

Matrix metalloproteinase 9 gene promoter region -1562 C/T single nucleotide polymorphism increases the susceptibility to hypertensive disorders of pregnancy: a meta-analysis

Yi Zhou¹, Ran Wang², Shi-Xian Chen², Li-Sheng Wu^{2,3,*}, Jun-Qing Zhu^{2,*}

¹Department of Obstetrics, Guangdong Women and Children Hospital, 510510 Guangzhou, Guangdong, China

²Department of Rheumatic & TCM Medical Center, Nanfang Hospital, Southern Medical University, 510510 Guangzhou, Guangdong, China

³Department of Internal Medicine of Traditional Chinese Medicine, College of Traditional Chinese Medicine, Southern Medical University, 510510 Guangzhou, Guangdong, China

*Correspondence: jzhuqj@yeah.net (Jun-Qing Zhu); wlsu@smu.edu.cn (Li-Sheng Wu)

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Hypertensive disorders of pregnancy (HDP) encompass a group of diseases. Single nucleotide polymorphisms (SNPs) are common in the matrix metalloproteinase 9 (MMP9) genes. The objective of this study was to analyse whether genetic polymorphisms in MMP9-1562 C/T alter the risk of HDP. Studies published up to October 2019 across PubMed, ScienceDirect, SpringerLink, and China National Knowledge Infrastructure database were searched. Case-control or cohort studies involving subtypes of HDP and distribution of genotypes and/or alleles within MMP9-1562 C/T in both patients and controls were selected. Number of genotypes and/or alleles for MMP9-1562 C/T polymorphisms were obtained and analyzed using Stata software. Eight published reports including 1300 HDP patients and 1612 controls were included in the meta-analysis. Results showed that a variant genotype and allele of MMP9-1562 C/T increased the risk of HDP, with pooled OR 1.50 (95% CI 1.16–1.95, $P = 0.002$) and 1.36 (95% CI 1.15–1.61, $P < 0.001$). Subgroup analyses showed that the variant genotype and allele of MMP9-1562 C/T also had increased risk of preeclampsia (OR = 1.48, 1.32; 95% CI 1.18–1.86, 1.08–1.62; $P = 0.001$, 0.007) and gestational hypertension (OR = 2.23, 1.88; 95% CI 1.52–3.28, 1.33–2.65; $P < 0.001$, < 0.001) in the fixed-effects models. This suggests that variant genotype (TT + TC) and allele (T) of MMP9-1562 C/T are associated with susceptibility of HDP, especially preeclampsia and gestational hypertension.

Keywords

Hypertensive disorders of pregnancy; Gestational hypertension; Preeclampsia; Matrix metalloproteinase 9; Single nucleotide polymorphism

1. Introduction

Hypertensive disorders of pregnancy (HDP) are one of the common complications occurring during pregnancy, including gestational hypertension (GH), preeclampsia (PE), eclampsia, superimposed pre-eclampsia, and chronic hypertension in pregnancy [1–3]. The worldwide prevalence of HDP varies from 5% to 10% in pregnancies that cause significant maternal and fetal morbidity and mortality [4]. Though the exact cause and pathogenesis of HDP have not been iden-

tified, it is widely considered that the diseases are multifactorial and result from the interplay between multiple genetic, immunologic, and environmental factors (for example ambient air pollution) [2, 5]. Impaired cytotrophoblast invasion and placental ischemia followed by systemic endothelial dysfunction and hemodynamics disorder are thought to play a key role in the development of the disease [6, 7].

Placentation involves trophoblast invasion through the uterine decidua with extracellular matrix degradation and remodeling [8]. The family of matrix metalloproteinases (MMPs) are structurally related; zinc-dependent enzymes that have ability to degrade and restructure the extracellular matrix by activating the secretion of collagenases, gelatinases, and proteolytic enzymes [9]. Also, it has been reported that the imbalance between MMPs and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs), plays a significant role in various adverse events such as high blood pressure [10, 11]. As a member of the MMP family, high-level expression of MMP9 is involved in the pathophysiology of trophoblast invasion [12, 13]. Single nucleotide polymorphisms (SNPs) are common within the MMP9 gene, and act as markers of disease susceptibility because of their potential to influence MMP-9 expression [14].

The relationship between susceptibility allele MMP9-1562 C/T (rs3918242) and the risk of HDP including GH and PE has been widely reported; however, the reported association between them has remained controversial [6, 15]. Two meta-analyses including six publications were performed respectively in 2014 and 2015 to evaluate the association between MMP9-1562 C/T polymorphisms and the susceptibility to PE [16, 17]. However, susceptibility to GH was not included in these studies or in more recent studies (i.e., Leonardo *et al.*, 2015; Sun *et al.*, 2016) [18, 19]. Given the inconsistent nature of these findings, it is essential to systematically analyse whether genetic polymorphisms in the MMP9-

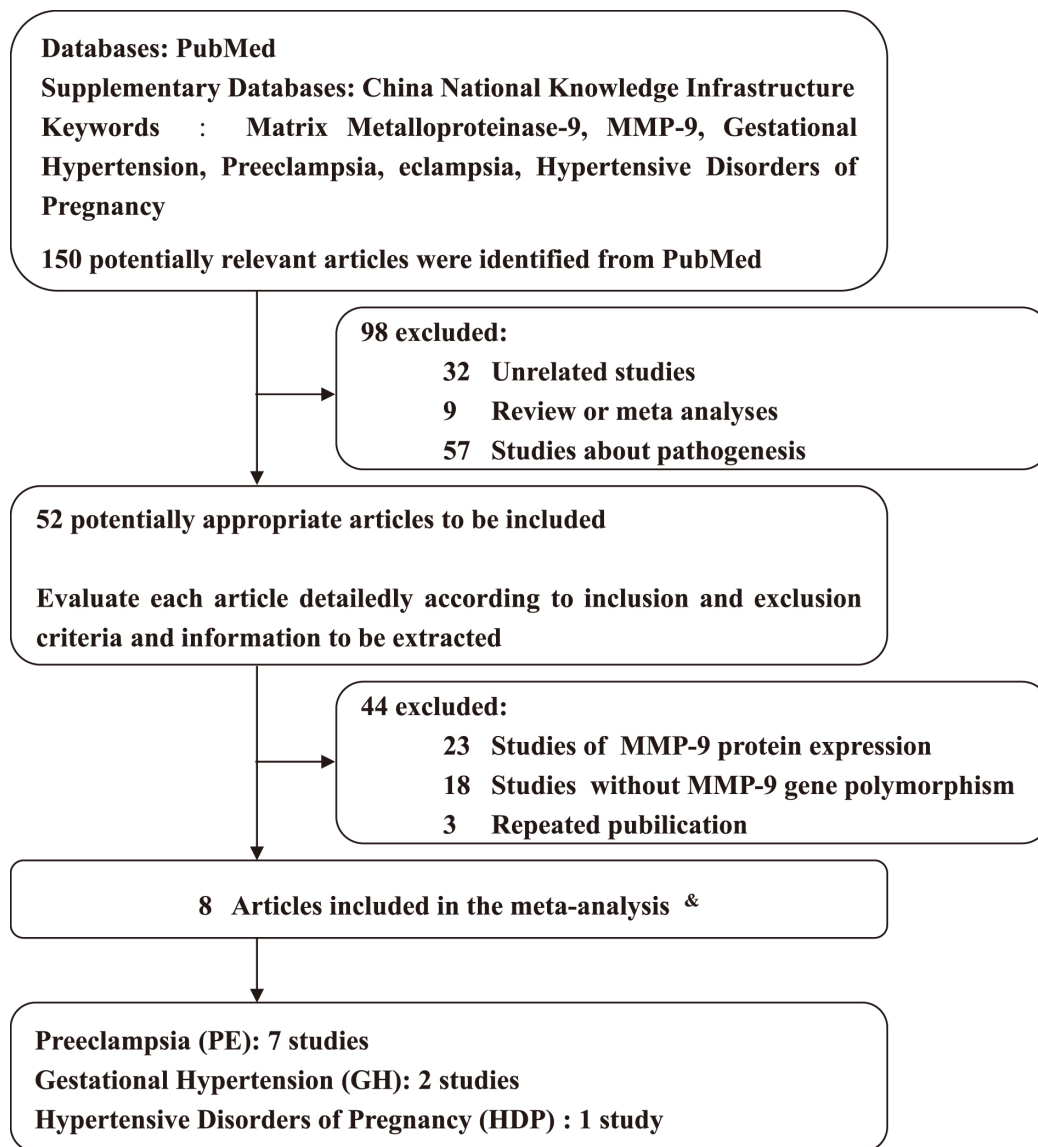


Fig. 1. Flow diagram of the selection in the study. &Two articles involved both preeclampsia and gestational hypertension studies.

1562 C/T alter the risk of HDP during pregnancy. This study was aimed at analysing whether genetic polymorphisms in MMP9-1562 C/T alter the risk of HDP.

2. Materials and methods

We conducted a primary electronic search of the PubMed database for studies published up to October 2019. China National Knowledge Infrastructure (CNKI) database were also searched as a supplementary source of data. The search was performed using combinations of the following search terms without any limits: “matrix metalloproteinase-9”, “MMP-9”, “gestational hypertension”, “preeclampsia”, “eclampsia”, and “hypertensive disorders of pregnancy”. References were checked to identify repeated literature.

For selection in the meta-analysis, each study was required to meet all of the following inclusion criteria: (1) clinical subtypes of HDP including GH, PE, eclampsia, super-

imposed pre-eclampsia, and chronic hypertension in pregnancy were defined according to guidelines of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy [20]; (2) the study must have been either a case-control or cohort study; (3) the distribution of genotypes and/or alleles within the MMP9-1562 C/T is provided for both patients and controls; and (4) demographic data including participant characteristics such as country/ethnicity, disease subtypes, maternal age, and gestational weeks must be indicated.

Exclusion criteria were as follows: (1) case reports, guidelines, review articles, meta-analyses, mechanistic studies, and unrelated studies; (2) a lack of normal pregnant women as controls; (3) no reporting concerning MMP9-1562 C/T polymorphisms associated with susceptibility to HDP; (4) studies without performing consistency tests of genotype frequencies with the Hardy-Weinberg equilibrium (HWE)

model; (5) duplicate data presented in multiple studies; (6) studies about the expression of MMP-9 protein, and (7) necessary data was unavailable.

Two authors independently evaluated the quality of the selected studies according to the Newcastle-Ottawa Scale (NOS) [21]. A total of three aspect parameters, including selection, comparability and exposure assessment, were assessed for each study. It was decided that a NOS score of 1–3 would indicate a “low-quality study”, a score of 4–6 a “moderate-quality study” and a score of 7–9 a “high-quality study” [22, 23]. Disagreements in quality assessment were resolved by discussion between the two authors.

The following information was extracted from each study: first author, publication year, country and primary race of the patients, classification diagnosis of HDP, sample size, maternal age, gestational weeks, consistency tests of genotype frequencies with the HWE model, and the distribution of genotypes and/or alleles within the MMP9-1562 C/T in the cases and controls. Two authors analyzed and extracted the data independently. Any disagreements were resolved by discussion.

The odds ratio (OR) and 95% confidence interval (95% CI) were used to calculate the risks of HDP with MMP9-1562 C/T polymorphisms [24]. An OR > 1.0 represented a risk factor while < 1.0 represented a protective factor. $P < 0.05$ was considered statistically significant. Among the pooled group with selected studies, the heterogeneity was tested by a χ^2 -based Q test and I^2 statistic. It was considered statistically significant in the heterogeneity analysis when $P < 0.10$ or $I^2 > 50\%$. When the heterogeneity was statistically significant, a random-effects model was used to calculate the pooled OR. Otherwise a fixed-effects model was considered a better choice for quantitative synthesis. Sensitivity analysis was also performed. Subgroups analyses were performed according to the variables that may influence the meta-analysis results, such as the disease subtype and study quality. Begg’s and Egger’s tests were performed to check publication bias [25]. When either of the p values were measured at < 0.10, the findings were considered statistically significant. All analyses were conducted by using Stata software version 11.0 (Stata Corporation, College Station, TX, USA).

3. Results

The electronic search was performed in the PubMed database and a total of 149 potentially relevant articles were identified. Additionally, China National Knowledge Infrastructure (CNKI) database were also searched for a supplementary search. And only one potentially relevant article was included. Therefore, a total of 150 of potentially relevant articles were evaluated. Per the inclusion and exclusion criteria, 8 articles meet our criteria for inclusion [6, 14, 15, 18, 19, 26–28]. It included 7 reports concerning PE, 2 reports concerning GH, and 1 concerning HDP without definitive disease classification (Fig. 1). Within these selected manuscripts, a total of 1300 patients with HDP and 1612 controls were in-

cluded in the meta-analysis. In the included reports, 9 (90%) were high-quality and 1 (10%) was moderate quality. Detailed information concerning first author, publication year, country and primary race of the patients, classification diagnosis of HDP, numbers of cases and controls, maternal age, gestational weeks, whether have performed HWE, quality assessment of the selected studies, number of genotypes and/or alleles for the MMP9-1562 C/T in the case and controls are described in Table 1.

We pooled data gleaned from the 10 reports (involving PE, GH, and HDP) to evaluate the HDP risk associated with the MMP9 gene promoter region -1562 C/T polymorphism. For the genotypes (TT + TC vs CC) and alleles (T vs C), the heterogeneity analysis of included in 10 reports indicates that the difference was statistically significant ($Q = 26.32, 22.95; P = 0.002, 0.006; I^2 = 65.8\%, 60.8\%$). Random-effect models were performed and the pooled ORs were found to be 1.33 (95% CI 0.97–1.83, $P = 0.077$; Fig. 2A) for the genotypes (TT + TC vs CC) and 1.21 (95% CI 0.93–1.57, $P = 0.166$; Fig. 2B) for the alleles (T vs C).

Further research is necessary to reduce the heterogeneity of pooled analysis. According to sensitivity analysis, the result showed that the study published by Coolman *et al.* in 2007 [26] has great influence on the stability of the model. Also, the study has been scored six and considered moderate quality study by NOS. Therefore, the study was eliminated from the meta-analysis. The result showed a significant association between the genotypes of MMP9-1562 C/T polymorphism (TT + TC vs CC) and the susceptibility of HDP in a pooled group of 9 reports (OR = 1.50, 95% CI 1.16–1.95, $P = 0.002$; Fig. 2C) with the random-effect model ($Q = 14.38, P = 0.072, I^2 = 44.4\%$). Similarly, for the alleles (T vs C) of MMP9-1562 C/T, the pooled OR was found to be 1.36 (95% CI 1.15–1.61, $P < 0.001$; Fig. 2D) with the fixed-effects model ($Q = 12.12, P = 0.146, I^2 = 34.0\%$).

In view of the heterogeneity in the pooled analysis, we performed a further subgroup analysis according to the classification diagnosis of HDP. According to the classification diagnosis of HDP, a total of 7 reports were included to analyse the relationship between PE susceptibility and MMP9-1562 C/T genotype and allele. The pooled ORs were found to be 1.27 (95% CI 0.91–1.77, $P = 0.165$; Fig. 3A) and 1.15 (95% CI 0.87–1.53, $P = 0.326$; Fig. 3B) with the random-effects model for each group in 7 studies ($Q = 13.73, 12.26; P = 0.033, 0.057; I^2 = 56.3\%, 51.0\%$). With the exclusion of the study published by Coolman *et al.* [26], no significant heterogeneity among the studies for the relationship between PE susceptibility and MMP9-1562 C/T genotype and allele was found ($Q = 2.84, 2.27; P = 0.725, 0.811; I^2 = 0.0\%, 0.0\%$). The variant genotype (TT + TC) and allele (T) of MMP9-1562 C/T exhibited an increased risk of PE (OR = 1.48, 1.32; 95% CI 1.18–1.86, 1.08–1.62; $P = 0.001, 0.007$; Fig. 3C,D) in the fixed-effects model.

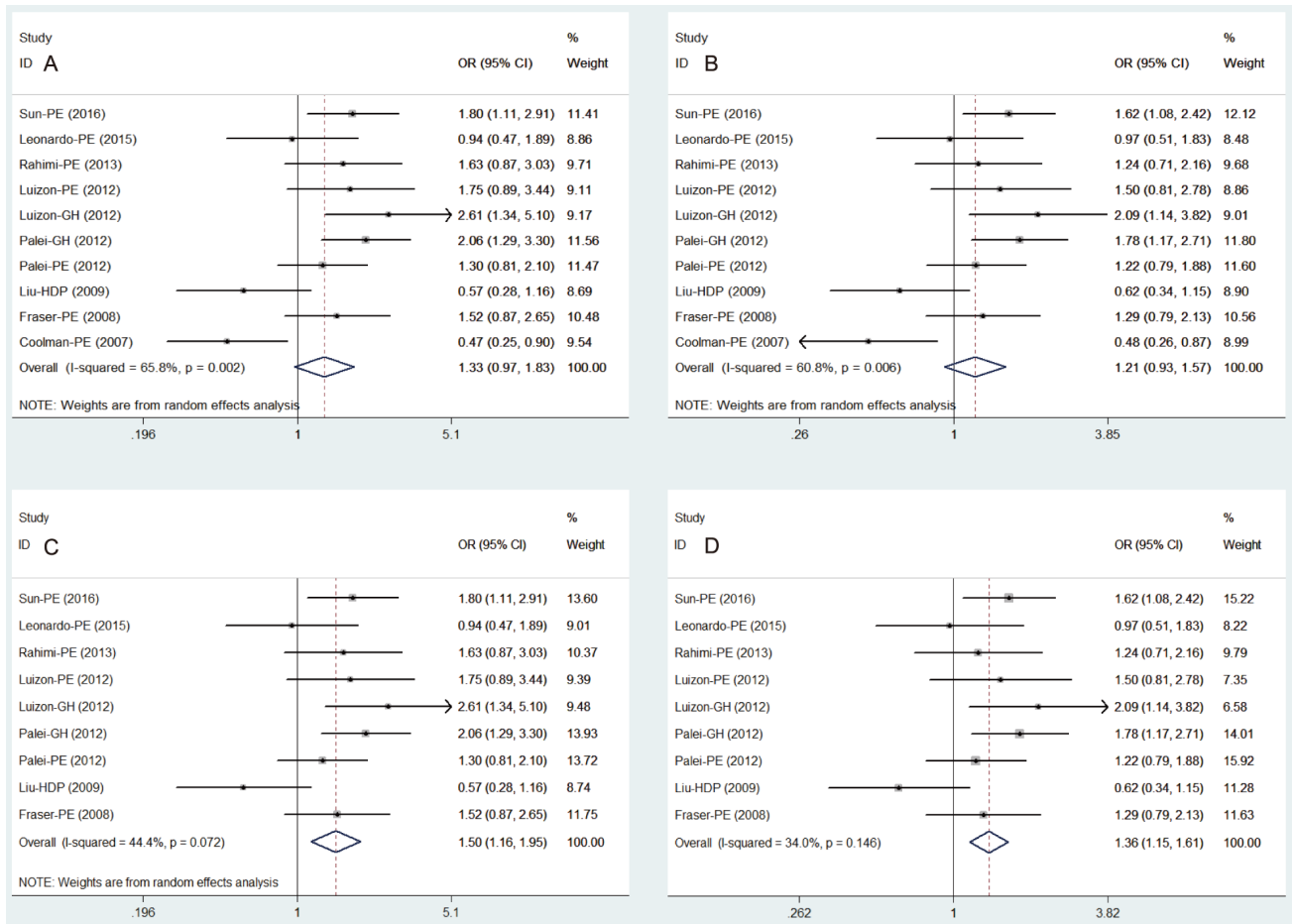


Fig. 2. Forest plot of the association between MMP9-1562 C/T polymorphism and HDP risk. (A,B) Pooled risk of HDP with the genotypes (TT + TC vs CC) and alleles (T vs C) of MMP9-1562 C/T. (C,D) Pooled risk of HDP with the genotypes (TT + TC vs CC) and alleles (T vs C) of MMP9-1562 C/T when one study (Coolman *et al.*, 2007) [26] was excluded. HDP, hypertensive disorders of pregnancy; GH, gestational hypertension; PE, preeclampsia; MMP, matrix metalloproteinases.

According to the classification diagnosis of HDP, a total of 2 reports were included in the relationship between GH susceptibility and MMP9-1562 C/T genotype and allele. The heterogeneity analysis of these two subgroups showed that there was also no heterogeneity among the included studies ($Q = 0.32, 0.18; P = 0.571, 0.667, I^2 = 0.0\%, 0.0\%$). Both ORs were calculated using the fixed-effects model in these two subgroups. The pooled ORs were found to be 2.23 (95% CI 1.52–3.28, $P < 0.001$; Fig. 3E) for the genotypes (TT + TC vs CC) and 1.88 (95% CI 1.33–2.65, $P < 0.001$; Fig. 3F) for the alleles (T vs C).

In all the pooled groups mentioned above, neither the Begg's ($P > 0.1$) nor Egger's tests ($P > 0.1$) showed statistical significance. This suggests that no publication bias exists within the reports selected for study.

4. Discussion

HDP is a pregnancy complication which manifests as multiple clinical subtypes. Many previous studies have reported the relationship between -1562 C/T polymorphism of MMP9 and HDP susceptibility, but disagreements between

these studies were noted. One study indicated that pregnant women carrying MMP9-1562 TT + TC genotype are 2.37 times at increased risk of developing PE compared with control pregnant women [15]. Another study did not find a correlation between these two variables (OR = 0.304, 95% CI 0.045–2.065) [27]. In addition, work from the Luizon and Palei groups did not find the same risk between the -1562 C/T polymorphism of MMP9 and PE, respectively [6, 14]. However, both studies found that the MMP9-1562 C/T polymorphism not only increased the susceptibility of GH but also influenced the response of antihypertensive therapy [6, 14]. Two meta-analyses which included six publications were performed in 2014 and 2015 to evaluate the association between MMP9 gene -1562 C/T polymorphisms and the susceptibility to PE [16, 17]. However, the susceptibility to GH was not included in the published meta-analyses [18, 19].

Our group performed this pooled analysis to assess the relationship between MMP9-1562 C/T polymorphism and susceptibility of HDP including its subtypes. The preliminary results showed that the genotypes (TT + TC vs CC) and

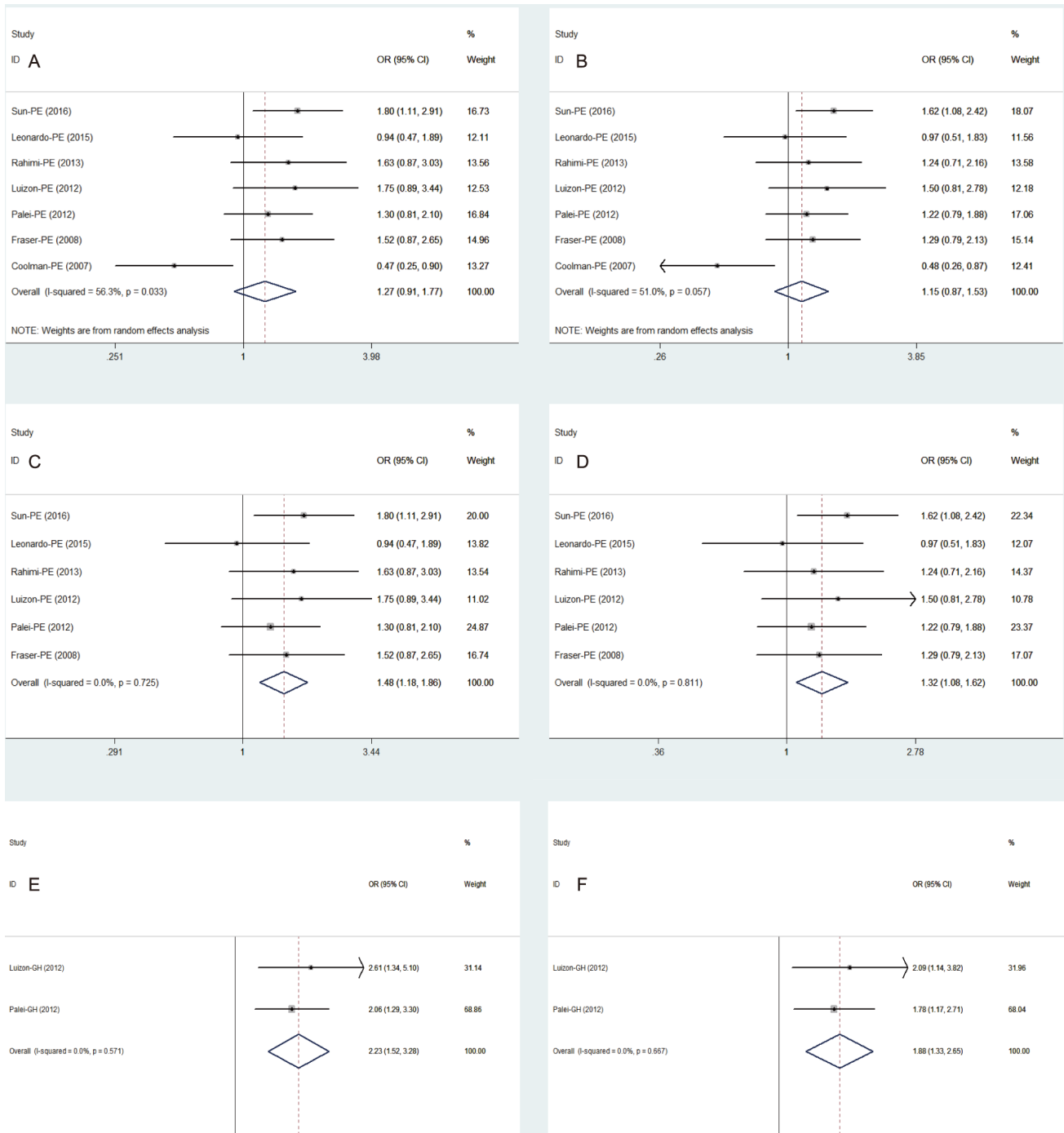


Fig. 3. Forest plot of the association between MMP9-1562 C/T polymorphism and PE/ GH risk. (A,B) Pooled risk of PE with the genotypes (TT + TC vs CC) and alleles (T vs C) of MMP9-1562 C/T. (C,D) Pooled risk of PE with the genotypes (TT + TC vs CC) and alleles (T vs C) of MMP9-1562 C/T when Coolman *et al.* (2007) [26] was excluded. (E) Pooled risk of GH with the genotypes (TT + TC vs CC) of MMP9-1562 C/T. (F) Pooled risk of GH with the alleles (T vs C) of MMP9-1562 C/T; PE, preeclampsia; GH, gestational hypertension; MMP, matrix metalloproteinases.

alleles (T vs C) did not increase the risk of the susceptibility to HDP with significant heterogeneity among the studies when data from all 10 reports were pooled together. When the study published by Coolman *et al.* [26], which had both a moderate-quality score and the greatest impact to the quantitative synthesis in sensitivity analysis, was eliminated, the results of meta-analysis revealed that the variant genotype (TT

+ TC) and allele (T) of MMP9-1562 C/T have the risk of 1.5 and 1.36 times in developing to HDP when compared with control pregnant women.

Previously, two meta-analyses including six publications in 2014 and 2015 revealed uniformly no association between MMP9-1562 C/T polymorphism and PE risk [16, 17].

Table 1. Characteristics of the individual studies for HDP included in the meta-analysis.

First author	Published Date	Country/ Ethnicity	Diagnosis	Cases/ Controls (n)	Maternal Age (cases vs controls) ^b	Gestational weeks (cases vs controls) ^b	HWE	NOS	MMP9-1562 C/T				MMP9-1562 C/T					
									Genotype (n)				Allele (n)					
									Case	Control	Case	Control	T	C	T	C		
Sun-PE	2016	China/ Asian	PE	107/242	28.85 ± 5.21/ 26.85 ± 5.50	27.75 ± 4.50/ 26.82 ± 5.25	Y	7	7	35	65	11	53	178	49	165	75	409
Leonardo-PE	2015	Brazil/ Caucasoid	PE	77/266 ^a	24.5 (24.8–28)/ 26.4 (25.3–28)	38.7 (38.4–39)/ 35.2 (34.4–36)	Y	8	1	11	60	3	43	217	13	131	49	477
Rahimi-PE	2013	Iran/ Caucasoid	PE	160/112	NA/27.3 ± 6.4	NA	Y	8	0	38	122	4	14	94	38	282	22	202
Luizon-PE	2012	Brazil/ Caucasoid	PE	122/102	27.4 ± 6.7/ 25.5 ± 5.9	36.2 ± 3.9/ 39.7 ± 1.4	Y	8	1	29	92	2	14	86	31	213	18	186
Luizon-GH	2012	Brazil/ Caucasoid	GH	107/102	26.6 ± 6.2/ 25.5 ± 5.9	39.1 ± 1.5/ 39.7 ± 1.4	Y	8	1	34	72	2	14	86	36	178	18	186
Palei-GH	2012	Brazil/ Caucasoid	GH	185/214	27.0 ± 0.5/ 24.5 ± 0.4	38.8 ± 0.1/ 39.8 ± 0.1	Y	7	3	54	128	4	34	176	60	310	42	386
Palei-PE	2012	Brazil/ Caucasoid	PE	214/214	26.0 ± 0.5/ 24.5 ± 0.4	36.0 ± 0.3/ 39.8 ± 0.1	Y	7	3	44	167	4	34	176	50	378	42	386
Liu-HDP	2009	China/ Asian	HDP	71/66	27.9 ± 3.4/ 28.1 ± 3.2	36.7 ± 4.5/ 37.2 ± 4.2	N	7	2	18	51	3	24	39	22	120	30	102
Fraser-PE	2008	UK/ Caucasoid	PE	117/146	29 (16–42)/ 30 (16–40)	35.6 (25–42)/ 39.5 (37–42)	Y	8	1	34	82	4	28	114	36	198	36	256
Coolman-PE	2007	Netherlands/ Caucasoid	PE	163/163 ^a	28.0 ± 0.3/ 28.0 ± 0.3	34.6 ± 0.4/ 39.4 ± 0.3	Y	6	1	16	128	2	31	118	17	273	35	267

Note: HDP, hypertensive disorders of pregnancy; GH, gestational hypertension; PE, preeclampsia; MMP, matrix metalloproteinases; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa Scale; n, number; Y, yes; N, no; ^a, the number of cases and controls are not coincident with the genotypes and/or alleles within the MMP9-1562 C/T due to the missing data; ^b, data collected by mean ± standard deviation or interval range; NA, no data available.

Our preliminary subgroup analyses based on 7 studies also found no increased risk of PE from MMP9-1562 C/T polymorphism with the heterogeneity analysis having statistically significant. However, following the exclusion of the Coolman *et al.* [26] study, the heterogeneity among the pooled 6 reports decreased to 0.0% and the quantitative synthesis showed that the variant genotype (TT + TC) and allele (T) of MMP9-1562 C/T increased the risk of PE by 1.48 and 1.32 times, respectively. There are some tangible reasons for the different PE risk reported in this study and previous meta-analyses. First, one study searched the supplementary CNKI database, and two new studies published recently (2014 and 2015) have not been included in the previous meta-analyses [18, 19, 28]. Second, previous meta-analyses included two studies published by Palei *et al.* (2010 and 2012) which was considered as duplicate data in our study [14, 29]. Third, further subgroup analysis has been performed to decrease the heterogeneity among the pooled reports in the present meta-analysis. Concerning the subgroup analyses with no heterogeneity detected, the variant genotype (TT + TC) and allele (T) of MMP9-1562 C/T had a higher risk of GH susceptibility when compared with the control pregnant women (OR = 2.23 and 1.89). Thus, it can be concluded that MMP9-1562 (T) may be a potential genetic marker associated with HDP (GH and PE) which can help identify a susceptible population.

This study showed that -1562 C/T polymorphism in MMP9 gene promoter region can raise the HDP susceptibility, especially in GH and PE patients. Although the mechanism of this phenomenon is unclear, previous studies have suggested that with the presence of T allele in MMP9-1562 C/T the gene has a higher transcriptional activity and can express higher levels of MMP9 protein in tissues [30]. A large increase in MMP9 expression combined with the action of oxidative stress and inflammatory mediators may participate in the development of PE by promoting vascular endothelial dysfunction [31, 32]. In addition, high level expression of MMP9 protein may also play an important role in the processes of trophoblast invasion, placenta and uterine artery remodeling, and the regulation of vascular tension [13, 33]. Therefore, it is worthwhile in future research to clarify the concrete mechanism of this disease by exploring phenotype/genotype relationships of SNPs within the MMP9 gene promoter region.

This meta-analysis also has several limitations. First, due to the quantity restriction of the original studies, ethnicity subgrouping has not been performed. Second, HDP risk analyses with MMP9-1562 C/T polymorphism showed no patients with eclampsia, superimposed pre-eclampsia, and chronic hypertension in pregnancy were involved. Third, the subgroup analysis of GH susceptibility only involved two studies, so caution should be exercised when interpreting these results obtained with a small sample size. At last, in order to clarify the relationship between genetic polymorphisms in MMP9-1562 C/T and the risk of hypertensive dis-

orders of pregnancy, it is necessary to balance the confounding factors with a larger sample size or conduct further mechanistic research.

Overall, this meta-analysis revealed that the variant genotype (TT + TC) and allele (T) of MMP9-1562 C/T are associated with the susceptibility of HDP, especially with susceptibility for PE and GH. Further research with more convincing evidence for the association between MMP9-1562 C/T polymorphisms and the risk of the clinical subtypes of HDP such as GH and the functional consequences of MMP9 polymorphism is necessary.

Author contributions

JZ and YZ designed the research study. YZ and LW performed data extraction. RW and LW performed quality review. JZ and SC analyzed the data. YZ and JZ wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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