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Vascular endothelial growth factor gene polymorphisms and hypertensive disorder of pregnancy: A meta-analysis

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ABSTRACT

Background: Whether vascular endothelial growth factor (*VEGF*) polymorphisms affect individual susceptibility to hypertensive disorder of pregnancy remain controversial. Therefore, we performed this meta-analysis to better evaluate associations between *VEGF* polymorphisms and hypertensive disorder of pregnancy in a larger pooled population.

Methods: Pubmed, Web of Science, Embase and CNKI were searched for eligible studies. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

Results: Totally 24 studies were eligible for analyses. In overall analyses, a significant association with hypertensive disorder of pregnancy was observed for rs3025039 polymorphism in dominant (p = 0.01, OR = 0.66, 95%CI 0.48–0.91), recessive (p = 0.002, OR = 1.79, 95%CI 1.25–2.58), overdominant (p = 0.04, OR = 1.35, 95%CI 1.01–1.80) and allele (p = 0.01, OR = 0.72, 95%CI 0.56–0.93) comparisons. But we did not observe any significant associations with hypertensive disorder of pregnancy for other *VEGF* polymorphisms in overall analyses. Further subgroup analyses by ethnicity showed that rs2010963 polymorphism was significantly associated with hypertensive disorder of pregnancy in Caucasians (dominant and recessive models) and Africans (allele model), whereas rs3025039 polymorphism was significantly associated with hypertensive disorder of pregnancy in Asians (recessive model).

Conclusions: In summary, our findings indicated that rs2010963 and rs3025039 polymorphisms were both significantly associated with the susceptibility to hypertensive disorder of pregnancy in certain populations.

1. Introduction

Hypertensive disorder of pregnancy refers to a group of pregnancy-specific diseases ('gestational hypertension', 'preeclampsia', 'eclampsia, 'chronic hypertension in pregnancy' and 'superimposed preeclampsia on chronic hypertension') that are characterized by hypertension, proteinuria and edema [1]. It occurs in 5%–10% of pregnancies, and accounts for 10%–15% of pregnancy-related deaths [2]. However, despite its relatively high prevalence, the exact cause of hypertensive disorder of pregnancy is still not completely understood, and it is believed that this group of disorders is resulted from a complex interaction of genetic and environmental factors [3,4].

Vascular endothelial growth factor (VEGF), a multi-functional glycoprotein that is predominantly produced by vascular endothelial cells and smooth muscle cells, could stimulate endothelial cell proliferation, increase micro-vascular permeability and promote vascular inflammation [5]. Previous studies showed that VEGF is also essential for proliferation of trophoblasts and development of embryonic vasculature during pregnancy [6,7]. Furthermore, it was found that the serum level of VEGF was significantly elevated in hypertensive disorder of pregnancy and was correlated with disease severity [8,9]. Consequently, it is possible that functional *VEGF* polymorphisms, which may lead to alternations in gene expression or changes in VEGF protein structure, may also affect biological functions of VEGF and ultimately impact individual susceptibility to hypertensive disorder of pregnancy. So far, some pilot studies already tried to assess the roles of *VEGF* polymorphisms in hypertensive disorder of pregnancy. But the results of these studies were controversial, especially when they were conducted in different populations [10–13]. Previous studies failed to reach a consensus regarding associations between *VEGF* polymorphisms and hypertensive disorder of pregnancy partially because of their relatively small sample sizes. Thus, we performed the present meta-analysis to better explore potential roles of *VEGF* polymorphisms in this disorder in a larger pooled sample size. Additionally, we also aimed to elucidate the potential effects of ethnic background on associations between *VEGF* polymorphisms and hypertensive disorder of pregnancy.

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2. Materials and methods

2.1. Literature search and inclusion criteria

The current meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist [14]. Pubmed, Web of Science, Embase and China National Knowledge Infrastructure were searched for potentially eligible articles using the combination of following terms: “vascular endothelial growth factor”, “VEGF”, “polymorphism”, “variant”, “mutation”, “genotype”, “allele”, “gestational hypertension”, “preeclampsia”, “eclampsia”, “chronic hypertension in pregnancy”, “superimposed preeclampsia on chronic hypertension” and “hypertensive disorder of pregnancy”. We also reviewed the reference lists of all retrieved articles for other potentially eligible studies.

To test the research hypothesis of this meta-analysis, included studies should meet all the following criteria: (1) evaluate associations between *VEGF* polymorphisms and hypertensive disorder of pregnancy; (2) providing sufficient data for calculating odds ratios (ORs) and 95% confidence intervals (CIs); (3) full text in English or Chinese available. Studies were excluded if one of the following conditions was fulfilled: (1) not related to *VEGF* polymorphisms and hypertensive disorder of pregnancy; (2) pedigree studies; (3) case reports or case series. In the case of duplicate reports by the same authors, we only included the most recent study.

2.2. Data extraction and quality assessment

We extracted the following information from eligible studies: (a) name of the first author; (b) year of publication; (c) country and ethnicity of participants; (d) sample size; and (e) genotypic distributions of *VEGF* polymorphisms in cases and controls. The probability value (*p* value) of Hardy-Weinberg equilibrium (HWE) was also calculated.

We used the Newcastle-Ottawa scale (NOS) to evaluate the quality of eligible studies. The NOS has a score range of zero to nine, and studies with a score of more than seven were thought to be of high quality.

Two reviewers conducted data extraction and quality assessment independently. When necessary, we wrote to the corresponding authors for extra information. Any disagreement between two reviewers was solved by discussion until a consensus was reached.

2.3. Statistical analyses

In the current study, we performed statistical analyses by using Review Manager Version 5.3.3. We calculated ORs and 95% CIs to estimate potential associations between *VEGF* polymorphisms and hypertensive disorder of pregnancy in dominant, recessive, overdominant and allele models, and a *p* value of 0.05 or less was defined as statistically significant. Between-study heterogeneities were evaluated by I^2 statistic. Random-effect models (REMs) would be used for analyses if I^2 was greater than 50%. Otherwise, analyses would be conducted with fixed-effect models (FEMs). Subgroup analyses were subsequently carried out by ethnicity and type of disease. Stabilities of synthetic results were tested in sensitivity analyses. Publication biases were assessed by funnel plots.

3. Results

3.1. Characteristics of included studies

We found 276 articles by using our searching strategy. After excluding irrelevant and duplicate articles, 46 articles were retrieved for further evaluation. Another 22 articles were subsequently excluded after reading the full text. Ultimately, a total of 24 eligible studies were enrolled for analyses (see Fig. 1). Characteristics of included studies were shown in Table 1.

3.2. Overall and subgroup analyses

Results of overall and subgroup analyses were summarized in Table 2. To be brief, a significant association with hypertensive disorder of pregnancy was observed for rs3025039 polymorphism in CC versus CT + TT (dominant comparison, $p = 0.01$, OR = 0.66, 95%CI 0.48–0.91), TT versus CC + CT (recessive comparison, $p = 0.002$, OR = 1.79, 95%CI 1.25–2.58), CT versus CC + TT (overdominant comparison, $p = 0.04$, OR = 1.35, 95%CI 1.01–1.80) and C versus T (allele comparison, $p = 0.01$, OR = 0.72, 95%CI 0.56–0.93) in overall analyses. But we did not detect any significant associations with hypertensive disorder of pregnancy for other *VEGF* polymorphisms in overall analyses.

Subgroup analyses by ethnicity showed that rs2010963 polymorphism was significantly associated with hypertensive disorder of pregnancy in Caucasians (dominant and recessive models) and Africans (allele model), whereas rs3025039 polymorphism was significantly associated with hypertensive disorder of pregnancy in Asians (recessive model). Furthermore, subgroup analyses by type of disease revealed that rs3025039 was significantly associated with preeclampsia under all genetic models (see Table 2 and Supplementary Fig. 1).

3.3. Sensitivity analyses

We conducted sensitivity analyses by eliminating studies that were not in accordance with HWE. The pooled results remained unchanged in all comparisons, which suggested that our findings were statistically stable.

3.4. Publication biases

We used funnel plots to evaluate potential publication biases. The shape of funnel plots was symmetry for every comparison, which indicated that severe publication biases were unlikely.

4. Discussion

The human *VEGF* gene is located on chromosome 6p21.3 and it is comprised of eight exons and seven introns [15]. The encoding product of *VEGF* gene exists as a homodimer and functions as a powerful regulator of angiogenesis [16]. Common functional single nucleotide polymorphisms (SNPs) of *VEGF* gene, such as rs699947, rs2010963, rs1570360 and rs3025039, were found to affect gene expression [17–20]. As a result, it is possible that these polymorphisms may cause maternal/fetal vascular dysfunction and impact the individual susceptibility to hypertensive disorder of pregnancy. Recently, several studies already tried to explore potential associations of *VEGF* polymorphisms with hypertensive disorder of pregnancy, but the results of these studies were inconsistent. Therefore, we conducted the present meta-analysis to obtain a more conclusive result. The pooled analyses suggested that rs2010963 polymorphism was significantly associated with hypertensive disorder of pregnancy in Caucasians and Africans, whereas rs3025039 polymorphism was significantly associated with hypertensive disorder of pregnancy in Asians. The stabilities of synthetic results were evaluated by sensitivity analyses, and no alterations of results were observed in any comparisons, which suggested that our findings were statistically stable.

There are several points that worth noting about this meta-analysis. First, previous functional analyses demonstrated that mutant alleles of rs699947 and rs1570360 located in the promoter region as well as rs2010963 and rs3025039 located in the 3′-untranslated region (UTR) were all associated with higher VEGF production and angiogenesis activity compared with their corresponding ancestor alleles [17–20]. The functional significances of these *VEGF* polymorphisms may

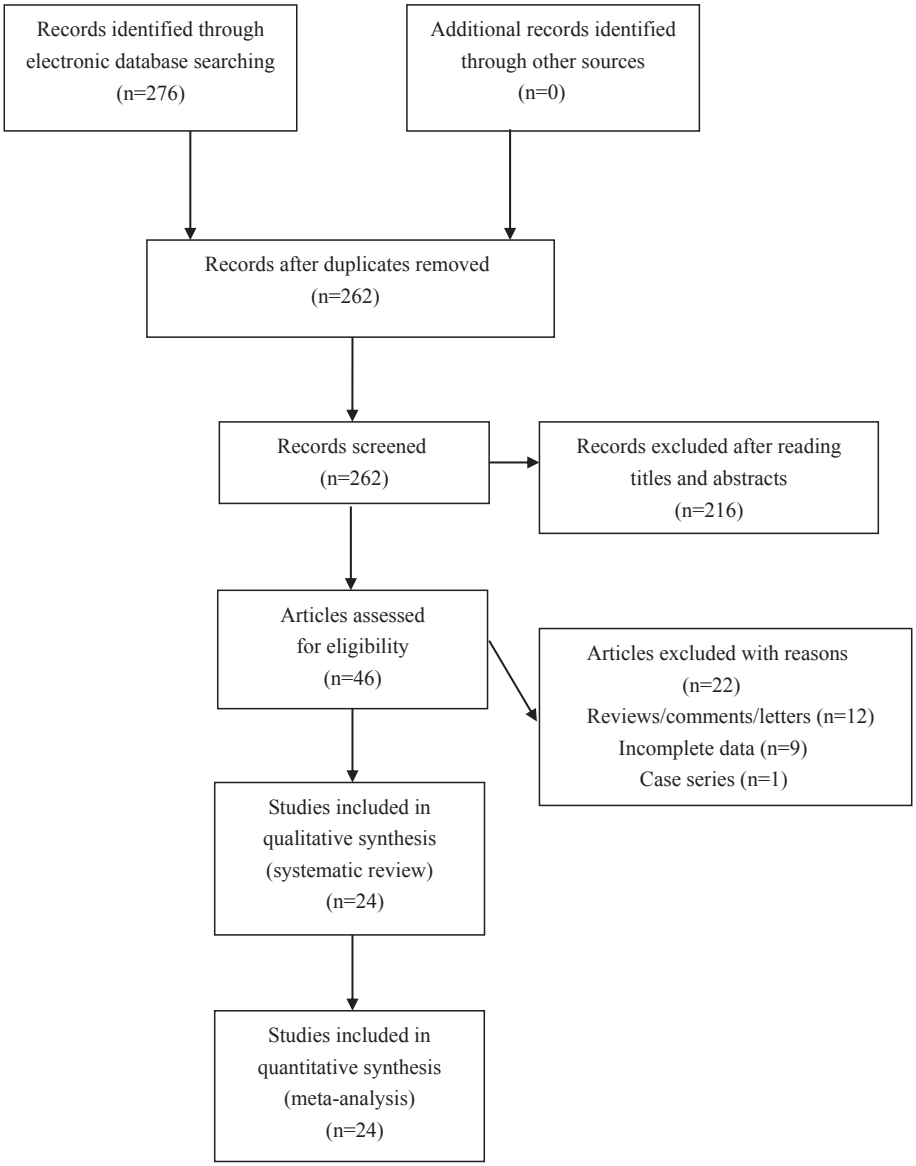

Fig. 1. Flowchart of study selection for the present study.

partially explain the observed positive findings in the current meta-analysis. It is also notable that the sample sizes of comparisons for rs699947 and rs1570360 were relatively small, and thus this meta-analysis may be statistically inadequate to detect the actual associations between these two polymorphisms and hypertensive disorder of pregnancy. Second, it is noteworthy that in 2013, Song et al. [21] also performed a meta-analysis about the roles of *VEGF* polymorphisms in preeclampsia. According to their pooled analyses, only rs3025039 polymorphism was significantly associated with preeclampsia and no any other positive results were found. Compared with the previous meta-analysis, we enrolled 14 more eligible studies, and the sample size of the current meta-analysis is twice that of the previous meta-analysis. Therefore, our results should be considered as more conclusive.

Some limitations of this meta-analysis should also be noted when interpreting our findings. First, our pooled analyses were based on unadjusted estimations due to lack of raw data, and we have to admit that failure to perform further adjusted analyses may impact the reliability of our findings [22,23]. Second, since our pooled analyses were based on retrospective case-control studies, despite our positive findings, future perspective studies are still needed to examine whether there is direct causal relationship between *VEGF* polymorphisms and hypertensive disorder of pregnancy [24,25]. Third, associations between *VEGF* polymorphisms and hypertensive disorder of pregnancy may also be modified by gene-gene and gene-environmental interactions. However, most studies did not consider these potential interactions, which impeded us to conduct relevant analyses [26,27]. Considering the above mentioned limitations, our findings should be interpreted with caution.

In summary, our meta-analysis suggested that rs2010963 polymorphism may serve as a potential genetic biomarker of hypertensive disorder of pregnancy in Caucasians and Africans, while rs3025039 polymorphism may serve as a potential genetic biomarker of hypertensive disorder of pregnancy in Asians. These two *VEGF* polymorphisms may be used to identify individuals with higher susceptibility to hypertensive disorder of pregnancy. However, further well-designed studies are still warranted to confirm our findings.

Authors' contributions

Meng Su and Xuejuan Xu conceived of the study, participated in its design. Meng Su and Zongyan Hu conducted the systematic literature review. Changmin Dong performed data analyses. Meng Su and

Table 1
The characteristics of included studies.

First author, year	Country	Ethnicity	Diagnosis criteria	Type of disease	Sample size	Genotype distribution		*P*-value for HWE	NOS score
						Cases	Controls		
rs699947 (−2578C > A)									
Andraweera 2013	Australia	Caucasian	ACOG criteria	Preeclampsia	174/168	42/87/45	40/89/39	0.440	8
Bányász 2006	Hungary	Caucasian	ACOG criteria	Preeclampsia	83/96	34/34/15	31/46/19	0.795	8
Ben Ali Gannoun 2017	Tunisia	Caucasian	ACOG criteria	Preeclampsia	300/300	NA	NA	NA	7
Chedraui 2013	Ecuador	African	ACOG criteria	Preeclampsia	31/31	12/16/3	12/16/3	0.479	8
Cunha 2011	Brazil	African	ACOG criteria	Preeclampsia	52/27	30/16/6	9/16/2	0.160	7
Garza-Veloz 2011	Mexico	African	ACOG criteria	Preeclampsia	86/78	29/47/10	35/34/9	0.865	8
Nagy 2008	Hungary	Caucasian	ACOG criteria	Preeclampsia	71/93	20/34/17	26/50/17	0.410	7
Papazoglou 2004	Sweden	Caucasian	ACOG criteria	Preeclampsia	42/73	10/22/10	23/30/20	0.131	8
Salimi 2015	Iran	Caucasian	ACOG criteria	Preeclampsia	192/201	48/105/39	66/103/32	0.435	8
Sandrim 2009	Brazil	African	ACOG criteria	Preeclampsia	100/100	38/53/9	42/41/17	0.210	8
Sandrim 2009	Brazil	African	ACOG criteria	Gestational hypertension	100/100	38/48/14	42/41/17	0.210	8
rs1570360 (−1154G > A)									
Ben Ali Gannoun 2017	Tunisia	Caucasian	ACOG criteria	Preeclampsia	300/300	NA	NA	NA	7
Chedraui 2013	Ecuador	African	ACOG criteria	Preeclampsia	31/31	23/8/0	22/8/1	0.797	8
Garza-Veloz 2011	Mexico	African	ACOG criteria	Preeclampsia	86/78	51/30/5	49/27/2	0.442	8
Keshavarzi 2017	Iran	Caucasian	ACOG criteria	Preeclampsia	84/103	37/33/14	39/47/17	0.657	8
Salimi 2015	Iran	Caucasian	ACOG criteria	Preeclampsia	192/201	76/91/25	83/89/29	0.519	8
Sandrim 2009	Brazil	African	ACOG criteria	Preeclampsia	100/100	53/32/15	59/32/9	0.142	8
Sandrim 2009	Brazil	African	ACOG criteria	Gestational hypertension	100/100	58/35/7	59/32/9	0.142	8
rs2010963 (−634G > C)									
Amosco 2016	Philippines	Asian	ACOG criteria	Preeclampsia	165/191	101/59/5	110/73/8	0.338	7
Bányász 2006	Hungary	Caucasian	ACOG criteria	Preeclampsia	84/96	31/35/18	38/46/12	0.738	8
Ben Ali Gannoun 2017	Tunisia	Caucasian	ACOG criteria	Preeclampsia	300/300	NA	NA	NA	7
Chedraui 2013	Ecuador	African	ACOG criteria	Preeclampsia	31/31	11/18/2	17/12/2	0.952	8
Garza-Veloz 2011	Mexico	African	ACOG criteria	Preeclampsia	86/78	28/45/13	26/43/9	0.164	8
He 2011	China	Asian	ACOG criteria	Preeclampsia	42/62	24/13/5	43/16/3	0.362	7
Keshavarzi 2017	Iran	Caucasian	ACOG criteria	Preeclampsia	84/103	17/48/19	44/47/12	0.918	8
Kim 2008	Korea	Asian	ACOG criteria	Preeclampsia	226/219	72/110/44	83/89/47	0.015	8
Nagy 2008	Hungary	Caucasian	ACOG criteria	Preeclampsia	71/93	47/15/9	61/28/4	0.732	7
Papazoglou 2004	Sweden	Caucasian	ACOG criteria	Preeclampsia	42/73	15/17/10	26/31/16	0.251	8
Salimi 2015	Iran	Caucasian	ACOG criteria	Preeclampsia	192/201	67/99/26	87/88/26	0.614	8
Sandrim 2009	Brazil	African	ACOG criteria	Preeclampsia	100/100	35/50/15	47/46/7	0.341	8
Sandrim 2009	Brazil	African	ACOG criteria	Gestational hypertension	100/100	36/49/15	47/46/7	0.341	8
Silva 2015	Brazil	African	ACOG criteria	Preeclampsia	79/209	26/36/17	62/102/46	0.688	7
Zhang 2014	China	Asian	ACOG criteria	Preeclampsia	58/70	20/34/4	39/26/5	0.816	8
Zhang 2015	China	Asian	ACOG criteria	Preeclampsia	120/100	56/46/18	34/40/26	0.051	7
Zhang 2015	China	Asian	ACOG criteria	Gestational hypertension	60/100	29/23/8	34/40/26	0.051	7
rs3025039 (+936C > T)									
Amin-Beidokhti 2018	Iran	Caucasian	ACOG criteria	Preeclampsia	204/191	148/54/2	143/46/2	0.418	8
Amosco 2016	Philippines	Asian	ACOG criteria	Preeclampsia	164/190	135/27/2	139/46/5	0.614	7
Andraweera 2013	Australia	Caucasian	ACOG criteria	Preeclampsia	174/168	140/29/5	139/28/1	0.748	8
Ben Ali Gannoun 2017	Tunisia	Caucasian	ACOG criteria	Preeclampsia	300/300	NA	NA	NA	7
Chedraui 2013	Ecuador	African	ACOG criteria	Preeclampsia	31/31	15/12/4	17/12/2	0.952	8
Chen 2011	China	Asian	ACOG criteria	Preeclampsia	84/71	49/34/1	56/15/0	0.320	8
Cunha 2011	Brazil	African	ACOG criteria	Preeclampsia	52/28	34/16/2	22/5/1	0.331	7
Huang 2009	China	Asian	ACOG criteria	Preeclampsia	128/231	64/49/15	158/61/12	0.067	7
Kim 2008	Korea	Asian	ACOG criteria	Preeclampsia	225/232	166/51/8	153/68/11	0.340	8
Liu 2010	China	Asian	ACOG criteria	Preeclampsia	84/71	49/35/0	56/15/0	0.320	7
Papazoglou 2004	Sweden	Caucasian	ACOG criteria	Preeclampsia	42/73	26/15/1	56/16/1	0.901	8
Procopciuc 2014	Romania	Caucasian	ACOG criteria	Preeclampsia	70/94	33/33/4	70/21/3	0.374	8
Shim 2007	Korea	Asian	ACOG criteria	Preeclampsia	110/209	58/45/7	150/55/4	0.686	8
Zhang 2014	China	Asian	ACOG criteria	Preeclampsia	58/70	15/30/13	33/34/3	0.112	8
Zhou 2017	China	Asian	ACOG criteria	Preeclampsia	156/286	117/33/6	200/77/9	0.635	8

Abbreviations: HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale; NA, Not available; ACOG criteria, American College of Obstetricians and Gynecologists Diagnostic Criteria of Hypertensive Disorder of Pregnancy (ACOG Committee on Practice Bulletins-Obstetrics, 2002).
HWE assumes that allele and genotype frequencies in a population will remain constant from generation to generation in the absence of other evolutionary influences. Consider a population of monoecious diploids, where each organism produces male and female gametes at equal frequency, and has two alleles at each gene locus. The allele frequencies at each generation are obtained by pooling together the alleles from each genotype of the same generation according to the expected contribution from the homozygote and heterozygote genotypes.

Xuejuan Xu drafted the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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None.

Declaration of Competing Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Table 2
Results of overall and subgroup analyses for *VEGF* polymorphisms and hypertensive disorder of pregnancy.

Population	Sample size	Dominant comparison (MM vs. Mm + mm)			Recessive comparison (mm vs. MM + Mm)			Overdominant comparison (Mm vs. MM + mm)			Allele comparison (M vs. m)		
		p value	OR (95%CI)	I^2 statistic	*p* value	OR (95%CI)	I^2 statistic	*p* value	OR (95%CI)	I^2 statistic	*p* value	OR (95%CI)	I^2 statistic
rs699947													
Overall	1231/1267	0.33	0.91 (0.75–1.10)	19%	0.77	1.04 (0.82–1.31)	0%	0.50	1.06 (0.89–1.28)	39%	0.99	1.00 (0.89–1.12)	0%
Caucasian	862/931	0.48	0.91 (0.71–1.18)	14%	0.31	1.16 (0.87–1.53)	0%	0.85	0.98 (0.78–1.23)	0%	0.96	1.00 (0.87–1.14)	23%
African	369/336	0.52	0.90 (0.67–1.22)	38%	0.28	0.78 (0.50–1.22)	0%	0.66	1.12 (0.68–1.82)	59%	0.96	1.01 (0.81–1.25)	0%
Preeclampsia	1131//1167	0.41	0.92 (0.75–1.13)	27%	0.62	1.07 (0.83–1.37)	0%	0.87	1.02 (0.78–1.34)	43%	0.98	1.00 (0.89–1.13)	5%
rs1570360													
Overall	1093/1113	0.73	0.96 (0.78–1.19)	0%	0.78	1.05 (0.73–1.51)	0%	0.84	1.03 (0.81–1.30)	0%	0.76	1.02 (0.89–1.18)	0%
Caucasian	576/604	0.84	1.03 (0.74–1.44)	0%	0.76	0.93 (0.59–1.48)	0%	0.98	1.00 (0.72–1.39)	13%	0.31	1.09 (0.92–1.30)	0%
African	517/509	0.54	0.92 (0.70–1.20)	0%	0.40	1.29 (0.71–2.33)	0%	0.78	1.05 (0.75–1.46)	0%	0.33	0.88 (0.68–1.14)	0%
Preeclampsia	893/913	0.74	0.96 (0.76–1.22)	0%	0.62	1.10 (0.75–1.63)	0%	0.98	1.00 (0.78–1.30)	0%	0.77	1.02 (0.88–1.19)	0%
rs2010963													
Overall	1840/2126	0.09	0.83 (0.67–1.03)	53%	0.29	1.11 (0.91–1.36)	41%	0.11	1.12 (0.98–1.29)	13%	0.13	0.89 (0.76–1.04)	60%
Caucasian	773/866	**0.01**	**0.72 (0.56–0.93)**	45%	**0.02**	**1.53 (1.08–2.17)**	13%	0.44	1.10 (0.86–1.42)	40%	0.09	0.82 (0.65–1.03)	54%
Asian	671/742	0.88	0.97 (0.64–1.46)	69%	0.05	0.74 (0.54–1.00)	20%	0.14	1.17 (0.95–1.45)	31%	0.76	1.05 (0.76–1.45)	72%
African	396/518	0.07	0.77 (0.58–1.02)	16%	0.07	1.44 (0.98–2.13)	0%	0.63	1.07 (0.82–1.40)	0%	**0.03**	**0.80 (0.66–0.97)**	20%
Preeclampsia	1680/1926	0.05	0.80 (0.64–1.00)	50%	0.23	1.14 (0.92–1.40)	30%	0.10	1.13 (0.98–1.31)	23%	0.08	0.87 (0.75–1.02)	54%
rs3025039													
Overall	1882/2245	**0.01**	**0.66 (0.48–0.91)**	76%	**0.002**	**1.79 (1.25–2.58)**	11%	**0.04**	**1.35 (1.01–1.80)**	69%	**0.01**	**0.72 (0.56–0.93)**	76%
Caucasian	790/826	0.05	0.61 (0.37–1.01)	64%	0.15	2.03 (0.78–5.25)	0%	0.09	1.55 (0.93–2.57)	63%	0.10	0.74 (0.52–1.06)	62%
Asian	1009/1360	0.12	0.68 (0.42–1.10)	85%	**0.007**	**1.76 (1.17–2.65)**	50%	0.26	1.26 (0.84–1.89)	78%	0.10	0.71 (0.47–1.07)	85%
African	83/59	0.22	0.64 (0.31–1.31)	0%	0.47	1.70 (0.40–7.16)	0%	0.38	1.40 (0.66–2.95)	0%	0.19	0.67 (0.37–1.22)	0%
Preeclampsia	1882/2245	**0.01**	**0.66 (0.48–0.91)**	76%	**0.002**	**1.79 (1.25–2.58)**	11%	**0.04**	**1.35 (1.01–1.80)**	69%	**0.01**	**0.72 (0.56–0.93)**	76%

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; NA, Not Available; M, Major allele; m, Minor allele.
The values in bold represent there is statistically significant differences between cases and controls.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.05.012.

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