

Risk factors and newborn outcomes associated with maternal deaths in the UK from 2009 to 2013: a national case–control study

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Objectives To identify the risk factors for and adverse newborn outcomes associated with maternal deaths from direct and indirect causes in the UK.

Design Unmatched case–control analysis.

Setting All hospitals caring for pregnant women in the UK.

Population Comprised 383 women who died (cases) from direct or indirect causes from 2009 to 2013 (Confidential Enquiry into Maternal Deaths in the UK) and 1516 women who did not have any life-threatening complications during pregnancy and childbirth (controls) obtained from UK Obstetric Surveillance System (UKOSS).

Methods Multivariable regression analyses were undertaken to examine potential risk factors, their incremental effects, and adverse newborn outcomes associated with maternal deaths.

Outcomes Odds ratios associated for risk factors for maternal death and newborn outcomes (stillbirth, admission to neonatal intensive care unit [NICU], early neonatal death) and incremental risk.

Results Seven factors, of 13 examined, were independently associated with increased odds of maternal death: pre-existing medical comorbidities (adjusted odds ratio [aOR] 8.65; 95% CI

6.29–11.90), anaemia during pregnancy (aOR 3.58; 95% CI 1.14–11.21), previous pregnancy problems (aOR 1.85; 95% CI 1.33–2.57), inadequate use of antenatal care (aOR 46.85; 95% CI 19.61–111.94), substance misuse (aOR 12.21; 95% CI 2.33–63.98), unemployment (aOR 1.81; 95% CI 1.08–3.04) and maternal age (aOR 1.06; 95% CI 1.04–1.09). There was a four-fold increase in the odds of death per unit increase in the number of risk factors. Odds of stillbirth, admission to NICU and early neonatal death were higher among women who died.

Conclusion This study reiterates the need for optimal care for women with medical comorbidities and older age, and the importance of adequate antenatal care. It demonstrates the existence of socio-economic inequalities in maternal death in the UK.

Keywords Early neonatal death, maternal death, risk factors, stillbirth, UK.

Tweetable abstract Medical comorbidities and socio-economic inequalities are important risk factors for maternal death in the UK.

Linked article This article is commented on by J Drife p. 1663 in this issue. To view this mini commentary visit <http://dx.doi.org/10.1111/1471-0528.14024>.

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Introduction

Previous studies have shown that medical comorbidities, inadequate use of antenatal care, hypertensive disorders during current pregnancy, previous pregnancy problems, obesity and sociodemographic factors such as older maternal age (>35 years), belonging to unemployed or manual socio-economic groups, substance misuse and being from minority ethnic groups were independently associated with increased risk of progression from severe pregnancy com-

plications to death among pregnant women in the UK.^{1,2} However, women who suffer severe complications may be different from the majority of women, who have an uncomplicated pregnancy and childbirth, and it is therefore important to examine whether women who die during pregnancy or childbirth differ from the normal pregnant population. Identifying these differences could help to update the existing pregnancy care pathways recommended by the National Institute for Health and Care Excellence (NICE)³ to improve management of the risk factors to

prevent complications and death during pregnancy and childbirth in the UK.

Furthermore, the health of the mother and care during pregnancy, childbirth and the postpartum period are strong determinants of fetal and neonatal wellbeing. Studies mainly from low- and middle-income countries show that maternal death is associated with increased risk of stillbirth and infant death.^{4–8} In the UK, 3286 babies were stillborn⁹ and a total of 2966 infants died^{10–12} in 2013. However, the association of stillbirth and newborn death with maternal mortality in the UK is not clearly understood from the available published literature. The objectives of our study were to identify the risk factors for and any adverse fetal and newborn outcomes associated with maternal deaths from direct and indirect causes in the UK in 2009–13.

Methods

We conducted an unmatched case–control analysis using data from two sources. Cases were 383 women who died from direct (obstetric causes) or indirect (pre-existing medical conditions aggravated by the physiological effects of pregnancy) causes during pregnancy or within 42 days of the end of pregnancy regardless of how the pregnancy ended (miscarriage, ectopic pregnancy, termination or birth) from 2009 to 2013 in the UK. Information on maternal deaths was extracted from the surveillance database of the Confidential Enquiry into Maternal Deaths.^{13,14} Population controls were obtained from the UK Obstetric Surveillance System (UKOSS)¹⁵ from three studies conducted between 2010 and 2012. These were 1516 women who did not have any severe life-threatening complications during pregnancy and childbirth (referred to henceforth as women who had an uncomplicated pregnancy).

Details of the MBRRACE-UK^{13,14} and UKOSS^{15,16} methodologies have been described elsewhere. The MBRRACE-UK collaboration conducts surveillance of maternal deaths in the UK. Deaths of women during or after pregnancy are notified to the MBRRACE-UK office directly from the hospital in which the death occurred. Deaths are also identified from a number of other sources including Coroners/Procurators Fiscal, pathologists, Local Supervising Authority Midwifery Officers, and inquest reports from the media. Case-ascertainment is also verified with routine birth and death vital statistics records from the Office for National Statistics (ONS) for England and Wales, National Records of Scotland (NRS)¹⁴ and Northern Ireland Statistics and Research Agency (NISRA).¹⁷ UKOSS is a research platform that was established in 2005 to conduct population-based studies of the aetiology, management and outcomes of uncommon disorders of pregnancy.¹⁵ This rolling programme is maintained through case notification cards sent to all consultant-led obstetric

units in the UK every month with an approach of ‘nil-reporting’. For every case reported, details are collected for the case and one or more controls (women who delivered immediately before the cases in the same hospital) on data collection forms by the clinician responsible for managing the case.^{15,16} Over a period of 10 years UKOSS has accrued detailed national data on women with severe complications during pregnancy and childbirth as well as detailed information on women who had an uncomplicated pregnancy and childbirth (control groups).

We examined the association with maternal death of 13 potential risk factors for maternal mortality and morbidity^{18–22} for which comparable information was available from the two sources (MBRRACE-UK and UKOSS): gestational diabetes, anaemia during current pregnancy, 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. Women were categorised into different ethnic groups according to the UK national census classification.²³ Women who concealed pregnancy, were booked late for antenatal care (after 12 completed weeks of gestation) or did not receive minimal antenatal care were categorised as women who did not receive adequate antenatal care and these factors were used to generate a binary variable ‘inadequate use of antenatal care services’.²¹ We did not categorise women who died in early pregnancy as having ‘inadequate antenatal care’. Based on the number of pregnancies beyond 24 weeks, women were grouped as nulliparous, multiparous (one to four pregnancies) and grand-multiparous (five or more pregnancies). Data on employment status of the women or their partners (where information about employment status of the women was not available) was used to generate a binary variable of employed or unemployed as a proxy for socio-economic status. Women who were reported to have suffered from any pregnancy-related problems in a previous pregnancy such as thrombotic events, placental problems, haemorrhage, pre-eclampsia, eclampsia, puerperal psychosis were grouped as having suffered a previous pregnancy problem.

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 variable.²⁴ Results showed that maternal age had a linear association with the outcome, but BMI did not, hence BMI was categorised into four groups—normal (18.5–24.9 kg/m²), underweight (<18.5 kg/m²), overweight (25–29.9 kg/m²) and obese (≥30 kg/m²).²⁵ As was done in a previous study,² medical comorbidities were grouped initially as a single variable, and subsequently into 16 clinically meaningful subgroups to explore any specific drivers of any association:

asthma, autoimmune diseases, inflammatory disorders and allergic/atopic conditions (excluding asthma, example eczema and ulcerative colitis), cardiac disease (congenital or acquired), diabetes mellitus, endocrine disorders (other than diabetes mellitus), epilepsy, haematological disorders, essential hypertension, blood-borne viruses, infection (other than blood-borne viruses, example sexually transmitted infections, tuberculosis, and group B streptococcus infection), neurological disorders, musculoskeletal disorders, mental health problems, renal problems and thrombotic event.

In addition, we examined the association of maternal death with three adverse newborn outcomes—stillbirth, admission to neonatal intensive care unit (NICU) and early neonatal death based on clinician-reported information on the data collection form for UKOSS and surveillance form for maternal deaths.

Study power

The fixed sample size of 383 cases (women who died) and 1516 controls (women with normal pregnancy) included in this analysis provided 80% power to detect an odds ratio of 1.34 or greater associated with maternal death at $P < 0.05$ (two-tailed) for the risk factor that had the highest prevalence among the controls (55% for multiparity) and an odds ratio of 8.6 or greater for substance misuse, which had the lowest prevalence (0.1%).

Statistical analysis

We conducted an initial descriptive analysis of the cases and controls to examine the crude associations between each of the 13 independent variables and the outcome. A core logistic regression model (model-1) was built including 12 variables (except parity) that were identified from previous literature to be associated with maternal death. Tests for correlation between the independent variables showed that parity and previous pregnancy problems were moderately correlated ($r = 0.40$, $P < 0.001$); hence, parity was not included in the multivariable model. We did not find any other significant moderate to strong correlations among the variables. We included maternal age as a continuous variable in the multivariable regression analysis and also tested an ordered categorical variable in a separate model to understand whether the risk of dying was higher in certain age groups. This did not materially change the adjusted odds ratios for other variables included in the analysis.

We analysed the odds of three adverse newborn outcomes (stillbirth, admission to NICU and early neonatal death) among women who died compared with the comparison pregnant women by conducting exact logistic regression analyses for each of these adverse events separately in models 2, 3 and 4. All pre-existing medical conditions were found to be significantly associated with

maternal death at $P < 0.05$ using univariable analyses, hence all 16 variables were included in a multivariable model (model-5).

We tested for plausible interactions by fitting interaction terms into the multivariable model-1 followed by likelihood ratio testing (LR-test). No significant interactions were identified. Missing information was $<1\%$ for seven variables, but higher for BMI, employment status, smoking, previous pregnancy problems, and anaemia and gestational diabetes during current pregnancy. Data were not assumed to be missing at random based on the findings of previous studies^{21,26} and a proxy variable was generated by categorising the missing data as a separate group for each variable. Sensitivity analysis was conducted for variables with $>1\%$ missing information by redistributing the missing observations into the different categories of the variables.

Employing the method used in a previous study,² we generated a risk factor score by assigning a score of one to each factor found to be significantly associated with increased odds of maternal death in the multivariable logistic regression analysis. This was used to estimate the incremental odds of maternal mortality in the UK associated with the presence of one or more risk factors. We calculated the population attributable fraction for the 'risk factors' score and the individual factors using standard methods for calculating population attributable fraction in case-control studies.²⁷ All analyses were performed using STATA version 13.1, SE (StataCorp, College Station, TX, USA).

Results

Multivariable logistic regression analysis (model 1) identified seven factors that were independently associated with increased odds of maternal death in the UK (Table 1), and that explained 36% of the variance in the outcome. The odds of maternal death (from direct or indirect causes) in the UK was almost nine-fold higher among women who had a pre-existing medical condition compared with women who did not (adjusted odds ratio [aOR] 8.65; 95% CI 6.29–11.90) and was more than three and a half times higher among women who had anaemia during their current pregnancy (aOR 3.58; 95% CI 1.14–11.21). Inadequate use of antenatal care (aOR 46.85; 95% CI 19.61–111.94) and previous pregnancy problems (aOR 1.85; 95% CI 1.33–2.57) were significantly associated with higher odds of maternal death. Women who were known substance misusers had more than 12 times the odds of death (aOR 12.21; 95% CI 2.33–63.98) and being unemployed was associated with almost twice the odds of death (aOR 1.81; 95% CI 1.08–3.04). The odds of maternal death increased linearly by 6% per year increase in maternal age (Table 1) after adjusting for the other risk factors for maternal death.

Table 1. Factors associated with direct and indirect maternal deaths in the UK in 2009–13 (Model-1*)

Risk factors	No. of cases (%) <i>n</i> = 383	No. of controls (%) <i>n</i> = 1516	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Pregnancy related factors				
Parity				
Nulliparous	132 (34.4)	652 (43.0)	1 (Ref)	*****
Multiparous	222 (58.0)	839 (55.3)	1.31 (1.03–1.66)	
Grand-multiparous	21 (5.5)	25 (1.7)	4.15 (2.26–7.63)	
Missing	8 (2.1)	0 (0)		
Multiple pregnancy during current pregnancy				
No	365 (95.3)	1495 (98.6)	1 (Ref)	1 (Ref)
Yes	10 (2.6)	21 (1.4)	1.95 (0.91–4.18)	1.96 (0.71–5.38)
Missing	8 (2.1)	0 (0)	Omitted	Omitted
Gestational diabetes during current pregnancy				
No	327 (85.4)	1471 (97.0)	1 (Ref)	1 (Ref)
Yes	20 (5.2)	39 (2.6)	2.31 (1.33–4.01)	1.30 (0.62–2.73)
Missing	36 (9.4)	6 (0.4)	27.0 (11.28–64.59)	Omitted
Anaemia during current pregnancy				
No	336 (87.7)	1498 (98.8)	1 (Ref)	1 (Ref)
Yes	11 (2.9)	12 (0.8)	4.09 (1.79–9.34)	3.58 (1.14–11.21)
Missing	36 (9.4)	6 (0.4)	26.75 (11.18–64.00)	Omitted
Inadequate use of antenatal care***				
No	276 (72.1)	1503 (99.1)	1 (Ref)	1 (Ref)
Yes	106 (27.7)	7 (0.5)	82.46 (37.97–179.09)	46.85 (19.61–111.94)
Missing	1 (0.3)	6 (0.4)	0.91 (0.11–7.57)	Omitted
Previous pregnancy problems*****				
No	213 (55.6)	1244 (82.1)	1 (Ref)	1 (Ref)
Yes	150 (39.2)	268 (17.7)	3.27 (2.55–4.19)	1.85 (1.33–2.57)
Missing	20 (5.2)	4 (0.3)	29.20 (9.88–86.27)	0.91 (0.09–9.76)
Pre-existing medical problems*****				
No	91 (23.8)	1189 (78.4)	1 (Ref)	1 (Ref)
Yes	278 (72.6)	324 (21.4)	11.21 (8.59–14.64)	8.65 (6.29–11.90)
Missing	14 (3.6)	3 (0.2)	60.97 (17.21–216.05)	12.51 (1.80–86.85)
Body mass index (kg/m²)				
<18.5	9 (2.4)	27 (1.8)	1.63 (0.75–3.54)	2.08 (0.80–5.44)
18.5–24	147 (38.4)	719 (47.4)	1 (Ref)	1 (Ref)
25–29	83 (21.7)	403 (26.6)	1.01 (0.75–1.35)	0.83 (0.56–1.22)
≥30	107 (27.9)	323 (21.3)	1.62 (1.22–2.15)	1.14 (0.78–1.68)
Missing	37 (9.7)	44 (2.9)	4.11 (2.57–6.59)	1.33 (0.62–2.86)
Sociodemographic factors				
Maternal age (years)				
Median age (interquartile range)	29 (25–33)	31 (26–36)	1.06 (1.04–1.08)	1.06 (1.04–1.09)
Five-year age bands**				
<20	17 (4.4)	101 (6.7)	0.94 (.52–1.72)	0.84 (0.36–1.99)
20–24	49 (12.8)	275 (18.1)	1 (Ref)	1 (Ref)
25–29	86 (22.5)	433 (28.6)	1.11 (0.76–1.63)	1.23 (0.72–2.12)
30–34	105 (27.4)	429 (28.3)	1.37 (0.95–1.99)	1.86 (1.10–3.15)
35–39	93 (24.3)	205 (13.5)	2.55 (1.72–3.76)	2.83 (1.62–4.95)
≥40	33 (8.6)	70 (4.6)	2.65 (1.58–4.42)	2.53 (1.25–5.15)
Missing	0 (0)	3 (0.2)	Omitted	Omitted
Smoking status				
Non-smoker	238 (62.1)	1181 (77.9)	1 (Ref)	1 (Ref)
Smoker	95 (24.8)	324 (21.4)	1.45 (1.11–1.90)	0.91 (0.61–1.36)
Missing	50 (13.1)	11 (0.7)	22.56 (11.57–43.96)	11.65 (4.50–30.17)
Substance misuse****				
No	347 (90.6)	1508 (99.5)	1 (Ref)	1 (Ref)
Yes	30 (7.8)	2 (0.1)	65.02 (16.37–564.08)	12.21 (2.33–63.98)
Missing	6 (1.6)	6 (0.4)	4.34 (1.15–16.34)	Omitted

Table 1. (Continued)

Risk factors	No. of cases (%) <i>n</i> = 383	No. of controls (%) <i>n</i> = 1516	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Employment status				
Employed	236 (61.6)	1118 (73.7)	1 (Ref)	1
Unemployed	60 (15.7)	101 (6.7)	2.81 (1.99–3.99)	1.81 (1.08–3.04)
Missing	87 (22.7)	297 (19.6)	1.39 (1.05–1.83)	0.63 (0.40–0.97)
Ethnicity				
White European	277 (72.3)	1216 (80.2)	1 (Ref)	1 (Ref)
Indian	17 (4.4)	59 (3.9)	1.26 (0.73–2.20)	1.56 (0.77–3.19)
Pakistani	19 (4.9)	61 (4.0)	1.37 (0.80–2.33)	1.90 (0.96–3.76)
Bangladeshi	6 (1.6)	19 (1.3)	1.39 (0.55–3.50)	1.75 (0.51–6.03)
Other Asian	7 (1.8)	40 (2.6)	0.77 (0.34–1.73)	0.55 (0.19–1.57)
Black Caribbean	6 (1.6)	19 (1.3)	1.39 (0.55–3.50)	2.08 (0.58–7.48)
Black African	33 (8.6)	57 (3.8)	2.54 (1.62–3.98)	1.71 (0.89–3.25)
Others/Mixed	18 (4.7)	45 (2.9)	1.76 (1.00–3.08)	1.11 (0.51–2.41)

*Model 1 includes all variables specified in the table except parity, which was significantly correlated with previous pregnancy problems.

**The ordered categorical variable for maternal age was analysed in a separate model.

***Inadequate use of antenatal care: women who concealed pregnancy, were late bookers (>12 weeks) or did not receive minimal antenatal care.

****For substance misuse, Fishers Exact test for univariable analysis was conducted;

*****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, puerperal psychosis.

*****Pre-existing medical problems: women who were reported to have any medical comorbidity during current pregnancy including the 16 specific conditions; Women were categorised as having gestational diabetes and anaemia during current pregnancy based on clinician recorded information in the medical records.

*****Excluded from the final model due to collinearity with previous pregnancy problems.

Obesity, gestational diabetes during current pregnancy, smoking and belonging to minority ethnic backgrounds were significantly associated with increased odds of death during univariable analysis, but their effects were attenuated after adjusting for other risk factors. Pre-existing medical problems explained the apparent adverse effects of obesity and gestational diabetes during the current pregnancy. The observed higher odds of death among women who smoked decreased after adjusting for substance misuse, suggesting that it is the substance misusers among the smokers who are at an increased risk of dying. Univariable analysis showed that compared with white European women, the odds of dying was two and a half times higher among women from black African ethnic backgrounds (Table 1). However, on adding the variables gestational diabetes during current pregnancy, medical comorbidities, previous pregnancy problems and inadequate use of antenatal care, the adjusted odds ratio decreased towards null and was not significant at the 5% level, suggesting that these factors explained a substantial proportion of the increased odds of death among the black African women. Although not statistically significant, the odds ratios were raised for all ethnic minority groups.

Analysis of the risk factor score showed that 5% (*n* = 19) of the cases had none of the seven identified risk factors compared with 33% (*n* = 506) of the con-

trols. Among the cases 21% (*n* = 79), 34% (*n* = 131), 26% (*n* = 101) and 11% (*n* = 43) had one, two, three and four of these risk factors, respectively compared with 44% (*n* = 671), 18% (*n* = 273), 4% (*n* = 63) and 0.2% (*n* = 3) for the controls. Ten cases (3%) had five risk factors, but none of the controls had more than four risk factors. The probability of death increased linearly with increase in the number of risk factors (Figure 1). There was an almost four-fold increase in the odds of death per unit increase in the number of risk factors (aOR 3.82; 95% CI 3.28–4.45; *P* < 0.001 for trend) after adjusting for other variables not included in the risk factor score. At a population level, 87% of the increased risk of maternal death in the UK could be attributed to the seven identified risk factors, the most important ones being medical comorbidities, maternal age ≥ 30 years and inadequate use of antenatal care services (Table 2). The calculated population attributable fractions for individual risk factors add up to more than 100% (Table 2) because several women had more than one risk factor.²⁸ In addition, multivariable regression model 5 showed that after adjusting for the other associated factors, 13 of the 16 specific medical comorbidities examined were associated with increased odds of maternal death (see Supplementary material, Table S1).

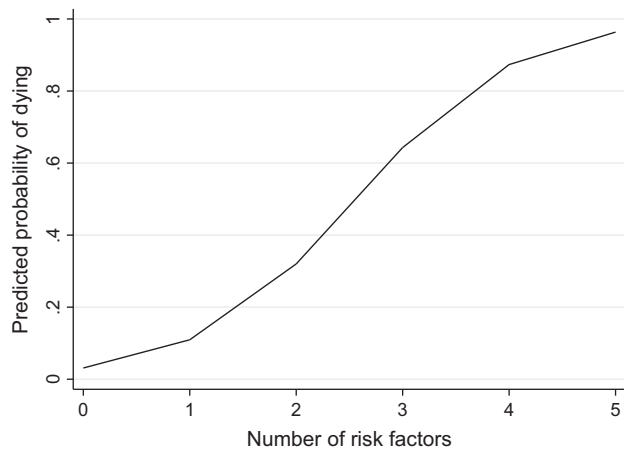


Figure 1. Incremental risk of death associated with an increase in the number of independent risk factors.

Table 2. Population attributable fractions (PAF) for factors associated with increased risk of death

Risk factors	PAF (%)	95% CI (%)
All seven risk factors combined	87	85–89
Specific factors		
Medical comorbidities	66	63–68
Age ≥ 30 years	29	19–38
Inadequate use of antenatal care	24	23–25
Previous pregnancy problems	19	8–28
Substance misuse	7	5–8
Anaemia during current pregnancy	2	1–3
Being unemployed	1	0.8–9

Investigation of the association of newborn outcomes with maternal death in models 2, 3 and 4 showed that after adjusting for known risk factors, the odds of stillbirth, admission to NICU and death during the early neonatal period were higher among women who died compared with women who did not (Table 3). Among the women who died, 54 (14%) had a peri-mortem caesarean section giving birth to 55 babies of which 26 (47%) were stillborn. Repeating the multivariable logistic regression analysis after removing the cases who had a peri-mortem caesarean section still showed a significant association between maternal death and stillbirth (aOR 43.1; 99% CI 9.2–201.9, $P < 0.001$).

Results of the sensitivity analysis for missing data were not different from the outputs of the multivariable model 1 for smoking, BMI, gestational diabetes during current pregnancy and anaemia during current pregnancy. However, re-grouping the pregnant women with missing information about employment status as 'employed' significantly increased the odds of death among the unemployed

(adjusted OR 2.04, 95% CI 1.23–3.38), whereas re-grouping them as 'unemployed' reduced the odds (aOR 0.91, 95% CI 0.63–1.31), but this was not statistically significant at $P < 0.05$. Sensitivity analyses for missing information on stillbirth, NICU admission and early neonatal death did not change the observed associations between maternal death and these outcomes.

Discussion

Main findings

We found seven factors to be associated with direct and indirect maternal deaths in the UK in 2009–13: medical comorbidities, anaemia during current pregnancy, inadequate use of antenatal care services, previous pregnancy problems, substance misuse, being unemployed and increasing maternal age. These factors together contributed to 87% of the increased risk of maternal death from direct and indirect causes at the population level. Almost two-thirds of the risk of maternal death from direct and indirect causes could be attributed to medical comorbidities and 13 specific conditions were found to be associated with these deaths although these were not necessarily the actual causes of death. The risk of stillbirth, admission to NICU and deaths during the early neonatal period was higher among the babies of women who died compared with women who did not.

Strengths and limitations

We were able to use 5 years of national data on maternal deaths from the MBRRACE-UK and compare these with data from women who had an uncomplicated pregnancy and childbirth during 2009–13 to identify the factors that increase the risk of maternal deaths. The cases and controls were from the same source population, which makes this comparison valid and the findings are generalisable to all direct and indirect maternal deaths within 42 days of the end of pregnancy in the UK. However, we acknowledge that hospital controls are a higher risk group, so we are likely to have underestimated the true risks from maternal comorbidities, inadequate antenatal care and the other factors found to be significantly associated with maternal deaths in the UK.

Although the variables included in this study were comparable for the cases and controls, we cannot rule out bias due to the different data sources. We demonstrated an association between maternal death and stillbirth, NICU admission and early neonatal death, but there is a high degree of uncertainty around the estimated odds ratios due to the low number of these adverse outcomes among women who had an uncomplicated pregnancy and childbirth. Medical comorbidities and anaemia during current pregnancy are based on clinician-reported general history, which does not define the severity and nature of these con-

Table 3. Fetal and infant outcomes for women who died compared with women with normal pregnancy

Fetal outcomes	Mother died, <i>n</i> (%)	Mother alive, <i>n</i> (%)	Unadjusted OR (99% CI)	Adjusted OR* (99% CI)
Stillbirth (model 2)**	<i>n</i> = 383	<i>n</i> = 1516		
No	285 (74.4)	1507 (99.4)	1 (Ref)	1 (Ref)
Yes	54 (14.1)	5 (0.3)	34.0 (10.1–172.9)	43.1 (9.2–201.9)
Missing	44 (11.5)	4 (0.3)		
Admission to NICU (model 3)***	<i>n</i> = 329	<i>n</i> = 1511		
No	185 (56.2)	1399 (92.6)	1 (Ref)	1 (Ref)
Yes	100 (30.4)	107 (7.1)	7.1 (4.6–10.8)	7.0 (3.9–12.6)
Missing	44 (13.4)	5 (0.3)		
Death during infancy (model 4)***	<i>n</i> = 329	<i>n</i> = 511		
No	263 (79.9)	1503 (99.5)	1 (Ref)	1 (Ref)
Yes	14 (4.3)	3 (0.2)	26.6 (5.4–268.6)	38.8 (5.1–297.3)
Missing	52 (15.8)	5 (0.3)		

*Each outcome was tested in a separate multivariable analysis that controlled for all factors included in Table 1 as well as parity and hypertensive disorders during current pregnancy, all associations were significant at $P < 0.001$.

**Analysis of stillbirth was restricted to women who did not have a perimortem caesarean section.

***Analyses for admission to NICU and death during infancy were restricted to women who did not have a stillbirth.

ditions, therefore additional studies are required for an in-depth investigation.

Interpretation (in light of other evidence)

The findings of this study are comparable to two previous studies that examined the risk factors associated with progression from severe maternal morbidity to death in the UK;^{1,2} however, this study includes all maternal deaths in the UK that resulted from direct or indirect causes during a period of 5 years (2009–13) and investigates the factors associated with maternal death compared with a general population of pregnant women. Similar to the study by Kayem et al.¹ we found that increasing maternal age and being unemployed increased the odds of dying during pregnancy and childbirth, but we did not find obesity to be associated with mortality per se. As was observed in a previous study, the effect of obesity was mainly mediated by medical comorbidities.² Belonging to minority ethnic backgrounds has been demonstrated to be associated with progression from severe morbidity to death in the UK;^{1,2} although we observed an increased odds of death among women from all minority ethnic groups compared with white European women, these associations were not statistically significant. Other findings such as increased odds of medical comorbidities, inadequate use of antenatal care, previous pregnancy problems and substance misuse among women who died have been shown to be important risk factors for maternal death in the UK^{2,29} and in other studies conducted in different countries.^{21,30–33}

Although we found a significant association between anaemia during current pregnancy and maternal deaths from direct and indirect causes in the UK, the previous study that examined the factors associated with progression

from severe morbidity to death did not find a significant association, although the adjusted odds ratio was 2.39 (95% CI 0.60–9.47).² The quality of the available evidence about the specific clinical outcomes of maternal anaemia is low to moderate, but studies have shown iron deficiency anaemia to be associated with increased risk of maternal sepsis³⁴ and postpartum haemorrhage,^{35,36} which are direct causes of maternal death in the UK. Compared with the suggested high prevalence of iron deficiency anaemia (24%) among pregnant women in the UK,³⁷ we found a smaller proportion of our study population to be diagnosed as having anaemia. Therefore, if anaemia is underdiagnosed, it could actually be associated with a higher population-attributable fraction than observed.

As shown by studies from the UK and other countries, individual medical comorbidities such as pre-existing asthma, autoimmune diseases, inflammatory disorders and allergic/atopic conditions, cardiac disease, diabetes mellitus, epilepsy, haematological disorders, essential hypertension, infection, musculoskeletal disorders, mental health problems, renal problems and thrombotic events were associated with maternal mortality^{20,38–44} and 66% of the risk of death from direct and indirect causes could be attributed to these conditions.

A study from Ethiopia that examined survival among neonates whose mothers died immediately or shortly after the end of pregnancy, found that children whose mothers die were 57 times more likely to die compared with those whose mothers survived after adjusting for socio-economic and maternal demographic factors.⁴ The high risk of neonatal death was observed for maternal deaths within 42 days of the end of pregnancy as well as late deaths (after 42 days and before 1 year of end of pregnancy).⁴ Other studies from

a number of low- and middle-income countries have also shown similar higher risk of death among infants and children whose mothers die.^{5,6} McClure et al.⁷ used data from 188 countries to examine the relationship between maternal deaths and stillbirths. The study showed a significant strong correlation ($r = 0.72$; $P < 0.001$) between maternal death and stillbirth with an overall 4.6 stillbirths for every maternal death along with a clear disparity in this correlation between high-income and low- and middle-income countries (high-income countries 16.7 stillbirths per maternal death; low- and middle-income countries 4.8 stillbirths per maternal death).⁷ Although this study showed a correlation, we were also able to conduct a multivariable logistic regression analysis using national data, which demonstrated a 43 times higher odds of stillbirth among women who died compared with women who were alive.

Conclusion

This national study demonstrates that seven factors, namely, medical comorbidities, increasing maternal age, inadequate use of antenatal care services, previous pregnancy problems, anaemia during current pregnancy, substance misuse and being unemployed, are associated with 87% of the increased risk of maternal deaths from direct and indirect causes at a population level in the UK. Reported high prevalence of iron deficiency anaemia among pregnant women in the UK suggests the need for further research to examine how different types of anaemia and their grade of severity are associated with maternal morbidity and mortality to develop clinical and policy guidance. Although statistically we were able to explain the higher odds of maternal death among ethnic minority groups (particularly among women from black African backgrounds) as being mediated by factors such as gestational diabetes, medical comorbidities, previous pregnancy problems and inadequate use of antenatal care, these women should still be considered a high-risk group. The study reiterates the need for optimal care for women with medical comorbidities and increasing maternal age across the entire pregnancy care pathway, and the importance of adequate use of antenatal care services, but it also demonstrates the continuing existence of socio-economic inequalities in maternal death in the UK.

Disclosure of interest

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

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

conceived and designed the study, contributed to the analysis plan and to the writing of 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).

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Supporting Information

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

Table S1. Medical co-morbidities associated with direct and indirect maternal deaths (Model-5*). ■

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