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RESEARCH ARTICLE

Maternal Medicine

Maternal race and pre-eclampsia: Cohort study and systematic review with meta-analysis

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Abstract

Objectives: To examine the association between race and pre-eclampsia and gestational hypertension after adjustment for factors in maternal characteristics and medical history in a screening study from the Fetal Medicine Foundation (FMF) in England, and to perform a systematic review and meta-analysis of studies on pre-eclampsia.

Design: Prospective observational study and systematic review with meta-analysis.

Setting: Two UK maternity hospitals.

Population: A total of 168 966 women with singleton pregnancies attending for routine ultrasound examination at 11–13 weeks of gestation without major abnormalities delivering at 24 weeks or more of gestation.

Methods: Regression analysis examined the association between race and pre-eclampsia or gestational hypertension in the FMF data. Literature search to December 2021 was carried out to identify peer-reviewed publications on race and pre-eclampsia.

Main outcome measure: Relative risk of pre-eclampsia and gestational hypertension in women of black, South Asian and East Asian race by comparison to white women.

Results: In black women, the respective risks of total-pre-eclampsia and preterm-pre-eclampsia were 2-fold and 2.5-fold higher, respectively, and risk of gestational hypertension was 25% higher; in South Asian women there was a 1.5-fold higher risk of preterm pre-eclampsia but not of total-pre-eclampsia and in East Asian women there was no statistically significant difference in risk of hypertensive disorders. The literature search identified 19 studies that provided data on several million pregnancies, but 17 were at moderate or high-risk of bias and only three provided risks adjusted for some maternal characteristics; consequently, these studies did not provide accurate contributions on different racial groups to the prediction of pre-eclampsia.

Conclusion: In women of black and South Asian origin the risk of pre-eclampsia, after adjustment for confounders, is higher than in white women.

KEYWORDS
first-trimester screening, gestational hypertension, meta-analysis, pre-eclampsia, race, systematic review

Tweetable abstract: In women of black and South Asian origin the risk of pre-eclampsia, after adjustment for factors in maternal characteristics and medical history, is higher than in white women.

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1 | INTRODUCTION

Pre-eclampsia, which complicates 2%–4% of pregnancies, is associated with a global annual rate of about 46 000 maternal deaths and 500 000 infant deaths.[1,2] The risk for development of pre-eclampsia is related to several maternal characteristics, including age, weight, race, method of conception, personal history and family history of pre-eclampsia, and pre-existing medical conditions, such as chronic hypertension, diabetes mellitus and autoimmune disease.[3]

Studies from countries with populations that are of predominantly white race have consistently reported that in minority groups, such as women of black race, the incidence of pre-eclampsia is increased.[4–19] In a small number of studies the incidence of pre-eclampsia in women of East Asian race tended to be lower than in white women, whereas in South Asian women the incidence tended to be similar to that in white women.[9,12,15,16,20–22] However, in most of these studies the observed relative incidence of pre-eclampsia was not adjusted for confounding factors in maternal characteristics and medical history. In a previous study of 76 158 singleton pregnancies with a live fetus at 11^{+0} to 13^{+6} weeks of gestation, we adjusted for confounders and reported that in women of black and South Asian race, but not in East Asian women, the incidence of pre-eclampsia was higher than in white women.[23]

The objectives of this extended study of 168 966 singleton pregnancies with a live fetus at 11^{+0} to 13^{+6} weeks of gestation are, first, to examine the association between maternal race and pre-eclampsia after adjustment for confounding factors in maternal demographic characteristics and medical history in the data from the Fetal Medicine Foundation (FMF), and second, to carry out a systematic review of the literature and meta-analysis of all studies on this topic.

2 | METHODS

2.1 | Fetal Medicine Foundation Study

2.1.1 | Study design and participants

The data were derived from prospective screening for pregnancy complications in women with singleton pregnancies attending their first routine hospital visit at 11^{+0} to 13^{+6} weeks of gestation at King's College Hospital, London or Medway Maritime Hospital, Kent from March 2006 to November 2020. The visit included the recording of maternal demographic characteristics and medical history, measurement of maternal weight and height, and ultrasound examination for the measurement of the fetal crown–rump length to determine gestational age,[24] measurement of the fetal nuchal translucency thickness, as part of screening for trisomies,[25] and examination of the fetal anatomy for the diagnosis of major fetal defects.[26]

Participants completed a questionnaire, which was then reviewed by a doctor together with the woman. In the case of language barrier, services of professional translation were offered to the participants. Patient characteristics included maternal age, race (white, black, South Asian, East Asian, and mixed), method of conception (natural or assisted by in vitro fertilisation or use of ovulation drugs), cigarette smoking during pregnancy, medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS), family history of pre-eclampsia in the mother of the patient and obstetric history that included parity (parous or nulliparous if no previous pregnancies at ≥24 weeks of gestation), previous pregnancy with pre-eclampsia and previous pregnancy with delivery of small-for-gestational-age (SGA) neonate with birthweight below the 10th centile of the FMF fetal and neonatal population weight charts.[27] In relation to race, the patients were asked to choose one of white, black, South Asian, East Asian, or mixed and they were also asked to record the country of origin of each parent.

The inclusion criteria for this study were singleton pregnancies delivering a non-malformed live birth or stillbirth at 24 weeks or more of gestation. We excluded pregnancies involving aneuploidies and major fetal abnormalities. Women gave written informed consent to take part in the study, which was approved by the NHS Research Ethics Committee. There was no patient involvement in the design of the study.

2.1.2 | Outcome measures

Outcome measures were delivery with pre-eclampsia or gestational hypertension. Data on pregnancy outcome were collected from the hospital maternity records or the general medical practitioners of the women. The obstetric records of all women with chronic hypertension or pregnancy-associated hypertension were examined to determine the diagnosis of pre-eclampsia or gestational hypertension. Diagnosis of gestational hypertension was based on the finding of hypertension (systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg on at least two occasions 4 hours apart developing after 20 weeks of gestation in previously normotensive women). Diagnosis of pre-eclampsia was based on the finding of new onset hypertension or chronic hypertension and at least one of the following: proteinuria (≥300 mg/24 h or protein to creatinine ratio ≥30 mg/mmol or ≥2+ on dipstick testing), renal insufficiency with serum creatinine greater than 97 μmol/l in the absence of underlying renal disease, hepatic dysfunction with blood concentration of transaminases more than twice the upper limit of normal (≥65 IU/l for our laboratory), thrombocytopenia (platelet count <100 000/μl), neurological complications (e.g. cerebral or visual symptoms), or pulmonary oedema.[28]

2.1.3 | Statistical methods

Data were expressed as mean (standard deviation) for continuous variables and *n* (%) for categorical variables. Student's

t test and chi-square test or Fisher's exact test, were used for comparing outcome groups for continuous and categorical data, respectively.

Univariable logistic regression analysis was performed to examine the association between race and pre-eclampsia and gestational hypertension; we used white racial group as the reference for three reasons: first, it represents the majority of our population, second, it allows comparisons with other studies and pooling of the results and third, it is the group with the lowest risk for the outcomes studied. Multiple logistic regression analysis was performed for modelling total pre-eclampsia, preterm pre-eclampsia with delivery before 37 weeks of gestation, early pre-eclampsia with delivery before 34 weeks and total gestational hypertension using race, maternal age, weight, height, mode of conception, smoking, history of chronic hypertension, diabetes mellitus, APS or SLE, history of pre-eclampsia in a previous pregnancy or family history of pre-eclampsia. Before performing the multiple regression analysis, continuous variables were centred by subtracting the median from each measured value (67 from maternal weight in kg, 1.65 from maternal height in meters and 30 from maternal age in years).

The statistical software R was used for data analyses.[29]

2.2 | Systematic review and meta-analysis

2.2.1 | Literature search and study selection

Searches of Ovid Medline, Embase, CENTRAL (The Cochrane Library), Cinahl and Emcare were carried out to identify studies reporting on race and pre-eclampsia. The search was carried out on 10 August 2021 with no restriction for starting date but was restricted to English language records only; the initial search was updated with autoalerts in Medline to 31 December 2021. A list of relevant citations was generated from these databases using the search strategies given in Appendix 1. This review was registered in the PROSPERO international database for systematic reviews (reference: CRD42021267548).

The abstracts of citations were examined by two reviewers (AA and DV) to identify all potentially relevant articles, which were then examined in full-text form. Reference lists of relevant original and review articles were hand-searched for additional reports. Agreement about potential relevance was reached by consensus and by consultation with a third reviewer (KHN). The inclusion criteria were peer-reviewed studies reporting on pre-eclampsia in singleton pregnancies according to the race of women so that the rate of pre-eclampsia in black and South and East Asian women could be compared with the rate in white women. We excluded twin pregnancies, case–control studies and review articles or guidelines and articles in which pre-eclampsia and gestational hypertension were not given separately.

2.2.2 | Data extraction and meta-analysis of data from all studies

Data were obtained from each study included in the systematic review and documented in contingency tables. We extracted the necessary data to calculate the incidence of pre-eclampsia in white women and in each other racial group. Whenever possible, we extracted the reported relative risk (RR) or odds ratio (OR) and 95% CI from each study. Where available we extracted separate relative risk estimates with different degrees of confounder adjustment for the following prespecified conventional risk factors: age, weight and height or body mass index, smoking status and parity. First, we used raw data to adjust random effect models for meta-analyses using inverse variance method for pooling and DerSimonian–Laird to estimate the between-study variance (τ^2). Second, we used adjusted odds ratio from the included studies to also adjust the random effect model for meta-analysis with inverse variance for pooling but, in this case, we used restricted maximum-likelihood estimator for the between-study variance estimation. Restricted maximum-likelihood estimator is a variation of the maximum likelihood used to correct the negative bias associated with the latter. It uses the Fisher scoring algorithm to iteratively search the value for which the change in τ^2 estimate is smaller than 10^{-5} from one iteration to the next.[30] The pooled relative risk and/or pooled odds ratio with 95% CI were estimated for race as a predictor for pre-eclampsia, using adjusted analysis as reported in the studies and a random effects model that considers both within-study and between-study variation.[31] Statistical heterogeneity among studies was evaluated using the I^2 and τ^2 statistics and the p value of the chi-square test of Q.[32] I^2 is the fraction of variance across studies that is due to heterogeneity and not due to chance; a large value of I^2 is interpreted as meaning that the effect size varies substantively across studies (less than 50 is generally considered low to intermediate and more than 75 would represent considerable heterogeneity). The I^2 value must be interpreted together with the p value. Finally, τ^2 statistics is a measure of the extent of variation, or heterogeneity, among the intervention effects observed in different studies and it is used to estimate the prediction intervals.[33] The prediction interval is an index of dispersion. It tells us how widely the effect size varies across studies and it is a property of the population, not the sample. Unlike the confidence interval, the true prediction interval stays constant regardless of how many studies we include in the analysis, although the estimate of the prediction interval will change as we add information.[34]

Publication bias, when the minimum number of included studies was ten, was assessed by plotting the relative risk estimate against precision (funnel plots).[35] A funnel plot is a scatter plot of individual studies, their precision and results. Each dot represents a study and their distribution should resemble a pyramid or inverted funnel. In the absence of publication bias, one would expect to see an even scattering of trials either side of this true underlying effect. When there

is publication bias, an asymmetry in the scatter of smaller studies (at the bottom of the pyramid) is expected.[35,36]

Risk of bias assessment was made with quality in prognostic studies (QUIPS) tool[37] presented and adjusted for this review. The following six domains were used: representativeness of study population, adequateness of follow-up period and attrition, appropriateness of race classification, appropriateness of the definition of the outcome (pre-eclampsia), adequateness of statistical analysis and reporting. Each element was classified as low, moderate or high risk of bias. If two of the domains were assessed as having high risk of bias or four of the domains were assessed as having moderate risk of bias, then the overall risk of bias for a study was graded as high risk of bias. If three of the domains were assessed as having moderate risk of bias, or one domain was at high risk of bias and one was at moderate risk then the overall risk of bias was graded as moderate risk of bias. If all the domains within a study were graded as low risk of bias, or less than three were moderate and none was high, then the overall judgement for the study was low risk of bias.

Statistical software R[29] was used in all analyses, packages 'meta'[38] and 'metafor'[30] were used for the meta-analysis and package 'car'[39] was used to clean the data.

3 | RESULTS

3.1 | Fetal Medicine Foundation study

3.1.1 | Study population

In the FMF study there were 168 966 singleton pregnancies with a live fetus at 11^{+0} to 13^{+6} weeks of gestation without major abnormalities that delivered at 24 weeks or more of gestation. In addition, there were 5406 (3.1% of the total) that were lost to follow up. The characteristics of the study population are summarised in Table 1. There were 127 762 (75.6%) white women, 25 749 (15.2%) black women, 7834 (4.6%) South Asian women, 3218 (1.9%) East Asian women and 4403 (2.6%) women of mixed origin. According to the Office for National Statistics, the distribution of racial groups in England and Wales in 2019 was white 84.8%, Asian 8%, black 3.5% and mixed 1.8%.[40]

The pregnancies included 4272 women that developed pre-eclampsia, 4344 that developed gestational hypertension and 160 350 that did not develop either pre-eclampsia or gestational hypertension. In the women of black race, compared with white women, there was a higher median weight, higher incidence of pre-eclampsia and gestational hypertension, chronic hypertension, type 2 diabetes mellitus and SLE or APS, and higher incidence of pre-eclampsia and SGA in a previous pregnancy, and lower incidence of conception using assisted reproductive technologies and lower incidence of nulliparity. In the women of South Asian race, compared with white women, there was a higher incidence of preterm pre-eclampsia, chronic hypertension, type 2 diabetes mellitus and SLE or APS, conception by in vitro fertilisation and higher incidence of SGA in a previous pregnancy. In the women of East Asian race, compared with white women, there was a lower median weight, lower incidence of gestational hypertension, smoking and incidence of pre-eclampsia in a previous pregnancy, and a higher incidence of diabetes mellitus type 2 and previous SGA.

In the women of black race the country of origin of their parents was one of the Caribbean countries in 39%, Nigeria or Ghana in 35%, and other African countries in 26%. In the South Asian women the country of origin of their parents was India in 44%, Pakistan in 15%, Bangladesh in 13%, Sri Lanka in 8% and other in 20%. In the East Asian women the country of origin of their parents was China in 40%, Japan in 17%, the Philippines in 14%, Vietnam in 12% and other in 17%.

3.1.2 | Odds ratio for pre-eclampsia and gestational hypertension

The results of univariable and multiple logistic regression analysis demonstrating the association of maternal race with pre-eclampsia and gestational hypertension are shown in Table 2. The univariable logistic regression analysis demonstrated that first, women of black race, compared with white women, had statistically significantly higher rates of all pre-eclampsia, preterm pre-eclampsia, early pre-eclampsia and gestational hypertension. Second, women of South Asian origin, compared with white women, had statistically significantly higher rates of preterm pre-eclampsia and early pre-eclampsia, but not all pre-eclampsia or gestational hypertension. Third, women of East Asian origin, compared with white women, had statistically significantly lower rate of gestational hypertension, but not different rates for all pre-eclampsia, preterm pre-eclampsia or early pre-eclampsia, and fourth, women of mixed origin, compared with white women, had no statistically significantly different rates for all pre-eclampsia, preterm pre-eclampsia, early pre-eclampsia or gestational hypertension. The effect of race on pre-eclampsia was attenuated by adjustment.

3.2 | Systematic review and meta-analysis

3.2.1 | Data sources

The search identified 3654 potentially relevant citations, but 3635 were excluded because they were non-relevant articles, abstracts or letters rather than peer-reviewed papers, case–control studies, review articles, opinions or guidelines, studies providing data on a mixture of singleton and twin pregnancies or a mixture of pre-eclampsia and gestational hypertension, and studies on parts of the same population (Figure 1). In total, only 19 studies were considered to be relevant and their data were combined with ours for the

TABLE 1 Characteristics of the study population

Characteristic	White (*n* = 127 762)	Black (*n* = 25 749)	*p* Value	South Asian (*n* = 7834)	*p* Value	East Asian (*N* = 3218)	*P* Value	Mixed (*n* = 4403)	*p* Value
Hypertensive disease									
Total pre-eclampsia	2708 (2.1)	1228 (4.8)	<0.001	185 (2.4)	0.162	63 (2.0)	0.570	88 (2.0)	0.855
Pre-eclampsia at <37 weeks	618 (0.5)	388 (1.5)	<0.001	65 (0.8)	<0.001	13 (0.4)	0.519	21 (0.5)	0.949
Gestational hypertension	3135 (2.5)	862 (3.3)	<0.001	179 (2.3)	0.367	61 (1.9)	0.049	107 (2.4)	0.960
Age (years)	31.2 (26.8–35.0)	30.6 (26.5–34.9)	<0.001	31.5 (28.1–34.9)	<0.001	32.6 (29.1–36.1)	<0.001	30.5 (25.5–34.6)	<0.001
Height (cm)	165 (161–170)	165 (160–169)	<0.001	160 (155–163)	<0.001	160 (156–164)	<0.001	164 (160–169)	<0.001
Weight (kg)	67.0 (59.7–77.0)	73.5 (64.0–85.0)	<0.001	61.0 (54.6–70.0)	<0.001	57.0 (52.0–63.8)	<0.001	66.0 (59.0–76.0)	<0.001
Conception by IVF	3642 (2.9)	265 (1.0)	<0.001	273 (3.5)	0.001	110 (3.4)	0.064	93 (2.1)	0.004
Conception after ovulation drugs	1360 (1.1)	170 (0.7)	<0.001	84 (1.1)	0.993	29 (0.9)	0.420	23 (0.5)	<0.001
Smoking	13 855 (10.8)	1020 (4.0)	<0.001	90 (1.1)	<0.001	44 (1.4)	<0.001	432 (9.8)	0.032
Chronic hypertension	1182 (0.9)	891 (3.5)	<0.001	101 (1.3)	0.002	20 (0.6)	0.091	44 (1.0)	0.671
Diabetes mellitus type 1	622 (0.5)	62 (0.2)	<0.001	21 (0.3)	0.008	5 (0.2)	0.010	15 (0.3)	0.205
Diabetes mellitus type 2	541 (0.4)	519 (2.0)	<0.001	200 (2.6)	<0.001	37 (1.1)	<0.001	33 (0.7)	0.002
SLE/APS	262 (0.2)	78 (0.3)	0.003	27 (0.3)	0.013	4 (0.1)	0.420	8 (0.2)	0.867
Family history of pre-eclampsia	5887 (4.6)	980 (3.8)	<0.001	232 (3.0)	<0.001	54 (1.7)	<0.001	191 (4.3)	0.421
Nulliparous	61 899 (48.4)	9653 (37.5)	<0.001	3634 (46.4)	<0.001	1622 (50.4)	0.0297	2106 (47.8)	0.429
Parous	65 863 (51.6)	16 096 (62.5)		4200 (53.6)		1596 (49.6)		2297 (52.2)	
Parous, previous pre-eclampsia	3829 (3.0)	1208 (4.7)	<0.001	229 (2.9)	0.735	46 (1.4)	<0.001	113 (2.6)	0.108
Parous, previous SGA	7530 (5.9)	2830 (11.0)	<0.001	1032 (13.2)	<0.001	291 (9.0)	<0.001	390 (8.9)	<0.001

Note: Values are given as median (interquartile range) or number (%).

Abbreviations: APS, antiphospholipid syndrome; GH, gestational hypertension; IVF, in vitro fertilisation; PE, pre-eclampsia; SGA, small for gestational age below 10th centile; SLE, systemic lupus erythematosus.

TABLE 2 Odds ratios obtained from univariable and multiple logistic regression analysis demonstrating association of maternal race with pre-eclampsia

	Maternal race							
Hypertensive disorder	**Black**	***p* Value**	**South Asian**	***p* Value**	**East Asian**	***p* Value**	**Mixed**	***p* Value**
Univariable analysis								
Pre-eclampsia (n = 4272)	2.31 (2.16–2.48)	<0.001	1.12 (0.96–1.29)	0.150	0.92 (0.71–1.18)	0.529	0.94 (0.75–1.16)	0.584
Pre-eclampsia <37 weeks (n = 1105)	3.15 (2.77–3.57)	<0.001	1.72 (1.32–2.21)	<0.001	0.83 (0.46–1.38)	0.519	0.99 (0.62–1.48)	0.949
Pre-eclampsia <34 weeks (n = 482)	3.98 (3.28–4.80)	<0.001	2.24 (1.53–3.17)	<0.001	0.99 (0.39–2.03)	0.978	1.20 (0.60–2.15)	0.565
Gestational hypertension (n = 4344)	1.38 (1.27–1.49)	<0.001	0.93 (0.80–1.08)	0.348	0.77 (0.59–0.98)	0.043	0.99 (0.81–1.20)	0.920
Multivariable analysis								
Pre-eclampsia (n = 4272)	1.99 (1.85–2.14)	<0.001	1.08 (0.92–1.26)	0.318	1.05 (0.80–1.34)	0.733	0.96 (0.77–1.18)	0.697
Pre-eclampsia <37 weeks (n = 1105)	2.58 (2.25–2.96)	<0.001	1.52 (1.15–1.97)	0.003	0.88 (0.48–1.48)	0.630	1.01 (0.63–1.52)	0.991
Pre-eclampsia <34 weeks (n = 482)	3.15 (2.57–3.86)	<0.001	1.84 (1.24–2.64)	0.002	0.95 (0.37–1.97)	0.892	1.21 (0.60–2.16)	0.566
Gestational hypertension (n = 4344)	1.24 (1.14–1.35)	<0.001	1.01 (0.86–1.17)	0.821	0.93 (0.71,1.19)	0.627	1.03 (0.84–1.25)	0.738

Note: Adjustment for maternal age, weight, height, mode of conception, smoking, history of chronic hypertension, diabetes mellitus, antiphospholipid syndrome or systemic lupus erythematosus, history of pre-eclampsia in a previous pregnancy or family history of pre-eclampsia and previous birth of small-for-gestational-age neonate. In the multivariable analysis there was adjustment for confounding factors in maternal demographic characteristics and medical history. Comparison of each maternal race group was with those of white race. Values are given as odds ratio (95% CI).

meta-analysis.[4–22] All 20 studies reported on pre-eclampsia in white women, 17 in black women, 8 in South Asian women and 6 in East Asian women. Most of the studies comparing the incidence of pre-eclampsia between black and white women were from the USA and demonstrated a higher incidence in African-Americans than in white wome n.[4–7,9,10,13–15,18,19]

3.2.2 | Methodological quality of the selected studies

The methodological quality of the selected studies, assessed using the QUIPS tool[37] is illustrated in Figure S1. Only two of the 19 previous studies were considered to be at low-risk of bias; 5 were at moderate-risk of bias and 12 were at high-risk of bias. The main problem with most studies was that they did not adjust for confounders.

3.2.3 | Nature of the studies

In all 19 included studies the populations were unselected singleton pregnancies and the definitions of pre-eclampsia necessitated the presence of hypertension in combination with proteinuria.

3.2.4 | Meta-analysis for comparison of rate of pre-eclampsia in white and other racial groups

The prevalence of pre-eclampsia for each study, weighted pooled data and heterogeneity between studies are provided in Figures 2, S2 and S3. In the meta-analysis of the combined data from 16 studies in the literature and the FMF study the relative risk for pre-eclampsia in black women, compared with white women, was 1.68 (95% CI 1.48–1.92), but the heterogeneity of the studies was 98% (Figure 2). Publication bias was graphically assessed in Figure S4. The funnel plot showed no obvious asymmetry, but small studies are probably not published.

In the combined data from eight studies, the incidence of pre-eclampsia in women of South Asian race, compared with white women, was not statistically significantly different (RR 1.08, 95% CI 0.97–1.21); the heterogeneity between studies was 30% (Figure S2). In the combined data from six studies, the incidence of pre-eclampsia in women of East Asian origin, compared with white women, was lower (RR 0.71, 95% CI 0.56–0.89); the heterogeneity between studies was 64% (Figure S3).

Only three previous studies provided adjusted odds ratios and the results of the combined meta-analysis from these four studies and our study are shown in Figures 3, S5 and S6. In black, compared with white women, the adjusted odds ratio for pre-eclampsia was 1.90 (95% CI 1.61–2.23). In women of South Asian race, compared with white women, the adjusted odds ratio for

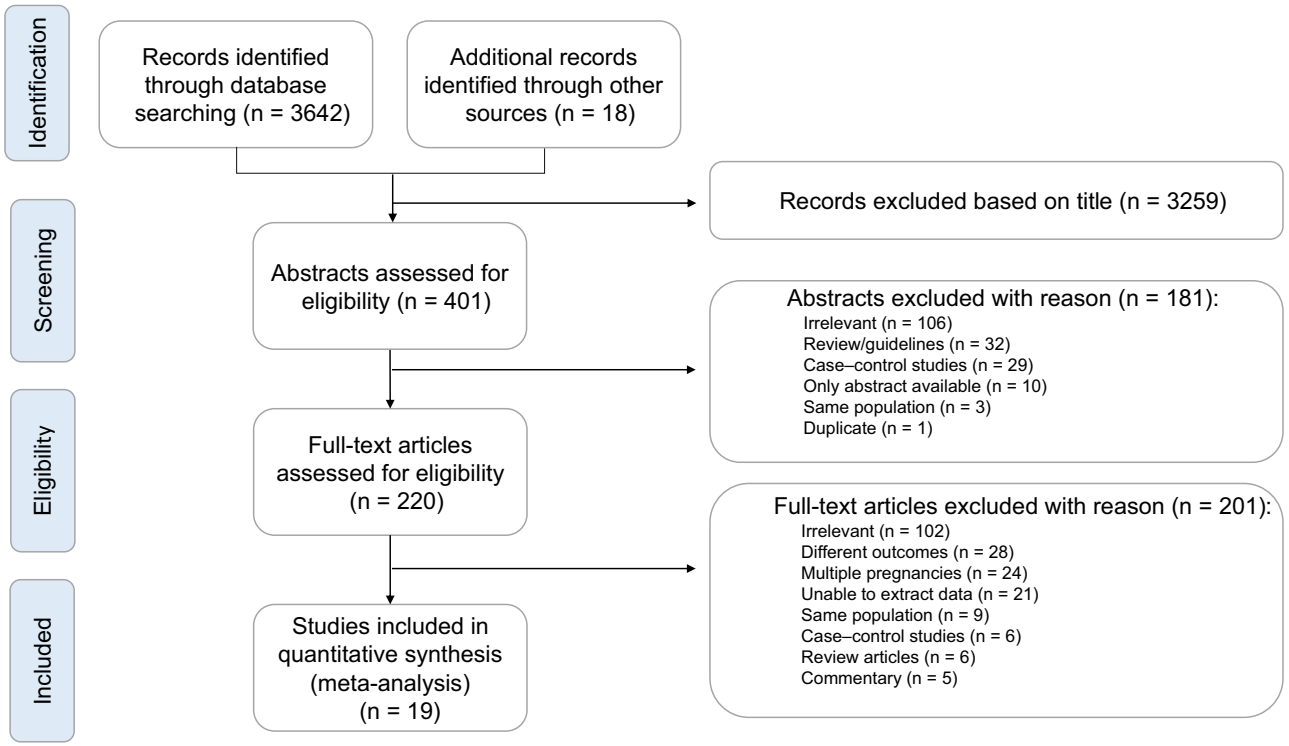

FIGURE 1 Flow chart for the systematic review.

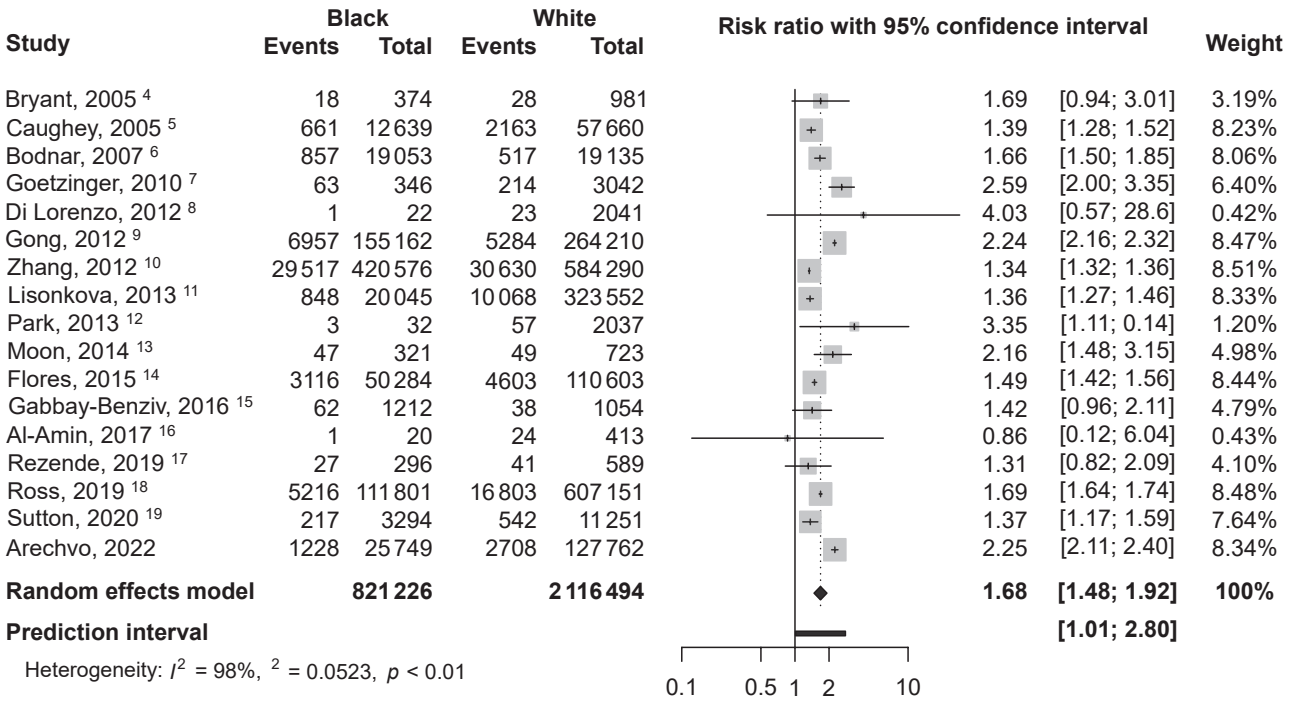

FIGURE 2 Forest plots of risk ratio for pre-eclampsia in women of black race compared with white women with 95% CI and weighted pooled summary statistics using bivariate random-effects model.

pre-eclampsia was 1.28 (95% CI 1.19–1.38). In women of East Asian race, there was no statistically significant difference from white women in the incidence of pre-eclampsia, after adjustment for confounding factors. However, there was a high risk of publication bias as shown in Figure S4.

4 | DISCUSSION

4.1 | Main findings

There are four main findings from the large FMF prospective study in women with singleton pregnancies living in

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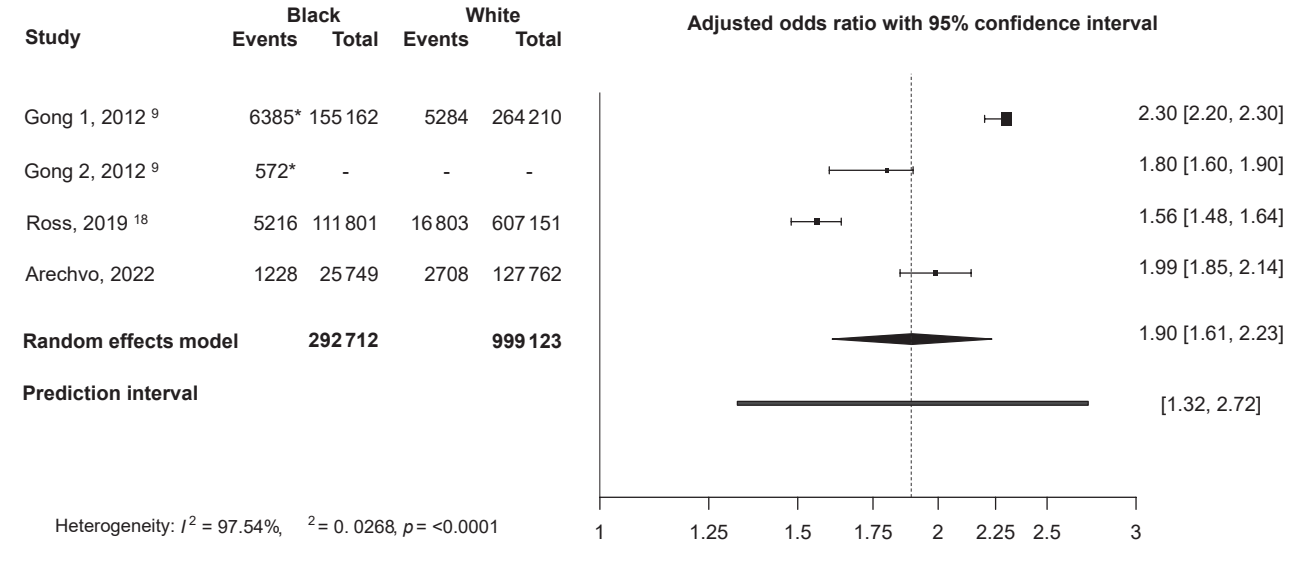

* African American
* Sub-Saharan African

Author	Adjustments
Gong	Maternal age, weight, smoking, parity, educational status
Ross	Maternal age, BMI, smoking, parity, diabetes
Arechvo	Maternal age, weight, height, parity, method of conception, smoking, history of chronic hypertension or diabetes, family history of pre-eclampsia, previous pregnancy affected by pre-eclampsia or birth of small-for-gestational-age neonate.

FIGURE 3 Forest plots of odds ratio for pre-eclampsia in women of black race compared with white women with 95% CI and pooled summary statistics using bivariate random-effects model.

England. First, multiple logistic regression analysis demonstrated that in addition to black race, increased risk for pre-eclampsia was provided by increasing maternal age and weight, conception by in vitro fertilisation, history of chronic hypertension and diabetes type 1, family history of pre-eclampsia and previous pregnancy affected by pre-eclampsia; the risk for pre-eclampsia decreases with increasing height, cigarette smoking, and previous birth of an SGA neonate; this is consistent with our previous studies reporting models for the prediction of pre-eclampsia.[3,41] Second, in black women, compared with white women, after adjustment for elements of maternal characteristics and medical history there were 2-fold, 2.5-fold and 3-fold higher risks of total pre-eclampsia, preterm pre-eclampsia and early pre-eclampsia, respectively, and a 25% increase in the risk of gestational hypertension. Although there still remains the possibility of unadjusted confounders, the effects are sufficiently large that they seem likely to be genuine. Third, in women of South Asian race, compared with white women, there was a 1.5-fold higher risk of preterm and early pre-eclampsia but no statistically significant difference in total pre-eclampsia or gestational hypertension. Fourth, in women of East Asian race, compared with white women, there was no statistically significant difference in the risk of pre-eclampsia or gestational hypertension. Our study examined the relative incidence of hypertensive disorders in the different racial groups and did not attempt to examine whether the origin of such differences was genetic or environmental.

The literature search identified only 19 studies that provided data on the incidence of pre-eclampsia in some of the racial groups as defined by the FMF study. In the assessment of the quality of the included studies only two were considered to be at low risk of bias. In the meta-analyses of data from previous studies combined with those of the FMF study the unadjusted risk of pre-eclampsia in black women, compared with white women, was higher and in women of East Asian origin, compared with white women, the risk was lower; in women of South Asian race, compared with white women, the risk was not statistically significantly different. However, in the meta-analysis of three previous studies that provided adjusted odds ratios, albeit with adjustment for very few relevant maternal characteristics, combined with our data the risk of pre-eclampsia in women of black and South Asian race, compared with white women, was increased, whereas in East Asian women the risk of pre-eclampsia was not statistically significantly different from that in white women.

4.2 | Strengths and limitations

The main strengths of the FMF study are first, prospective examination of a large population of women with singleton pregnancies attending for routine pregnancy care at 11–13 weeks of gestation. Second, we recorded maternal and pregnancy characteristics that have previously been reported to be associated with development of hypertensive disorders of pregnancy. Third, we used a recently updated definition

of pre-eclampsia that requires the development of hypertension with either proteinuria or renal insufficiency, hepatic dysfunction, thrombocytopenia, neurological complications or pulmonary edema,[28] and fourth, we carried out multiple logistic regression analysis and found that a statistically significant independent contribution to pre-eclampsia, in addition to race, was provided by maternal age, weight, height, method of conception, smoking, history of chronic hypertension or diabetes, parity, family history of pre-eclampsia, previous pregnancy affected by pre-eclampsia or birth of an SGA neonate.

A limitation of the FMF study is that race was classified into five broad categories and it is likely that there would be variations in outcome in subgroups within each category, such as different regions of Africa and between African and Caribbean women classified as black. Additionally, we did not record data on the social determinants of health or Index of Multiple Deprivation. The main limitations of the study relate to the findings of the systematic review of the literature and meta-analysis. For example, 16 studies provided data on the comparison of the incidence of pre-eclampsia between black and white women and although in most the incidence in black women was higher, the heterogeneity between studies was 98%; furthermore, only two of the studies reported adjusted odds ratios and adjustments were made for very few of the maternal characteristics. Similarly, there were only seven studies reporting on South Asian women and five on East Asian women, by comparison with white women and only two of these studies reported adjusted odds ratios. Consequently, although the combined data included more than 800 000 black women and more than two million white women, the meta-analysis does not provide useful information on the true contribution of black race to the prediction of pre-eclampsia because of the heterogeneity between studies and the lack of adjustment for confounders in most of the studies; the same is true for women of South Asian and East Asian race.

4.3 | Interpretation of results and implications for clinical practice

The observed patterns of racial differences in development of hypertensive disorders of pregnancy are consistent with those observed in the development of cardiovascular diseases in non-pregnant women.[42] In a large UK registry of 1 068 318 patients between 1997 and 2010 from 225 general practices across England, black, compared with white, patients were more likely to present with ischaemic stroke and intracerebral haemorrhage while South Asian patients had statistically significantly higher hazard ratios for angina and myocardial infarction.[43] This study also showed that the median age of first cardiovascular disease diagnosis was substantially lower in women of black and South Asian race than white women.

Prediction of pre-eclampsia and gestational hypertension necessitates first, data obtained from large prospective observational studies with accurate recording of maternal demographic characteristics and medical history and the appropriate infrastructure for obtaining the necessary outcome measures, and second, multiple logistic regression analysis that defines the independent contribution of each risk factor. The data from the FMF study fulfil these criteria and there are several elements from the maternal history that contribute to pre-eclampsia and gestational hypertension; in defining the specific contribution of one risk factor, such as black race, it is essential that all other factors are taken into account. In the development of the FMF competing risks model for prediction of pre-eclampsia a wide range of maternal factors are taken into account to derive the previous risk which is then adjusted with the addition of biomarkers to obtain the posterior risk.[41]

This systematic review and meta-analysis has highlighted the weakness of such an approach in defining the contribution of one specific risk factor such as race. Although the combined number of patients arising from such studies can be very large, the heterogeneity between individual studies and the lack or minimal adjustment for confounders produces results that cannot be used for accurate prediction of the outcome under investigation.

5 | CONCLUSIONS

In women of black race, compared with white women, the risk of gestational hypertension is 25% higher and the risk of pre-eclampsia is two-fold higher after adjustment for confounding factors in maternal characteristics and medical history. In women of South Asian origin, the risk of preterm pre-eclampsia is 1.5-fold higher than in white women. Accurate assessment of the contribution of different racial groups to the prediction of pre-eclampsia necessitates prospective examination of pregnancies and appropriate adjustment for confounders rather than meta-analyses of heterogeneous studies with no or minimal adjustment for confounders.

AUTHOR CONTRIBUTIONS

KHN and AA conceptualised and designed the study and wrote the first draft of the paper. AS and RA were involved in the sample collection for the FMF study. AA and DV carried out the systematic review of the literature and quality assessment of the selected articles. MMG conducted the statistical analysis. All authors revised and contributed to the intellectual content of the manuscript.

DISCLOSURE OF INTERESTS

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

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS APPROVAL

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the NHS Research

Ethics Committee (REC reference: 02-03-033 on 11 March 2003).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX 1

Search strategies

Ovid MEDLINE® ALL <1946 to 10 August 2021>

1	exp African continental ancestry group/ or American native continental ancestry group/ or asian continental ancestry group/ or oceanic ancestry group/ or exp European Continental Ancestry Group/
2	(African-american* or Caucasian* or Black* or White* or African-caribbean* or Afro-caribbean* or Asian* or BAME or Latin* or Hispanic*).mp.
3	1 or 2
4	hypertension, pregnancy-induced/ or pre-eclampsia/
5	(pre?eclampsi* or (gestational adj1 hypertension) or (hypertensive disease adj1 pregnan*) or (hypertensi* adj4 pregnan*)).ti,ab.
6	4 or 5
7	3 and 6
8	exp animals/ not humans.sh.
9	7 not 8
10	limit 9 to english language

Embase <1974 to 2021 Week 31>

1	exp African/ or exp Black person/ or asian continental ancestry group/ or ancestry group/ or Asian american/ or British asian/ or Caucasian/ or Hispanic/ or indigenous people/ or oceanic ancestry group/ or european/ or exp central european/ or exp Eastern European/ or exp Northern European/ or exp Southern European/ or exp Western European/
2	(African-american* or Caucasian* or Black* or White* or African-caribbean* or Afro-caribbean* or Asian* or BAME or Latin* or Hispanic*).mp.
3	1 or 2
4	maternal hypertension/ or preeclampsia/
5	(pre?eclampsi* or (gestational adj1 hypertension) or (hypertensive disease adj1 pregnan*) or (hypertensi* adj4 pregnan*)).ti,ab.
6	4 or 5
7	3 and 6
8	(exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) and (human/ or normal human/ or human cell/)
9	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
10	9 not 8
11	7 not 10

12	limit 11 to english language
13	limit 12 to exclude Medline records

Cinahl database 1981—Present

S1	MH "Ethnic Groups+"
S2	African-american* or Caucasian* or Black* or White* or African-caribbean* or Afro-caribbean* or (East N1 Asian*) or (South N1 Asian*) or Asian* or mixed race or BAME or Latin* or Hispanic*
S3	S1 OR S2
S4	MH "Pregnancy-Induced Hypertension" or MH "Pregnancy-Induced Hypertension"
S5	pre?eclampsi* or (gestational N1 hypertension) or (hypertensive disease N1 pregnan*) or (hypertensi* N4 pregnan*)
S6	S4 OR S5
S7	S3 AND S6
S8	MH Animals+
S9	MH (ANIMAL STUDIES)
S10	TI (ANIMAL MODEL*)
S11	S8 OR S9 OR S10
S12	MH (HUMAN)
S13	S11 not S12
S14	S7 not S13
S15	S7 not S13

Emcare 1995—Present

1	exp AFRICAN/ OR "AFRICAN AMERICAN"/ OR "AFRICAN BRAZILIAN"/
2	exp ASIAN/ OR "ASIAN AMERICAN"/ OR "ASIAN CONTINENTAL ANCESTRY GROUP"/
3	exp "OCEANIC ANCESTRY GROUP"/
4	exp EUROPEAN/
5	(African-american* OR Caucasian* OR Black* OR White* OR African-caribbean* OR Afro-caribbean* OR (east ADJ1 asian*) OR (South ADJ1 Asian*) OR Asian* OR mixed race OR BAME OR Latin* OR ispanic*).ti,ab
6	(1 OR 2 OR 3 OR 4 OR 5)
7	"MATERNAL HYPERTENSION"/ OR PREECLAMPSIA/
8	(pre?eclampsi* OR (gestational ADJ1 hypertension) OR (hypertensive disease ADJ1 pregnan*) OR (hypertensi* ADJ4 pregnan*)).ti,ab
9	(7 OR 8)
10	(6 AND 9)
11	exp ANIMAL/
12	exp HUMAN/
13	11 not 12
14	10 not 13
15	14 [English language]

Cochrane Library Reviews

1	African-american* or Caucasian* or Black* or White* or African-caribbean* or Afro-caribbean* or (East NEAR/1 Asian*) or (south NEAR/1 asian*) or Asian* or mixed race or BAME or Latin*
2	pre?eclampsi* or (gestational NEAR/1 hypertension) or (hypertensive disease NEAR/11 pregnan*) or (hypertensi* NEAR/4 pregnan*)
3	1 and 2