnancy, compared with the women who survived. Furthermore, the odds of belonging to the Indian ethnic group was more than two and a half times greater among cases compared with controls; this was not observed for other ethnic minority groups. Model 1 explained 22% of the variance in the outcome.

The findings of the sensitivity analyses did not materially differ from the results from model 1, with the exception of ethnicity. The sensitivity analysis examining the disease

Table 1. Factors associated with maternal death from direct pregnancy complications (model 1)*

Risk factors	Cases no. (%) n = 135	Controls no. (%) n = 1661	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Age (years)				
<20	7 (5.2)	105 (6.3)	0.83 (0.37–1.84)	0.76 (0.29–2.03)
20–34	84 (62.2)	1044 (62.9)	1	1
≥35	44 (32.6)	512 (30.8)	1.06 (0.73–1.56)	0.94 (0.60–1.48)
Parity				
Nulliparous	49 (36.3)	692 (41.7)	0.81 (0.55–1.19)	1.05 (0.62–1.78)
1–3	61 (45.2)	697 (41.9)	1	1
>3	23 (17.0)	269 (16.2)	0.98 (0.59–1.61)	0.79 (0.43–1.43)
Missing	2 (1.5)	3 (0.2)	7.62 (1.25–46.46)	1.22 (0.02–67.56)
Body mass index (kg/m^2)				
<18.5	6 (4.4)	45 (2.7)	1.83 (0.76–4.41)	1.56 (0.57–4.28)
18.5–30	84 (62.2)	1152 (69.4)	1	1
≥30	35 (25.9)	325 (19.6)	1.48 (0.98–2.23)	1.05 (0.66–1.70)
Missing	10 (7.4)	139 (8.3)	0.99 (0.50–1.95)	0.35 (0.13–0.94)
Multiple pregnancy				
No	129 (95.5)	1588 (95.6)	1	1
Yes	4 (3.0)	73 (4.4)	0.67 (0.24–1.87)	0.67 (0.22–2.01)
Missing	2 (1.5)	0 (0.0)	Omitted	
Gestational diabetes				
No	118 (87.4)	1605 (96.6)	1	1
Yes	8 (5.9)	50 (3.0)	2.18 (1.01–4.70)	1.43 (0.59–3.44)
Missing	9 (6.7)	6 (0.4)	20.40 (7.14–58.29)	
Hypertensive disorders of pregnancy				
No	106 (78.5)	1555 (93.6)	1	1
Yes	20 (14.8)	100 (6.0)	2.93 (1.75–4.93)	2.44 (1.31–4.52)
Missing	9 (6.7)	6 (0.4)	22.0 (7.69–62.98)	
Anaemia				
No	123 (91.1)	1632 (98.2)	1	1
Yes	3 (2.2)	23 (1.4)	1.73 (0.51–5.84)	2.39 (0.60–9.47)
Missing	9 (6.7)	6 (0.4)	19.90 (6.97–56.82)	
Inadequate use of antenatal care**				
No	106 (78.5)	1637 (98.6)	1	1
Yes	21 (15.6)	18 (1.1)	18.02 (9.32–34.84)	15.87 (6.73–37.41)
Missing	8 (5.9)	6 (0.3)	20.59 (7.02–61.43)	
Smoking status				
Non-smoker	95 (70.4)	1285 (77.4)	1	1
Smoker	27 (20.0)	346 (20.8)	1.05 (0.68–1.64)	0.79 (0.45–1.39)
Missing	13 (9.6)	30 (1.8)	5.86 (2.96–11.61)	2.92 (0.93–9.14)
Substance misuse				
No	123 (91.1)	1651 (99.4)	1	1
Yes	6 (4.4)	4 (0.2)	20.13 (5.61–72.29)	10.16 (1.81–57.04)
Missing	6 (4.4)	6 (0.4)	13.42 (4.27–42.24)	2.94 (0.19–47.67)
Previous pregnancy problems***				
No	76 (56.3)	1247 (75.1)	1	1
Yes	56 (41.5)	407 (24.5)	2.26 (1.57–3.25)	2.21 (1.34–3.62)
Missing	3 (2.2)	7 (0.4)	7.03 (1.78–27.73)	0.25 (0.01–5.32)
Pre-existing medical problems****				
No	37 (27.4)	1175 (70.7)	1	1
Yes	93 (68.9)	481 (29.0)	6.14 (4.13–9.12)	4.82 (3.14–7.40)
Missing	5 (3.7)	5 (0.3)	31.76 (8.81–114.45)	18.93 (1.63–220.32)
Employment status				
Employed	91 (67.4)	1211 (72.9)	1	1
Unemployed	17 (12.6)	188 (11.3)	1.20 (0.70–2.07)	1.27 (0.65–2.47)

Table 1. (Continued)

Risk factors	Cases no. (%) n = 135	Controls no. (%) n = 1661	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Missing	27 (20.0)	262 (15.8)	1.37 (0.87–2.15)	0.81 (0.44–1.51)
Ethnicity				
White European	88 (65.2)	1226 (73.8)	1	1
Indian	8 (5.9)	47 (2.8)	2.37 (1.09–5.17)	2.70 (1.14–6.43)
Pakistani	7 (5.2)	73 (4.4)	1.34 (0.60–2.99)	2.10 (0.86–5.11)
Bangladeshi	2 (1.5)	39 (2.4)	0.71 (0.17–3.01)	1.21 (0.27–5.45)
Other Asian	4 (3.0)	66 (4.0)	0.84 (0.30–2.37)	1.08 (0.36–3.27)
Black Caribbean	3 (2.2)	40 (2.4)	1.04 (0.32–3.45)	0.93 (0.24–3.64)
Black African	13 (9.6)	105 (6.3)	1.72 (0.93–3.19)	1.09 (0.51–2.31)
Other/mixed	10 (7.4)	65 (3.9)	2.14 (1.06–4.32)	1.46 (0.59–3.61)

*Model 1 includes all 14 variables specified in the table.
**Inadequate use of antenatal care: women who concealed pregnancy, were late in booking an appointment, or who did not receive minimal antenatal care.
***Previous pregnancy problems: women who were reported to have suffered from any pregnancy-related problem in a previous pregnancy, the major categories of which included thrombotic events, placental problems, haemorrhage, pre-eclampsia, eclampsia, and puerperal psychosis.
****Pre-existing medical problems: women who were reported to have any medical comorbidity during the current pregnancy, including the 18 specific conditions described in Box 1. Women were categorised as having gestational diabetes, hypertensive disorders of pregnancy, or anaemia based on clinician-recorded condition/s in the medical records.

conditions separately (severe sepsis and haemorrhage in one model and the other three conditions in another model) showed that the odds ratio of belonging to the Indian ethnic group was significantly higher among women who died of severe sepsis and haemorrhage, compared with women who survived these conditions (aOR 3.37, 95% CI 1.29–8.85), but that the same was not true for AFE, pulmonary embolism, and eclampsia (aOR 0.98, 95% CI 0.09–10.60). The odds ratios for the other ethnic minority groups were not significantly different for cases and controls.

The results of model 2 showed that eight of the 18 medical comorbidities were significantly associated with maternal death (Table 2). The odds of pre-existing musculoskeletal disorders was 12 times higher and the odds of inflammatory/atopic disorders (excluding asthma) was ten-fold higher among women who died compared with women who survived. Women who died had five times higher odds of suffering from autoimmune diseases and infections, such as sexually transmitted infections, tuberculosis, and group–B *Streptococcus* infection, four-fold higher odds of having a pre-existing haematological disorder, and more than three times higher odds of essential hypertension, compared with the women who survived. The odds of suffering from mental health problems and asthma were more than two times higher among women who died, compared with women who survived.

Analysis of the factors associated with medical comorbidities in the study population showed that women with medical comorbidities had a significantly higher odds of inadequate use of antenatal care, belonging to an older age group (≥35 years), smoking, substance misuse, nulliparity, obesity, gestational diabetes, hypertensive disorders of pregnancy, and problems during a previous pregnancy (Table S1).

Analysis of the 'risk factors' score showed that half of the women who survived did not have any of the six associated factors, 38% had one, 12% had two, 1% had three, and none had four or more. Among women who died, 19% did not have any of these associated factors, 27% had one, 39% had two, 13% had three, and 1.5% (two women) had four out of six associated factors. None of the women had a score of more than four associated risk factors. The odds associated with maternal death increased by more than three and a half times per unit increase in the 'risk factor' score (aOR 3.59; 95% CI 2.83–4.56; $P < 0.001$), after controlling for other variables that are not included in the score. On a population basis, 70% (95% CI 66–73%) of the increased risk associated with maternal death could be attributed to the six identified factors, the most important being medical comorbidities followed by previous pregnancy problems, hypertensive disorders of pregnancy, inadequate use of antenatal care services, and Indian ethnicity (Table 3).

Discussion

Main findings

We found six factors to be associated with maternal death from direct pregnancy complications: inadequate use of

Table 2. Medical co-morbidities associated with maternal death from direct pregnancy complications (model 2)*

Risk factors	Cases no. (%) n = 135	Controls no. (%) n = 1661	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Asthma				
No	111 (82.2)	1562 (94.0)	1	1
Yes	19 (14.1)	94 (5.7)	2.84 (1.68–4.83)	2.36 (1.19–4.65)
Inflammatory disorders and allergic/atopic conditions (excluding asthma)				
No	116 (85.9)	1645 (99.0)	1	1
Yes	14 (10.4)	11 (0.7)	18.05 (8.01–41.65)	9.79 (3.50–27.36)
Haematological disorders				
No	117 (86.7)	1617 (97.4)	1	1
Yes	13 (9.6)	39 (2.3)	4.61 (2.39–8.87)	4.29 (1.88–9.76)
Infertility				
No	122 (90.4)	1640 (98.7)	1	1
Yes	8 (5.9)	16 (1.0)	6.72 (2.82–16.02)	3.08 (0.87–10.84)
Neurological disorders				
No	125 (92.6)	1650 (99.3)	1	1
Yes	5 (3.7)	6 (0.4)	11.00 (3.31–36.55)	3.83 (0.71–20.74)
Musculoskeletal disorders				
No	120 (88.9)	1648 (99.2)	1	1
Yes	10 (7.4)	8 (0.5)	17.17 (6.65–44.30)	12.65 (3.56–44.98)
Mental health problems				
No	110 (81.5)	1585 (95.4)	1	1
Yes	20 (14.8)	71 (4.3)	4.06 (2.38–6.91)	2.63 (1.28–5.44)
Infection (other than blood-borne viruses)				
No	122 (90.4)	1646 (99.1)	1	1
Yes	8 (5.9)	10 (0.6)	10.79 (4.18–27.84)	5.31 (1.63–17.23)
Essential hypertension				
No	122 (90.4)	1626 (97.9)	1	1
Yes	8 (5.9)	30 (1.8)	3.55 (1.59–7.92)	3.35 (1.25–9.00)
Thrombotic event				
No	125 (92.6)	1640 (98.7)	1	1
Yes	5 (3.7)	16 (1.0)	4.10 (1.48–11.38)	2.74 (0.68–11.08)
Autoimmune diseases				
No	125 (92.6)	1637 (98.6)	1	1
Yes	5 (3.7)	19 (1.1)	3.45 (1.27–9.38)	5.16 (1.63–16.39)
Cardiac disease (congenital or acquired)				
No	126 (93.3)	1632 (98.3)	1	1
Yes	4 (3.0)	24 (1.4)	2.16 (0.74–6.32)	1.32 (0.34–5.15)
Diabetes mellitus				
No	127 (94.1)	1641 (98.8)	1	1
Yes	3 (2.2)	15 (0.9)	2.58 (0.74–9.04)	2.09 (0.50–8.79)
Blood-borne viruses				
No	127 (94.1)	1644 (99.0)	1	
Yes	3 (2.2)	12 (0.7)	3.24 (0.90–11.62)	Excluded
Renal problems				
No	126 (93.3)	1629 (98.1)	1	
Yes	4 (3.0)	27 (1.6)	1.92 (0.66–5.56)	Excluded
Endocrine disorders				
No	127 (94.1)	1625 (97.8)	1	
Yes	3 (2.2)	31 (1.9)	1.24 (0.37–4.11)	Excluded
Known malignancies				
No	129 (95.6)	1650 (99.3)	1	
Yes	1 (0.7)	6 (0.4)	2.13 (0.25–17.84)	Excluded

Table 2. (Continued)

Risk factors	Cases no. (%) n = 135	Controls no. (%) n = 1661	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Epilepsy				
No	130 (96.3)	1642 (98.9)	1	
Yes	0 (0.0)	14 (0.8)	1 (omitted)	Excluded

Data were missing for five cases (3.7%) and for five controls (0.3%) with regards to all pre-existing medical conditions.
*Model 2 includes 13 of the 18 medical conditions listed in the table and all variables included in Table 1, except 'pre-existing medical conditions'. Five medical comorbidities were excluded from adjusted model 2 because they were not found to be significantly associated with the outcome at $P < 0.05$ after univariable analysis: blood-borne viruses; renal problems; endocrine disorders; known malignancies; and epilepsy. Diabetes mellitus and cardiac disease were retained in the model because these are known important risk factors for maternal morbidity and mortality.

Table 3. Population-attributable fractions (PAFs) for specific associated factors

Risk factors	PAF (%)	95% CI
'Risk factors' score	69.8	66.1–73.0
Specific factors		
Medical comorbidities	48.9	40.5–56.2
Previous pregnancy problems	21.1	11.7–29.5
Hypertensive disorders of pregnancy	12.0	7.7–16.1
Inadequate use of antenatal care	10.5	9.7–11.4
Indian ethnicity	2.9	0.3–5.5
Substance misuse	1	0.03–1.4

antenatal care; substance misuse; medical comorbidities; hypertensive disorders of pregnancy; previous pregnancy problems; and Indian ethnicity. Together, these contributed 70% of the increased population risk. Belonging to other ethnic minority backgrounds was also associated with increased odds of death, but the odds ratios were not statistically significant, possibly because of a smaller number of cases in each of these groups, resulting in low statistical power. Specific medical comorbidities, including asthma, autoimmune diseases, inflammatory/atopic disorders, mental health problems, essential hypertension, haematological disorders, musculoskeletal disorders, and infections, were found to be associated with a higher risk of dying from the conditions included in this study. Medical comorbidities contributed 49% of the increased risk of fatality in the study population.

Strengths and limitations

The low incidence of maternal mortality in the UK makes studies on the risk of death among pregnant women who develop severe morbidity difficult; however, we were able to perform an unmatched case–control analysis using data from two national databases to investigate the effects of known factors associated with maternal mortality, and conducted further analyses to investigate the association with medical comorbidities. As the analysis was based on national data, available from MBRRACE-UK and UKOSS, the cases (maternal deaths) and controls (women who suffered severe morbidity, but who survived) were from the same source population, thereby making the comparison valid.

Although the findings of the sensitivity analyses comparing models for 2005–09 and 2009–13 did not differ from the complete model, we cannot completely rule out any bias arising from the differing time periods of data collection between UKOSS and MBRRACE-UK. We also cannot rule out bias arising from the different data sources of cases and controls. We specifically did not include cases of indirect maternal death, as we wished to investigate the association of medical comorbidities with direct maternal death; this does mean that the findings cannot be generalised to all maternal deaths, but are instead limited to the five conditions causing the majority of direct maternal deaths in the UK. We identified pre-existing medical conditions based on clinician-reported general history. We do not have information about the severity of these conditions and modalities of treatment, which may have a differential effect on the risk of progression to death. Thus, further studies are required to examine these factors.

Interpretation (in light of other evidence)

The presence of medical comorbidities was significantly more frequent among women who died compared with the women who suffered severe morbidity but survived. Several studies have demonstrated individual medical comorbidities such as pre-existing asthma, hypertension, malignancy, chronic ischaemic and congenital heart disease, chronic renal disease, systemic lupus erythematosus, hypercoagulability states, human immune deficiency virus, and diabetes mellitus to be associated with both severe maternal morbidity and mortality,[18,25–31] but the extent of the population risk attributable to medical comorbidities as a whole

in the UK has not previously been quantified. Uptake of antenatal care was found to be poorer among women with medical comorbidities in our study population, which could increase the adverse effects associated with these conditions. Our findings suggest that the association of older maternal age and obesity with increased odds of dying observed in a previous study,[5] could be mediated through medical comorbidities. Unlike other studies,[18,25] we did not find pre-existing diabetes mellitus and cardiac conditions to be associated with maternal death. Whether this reflects improved obstetric care of women with diabetes and cardiac disease is unclear and requires further research.

Hypertension during pregnancy has been shown in other analyses to be associated with an increased risk of intracerebral haemorrhage, eclampsia, or end-organ dysfunction culminating in death.[3,32–34] Studies from different parts of the world, including the UK, show a higher risk of mortality among women who do not receive adequate antenatal care.[3,14,33,35] Although there is a debate about the role of antenatal care in preventing maternal deaths caused by acute conditions that emerge close to the time of delivery, its role in identifying pregnant women at high risk (such as women with hypertensive disorders, medical comorbidities, anaemia, and infections) and lowering their risk of mortality is widely accepted.[36]

Confidential enquiries into maternal deaths in the UK have identified that a number of women who die during or after pregnancy are substance misusers, although the association with maternal death has not been formally quantified before now.[37,38] Studies have shown that women who suffered problems during a previous pregnancy were more likely to develop severe morbidity in subsequent pregnancies.[14,39,40] There is mixed evidence about ethnic inequalities in maternal death. Whereas Kayem et al.[5] found an association with black African and Caribbean ethnicity in the UK, Geller et al.[1] did not find any association with minority ethnicity in the USA. Among the ethnic minority groups examined in this study, the association with maternal death was higher among the Indian group, but only for sepsis and haemorrhage. This is likely to explain the difference between our findings and the previous UK study, which did not include these conditions.[5] Although factors such as pre-existing medical conditions, previous pregnancy problems, and being of Indian origin cannot be altered, their adverse consequences can be potentially minimised through extra vigilance and proactive management.

Conclusion

This national study has identified six risk factors associated with maternal death from direct pregnancy complications: inadequate use of antenatal care services; substance misuse; medical comorbidities; hypertensive disorders of pregnancy; previous pregnancy problems; and Indian ethnicity. Maternal deaths arising from indirect (medical) causes now outnumber direct deaths arising from obstetric causes in most high-resource countries, with mortality rates either remaining static or increasing.[38,41–44] This study shows that medical comorbidities are also important factors associated with deaths arising from obstetric causes (direct deaths) in the UK: almost 50% of the population-attributable risk is associated with the presence of medical comorbidities. This highlights the importance of optimal care for women with pre-existing medical problems in pregnancy. Further studies are required to understand whether specific aspects of care could be improved to reduce maternal deaths among women with medical comorbidities.

Disclosure of interests

We declare that we have no competing interests.

Contribution to authorship

MN coded the data, carried out the analysis, and wrote the first draft of the article. JJK contributed to the design of the study and the writing of the article. PB contributed to the design of the study and the writing of the article. SS and GL contributed to the writing of the article. MK designed the study, supervised the data collection and analysis, and contributed to writing the article.

Details of ethics approval

The London Multi-centre Research Ethics Committee approved the UK Obstetric Surveillance System (UKOSS) general methodology (04/MRE02/45) and the surveillance of individual near-miss maternal morbidities using UKOSS (04/MRE02/46, 07/MRE02/24, 04/MRE02/72, 04/MRE02/73, 04/MRE02/74, 10/H0717/20).

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Factors associated with the presence of medical co-morbidities. ■

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