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Association between MMP-9-C1562Tpolymorphism and susceptibility to preeclampsia: a systematic review and meta-analysis

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ABSTRACT

Objectives: This meta-analysis aims to explore the association between MMP-9-C1562T polymorphism and susceptibility to preeclampsia (PE).

Material and methods: Four English databases were searched to collect relevant records up to April 2024. The pooled odds ratio (OR) was calculated using Stata 15.0.

Results: A total of 10 studies were enrolled in our systematic review. The results showed that genotype CT at MMP-9-C1562T locus increased the risk of PE versus genotype TT (Genotype CT vs TT: OR = 2.32, 95% CI: 1.27–4.24, P = 0.006), but no significant differences were found in other gene models (C vs T: OR = 0.88, 95% CI: 0.71–1.08, P = 0.225; Genotype CC vs TT: OR = 1.51, 95% CI: 0.87–2.61, P = 0.139; Genotype CC + CT vs TT: OR = 1.63, 95% CI: 0.95-2.81, P = 0.079; Genotype CC vs CT + TT: OR = 0.80, 95% CI: 0.63–1.03, P = 0.086). Subgroup analysis by ethnicity showed a statistically significant difference in the heterozygous model in China (Genotype CT vs TT: OR = 2.38, 95% CI: 1.15 –4.91, *P* = 0.019).

Conclusions: Association of MMP-9-C1562T polymorphism with susceptibility to PE exists. Specifically, genotype CT increases the risk of PE versus genotype TT, particularly in Caucasian populations.

Keywords: MMP-9; polymorphism; susceptibility; meta-analysis

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INTRODUCTION

Preeclampsia (PE) is a syndrome of pregnancy and a major contributor to high maternal and fetal mortality. The risk of cardiovascular disease is significantly increased within the next 10–15 years after PE, and additionally offspring exposed to PE has a markedly increased risk of hypertension at an early age and in adulthood [1]. Therefore, this disease is regarded as one of the most common serious complications in obstetrics. Worldwide the overall incidence of PE is 4.6%, with the lowest incidence in the Mediterranean region (about 1.0%) and the highest incidence in Africa (about 5.6%) [2]. There are many studies on PE, but its pathogenesis has not been clearly elucidated. In recent years, genetics has been reported to be associated with the pathogenesis of PE in some articles [3, 4], and thus increasing studies on the two emerged.

Matrix metalloproteinases (MMPs), a group of zinc-dependent endopeptidases, are one of the main enzymes for degradation of all components of extracellular matrix (ECM) such as basement membrane, collagen, elastin, and fibrin [5, 6]. MMP-9, a type of gelatinase, also known as gelatinase-B, is required for degradation of the ECM [7]. ECM plays a crucial role in maintaining normal tissue structure and function and regulating cell growth and differentiation [8]. The MMP-9 gene is located on 20q13.12 with a length of 7.7 kb, consisting of 13 exons and 12 introns [9]. Etesami et al. [10] proved that MMP-9 levels were significantly increased in the blood of pregnant women with PE compared with normal controls. Currently many studies have discussed the association between MMP-9-C1562T locus (rs3918242) single nucleotide polymorphism (SNP) and susceptibility to PE [11–13], but failed to reach a consensus. Therefore, in this study, we used meta-analysis to explore the association between MMP-9-C1562T polymorphism and susceptibility to PE, thus providing evidence-based medicine for the pathogenesis of PE.

MATERIAL AND METHODS

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14], we conducted this meta-analysis.

Search strategy

We utilized four English databases (Pubmed, Embase, Cochrane library, Web of Science) to find records that investigated the association between rs3918242 SNP and susceptibility to PE, with the time span from inception to April 2024. The references of included studies were also searched. The main search terms included: (‘‘Matrix metalloproteinase-9’’ OR ‘‘MMP-9’’) AND (‘Pre-eclampsia’’ OR ‘‘pregnancy hypertensive disorders’’ OR ‘‘gestational hypertension’’) AND (‘‘polymorphism’’ OR ‘‘single nucleotide polymorphism’’ OR ‘‘mutation’’). The search was performed independently through two investigators and finally cross-checked.

Literature selection criteria

Literature that met the following requirements was entered into our review: (1) Patients with clinically confirmed PE: after 20 weeks of gestation, patients had systolic blood pressure equal to or more than 140 mmHg or diastolic blood pressure equal to or more than 90 mmHg (1 mmHg = 0.133kPa), accompanied by proteinuria ≥ 0.3 g/24h or random urine protein ≥ (+); (2) With MMP-9-C1562T polymorphism as exposure factor; (3)

With risk of PE as outcome measure; (4) With pregnant women without hypertension as controls; (5) Case-control or cohort study; (6) English literature. Articles satisfying the following items were excluded from our study: (1) literature with incomplete study data, duplicate literature, non-published studies; (2) review, letter, conference abstract, animal or cell experiments; (3) Newcastle-Ottawa Scale (NOS) scores less than 6.

Literature quality evaluation

We chose the 9-point NOS [15] to evaluate the methodological quality of the included records. Literature, whose scores were not less than six, was considered high-quality.

Literature screening and data extraction

Two investigators independently extracted data, and cross-checked. Inconsistencies were checked and settled by a third investigator. The information collected was listed below: (1) Basic information: first author of the article, year, sample size of cases and controls, and Hardy-Weinberg equilibrium (HWE) of frequency of genotype in the group of control; (2) Key data of gene model analysis: frequency distribution of mutant genotypes in cases and controls.

Statistical analysis

We analyzed the data by Stata 15.0 software. The HWE test was performed on the genotypes of the controls included in the study, and if $P \leq 0.05$, the genotypes of the controls failed to be in HWE. Five genetic models [16, 17] were used in the current meta-analysis. Heterogeneity was assessed by Cochrane Q and I^2 statistic [18]. A fixed-effects model (FEM) was chosen for analysis in case of no statistical heterogeneity ($I^2 < 50\%$, and $P > 0.1$); otherwise, a random-effects model was adopted. Subgroup analyses were performed by ethnicity and HWE. The stability of all obtained results was verified by the sensitivity analyses. The odds ratio (OR) and 95% CIs were used as effect size. The funnel plot created for the allelic model, as well as Egger's test, was chosen to judge whether the publication bias existed or not.

RESULTS

Literature search results

A total of 10 records were finally entered into this meta-analysis [11–13, 19–25] (Fig. 1). Eight involved Caucasian populations and the other two were from Asian populations. There were 1482 pregnant women with PE and 1749 controls. Genotype frequencies in the control group met HWE in 7 studies and did not meet HWE in the other 3 studies. In addition, all included studies had NOS scores greater than 6 and were of high quality (Tab. 1).

Meta-analysis results

Heterogeneity analysis

Except for significant heterogeneity in allelic ($I^2 = 40.2\%$, $P = 0.09$) and recessive gene models ($I^2 = 46.8\%$, $P = 0.05$), heterogeneity was not significant in dominant ($I^2 = 0.0\%$, $P = 0.548$), homozygous ($I^2 = 0.0\%$, $P = 0.495$), and heterozygous gene models ($I^2 = 0.0\%$, $P = 0.533$). Therefore, allelic and recessive gene models were analyzed using random-effects models, and the other genetic models using the fixed-effects models.

Allelic model

Allele C at the MMP-9-C1562T locus was not found to influence the risk of PE compared with T allele (Fig. 2A) (OR = 0.88, 95% CI: 0.71–1.08, P = 0.225). Based on ethnicity, allele C at the MMP-9-C1562T locus SNP reduced the risk of PE in Asians

compared with allele T (OR = 0.68, 95% CI: 0.49–0.94, P = 0.019), with heterogeneity decreased (I^2 = 0.0%, P = 0.442). However, this association was not observed in Caucasian (OR = 0.94, 95% CI: 0.74–1.20, P = 0.632). No significant decrease in heterogeneity in the subgroup with genotype frequencies satisfying HWE (I^2 = 45.9%, P = 0.086) (Supplementary Fig. 1A), while the difference was also not significant (OR = 0.98, 95% CI: 0.74–1.31, P = 0.895).

Homozygous and heterozygous models

The significant difference was identified under the heterozygous model (CT vs TT: OR = 2.15, 95% CI: 1.22–3.78, P = 0.008), but not under the homozygous model (CC vsTT: OR = 1.51, 95% CI: 0.87–2.61, P = 0.139) (Fig. B, C). Subgroup analysis by ethnicity showed that in Caucasian, the significant difference was identified only under the heterozygous model (CT vsTT: OR = 2.38, 95% CI: 1.15–4.91, P = 0.019). In the Asian populations, however, there were no marked differences in these two gene models. Subgroup with genotype frequencies satisfying HWE (Supplementary Fig. 1B, C) showed no significant decrease in heterogeneity both in the homozygous (I^2 = 0.0%, P = 0.891) and heterozygous gene models (I^2 = 0.0%, P = 0.840).

Dominant and recessive gene models

No significant differences were identified both in the dominant (Fig. 2D) and recessive gene models (Genotype CC + CT vs Genotype TT: OR = 1.63, 95% CI: 0.95–2.81, P = 0.079; Genotype CC vs Genotype CT + TT: OR = 0.80, 95% CI: 0.63–1.03, P = 0.086, Figure 2E). Based on ethnicity, the risk of PE in Asians was reduced by genotype CC compared to genotype CT + TT at MMP-9-C1562T locus SNP (OR = 0.62, 95% CI: 0.47–0.83, P = 0.005), but not in the dominant model. In the Caucasian population, no significant differences were observed both in the recessive and dominant models. Subgroup with genotype frequencies satisfying HWE suggested no significant decrease in heterogeneity (Figure 2D, E) in the dominant (I^2 = 0.0%, P = 0.894) and recessive models (I^2 = 51.9%, P = 0.052).

Publication bias test

In the allele model, the Egger 's Test displayed no significance (P = 0.141), but the funnel plot asymmetry was observed (Fig. 3), so there might be some publication bias in this study.

Sensitivity analysis

In allelic [21], dominant [13], homozygous [13] and recessive gene models [12, 21], the meta-analysis results after removing 1, 1, 1 and 2 articles were significantly changed from the original results (Fig. 4A–E). In the heterozygote model (Fig. 4C), however, the conclusion did not change significantly after removing any of the included studies. This suggests that we should be cautious in agreeing with the conclusions of other genetic models, but the conclusion of heterozygote genetic models has good stability.

DISCUSSION

Changes in MMP-9 levels affect the pathophysiology of PE. Orlovic et al. [26] have shown that MMP-9 expression was significantly decreased in placental CD8 cells in severe PE. Sahay et al. [27] also demonstrated a marked reduction in MMP-9 mRNA expression in placentas after PE, and such reduction in pregnant women lead to disturbed placental angiogenesis.

Meta-analysis of the 10 studies included showed significant differences in heterozygote models, but not in allelic, dominant, recessive, and homozygous gene models.

That is, the CT genotype at the MMP-9-C1562T locus increases the risk of PE compared with TT genotype. Further according to sensitivity analysis, newly obtained results of the heterozygous genetic model had no significant change from the original results after removing any of the included literature. Except for allelic and recessive gene models with high heterogeneity, other gene models were not highly heterogeneous. Subgroup analysis of studies where genotype frequencies in controls satisfied HWE showed no significant changes of heterogeneity in all gene models. Thus, HWE may not be a major source of heterogeneity.

Among the included records, eight were from the Caucasian population and the other two were from Asian population. The subgroup analysis following ethnicity revealed that in the Caucasian population, the difference of pooled effect size was statistically significant in only in heterozygous genetic model. That is, CT genotype increases the risk of PE in Caucasian populations relative to TT genotype. By contrast, the difference was statistically significant in allelic and recessive models in Asian populations. That means C allele and CC genotype reduce the risk of PE in Asian populations. The different conclusions in the two populations may be due to different ethnicity resulting in different susceptibility of pregnant women to MMP-9-C1562T gene mutation. Abbasi et al.[28] also

proved different susceptibility to PE in different populations using genetic models. But it is worth noting that the conclusions regarding Asian populations were based on only 2 articles; such small number of included studies limited the stability the conclusions obtained. Therefore, conclusions for Asian populations cannot be determined with certainty.

From the funnel plot of the allele model, publication bias existed in this review. In addition, sensitivity analysis in allelic, dominant, recessive and homozygous gene models showed some instability. Therefore, the conclusions drawn from this study must be treated with caution. In a 2014 meta-analysis by Gong et al. [29], no correlation was shown between the MMP-9-C1562T locus SNP and susceptibility to PE. Unlike the previous meta-analysis, this meta-analysis showed an association between the MMP-9-C1562T polymorphism and susceptibility to PE in the overall analysis, as well as subgroup analysis by ethnicity. The possible reason for such difference is that we included more new studies based on the study by Gong et al. [29].

There were several limitations in this review. First, the number of included records was small, with only 10 eligible studies for overall analysis, and only two studies involving Asian populations. This may have some impact on the stability of the conclusions. Second, only studies published in English language were entered into our study, while possible high-quality studies published in other languages were excluded. This may lead to certain publication bias. Third, no further analysis of gene-gene and gene-environment interactions was performed because the information available was limited.

CONCLUSIONS

There is an association between the MMP-9-C1562T locus SNP and susceptibility. The risk of PE is increased by the genotype CT compared with TT at the MMP-9-C1562T locus SNP, especially in the Caucasian population. Despite several limitations, this study is an updated systematic analysis to investigate the MMP-9-C1562T locus SNP related to PE, which is of significance for elucidating the pathogenesis of PE. In the future, research with more rigorous design and larger sample sizes are needed to verify the above findings.

Author contributions

RL, YY, HG — critical revision of the manuscript; RL, YY, JS, HG — substantial contribution to the conception and design of the work; JS, HY, LW — manuscript drafting; RLan, JS, HY, LW — acquisition, analysis, and interpretation of the data; RL, YY, JS, HY,

LW, HG

— revising the manuscript critically, final approval of the version to be published. All authors have read and approved the final manuscript.

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None.

Conflict of interest

All the authors declare that they have no conflict of interest.

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Table 1. The basic characteristics of the included studies

Study	Year	Country	Study design	Numbers Cases/Con	Genotyping methods	Cases			Con			HWE(p)	NOS
						CC	CT	TT	CC	CT	TT		
Coolman	2007	Netherlands	CC	145/151	RFLP-PCR	128	16	1	118	31	2	0.982	8
Fraser	2008	UK	CC	117/146	RFLP-PCR	82	34	1	114	28	4	0.1727	9
Palei	2010	Brazil	CH	154/176	RFLP-PCR	118	34	2	143	31	2	0.8268	8
Palei	2012	Brazil	CH	214/214	RFLP-PCR	167	44	3	176	34	4	0.134	8

Luizon	2012	Brazil	CH	82/79	PCR	61	20	1	67	10	2	20.0546	8
Rahimi	2013	Iran	CC	160/112	RFLP-PCR	122	38	0	94	14	4	0.0018	7
Leonardo	2015	Brazil	CC	72/263	RFLP-PCR	60	11	1	217	43	3	0.600044	8
Sun	2016	China	CC	107/242	RFLP-PCR	65	35	7	178	53	11	0.01099	7
Sakowicz	2018	Poland	CC	86/85	RFLP-PCR	67	19	0	61	21	3	0.48711	8
Gannoun	2021	Tunisia	CC	345/281	RFLP-PCR	281	62	2	243	33	5	0.00466	7

CC:case-control;CH: cohort;Con:control;HWE:Hardy-Weinberg equilibrium;RFLP:restriction fragment-length polymorphism;PCR:polymerase chain reaction; NOS:Newcastle-Ottawa Scale

Figure 1. Literature retrieval flow chart

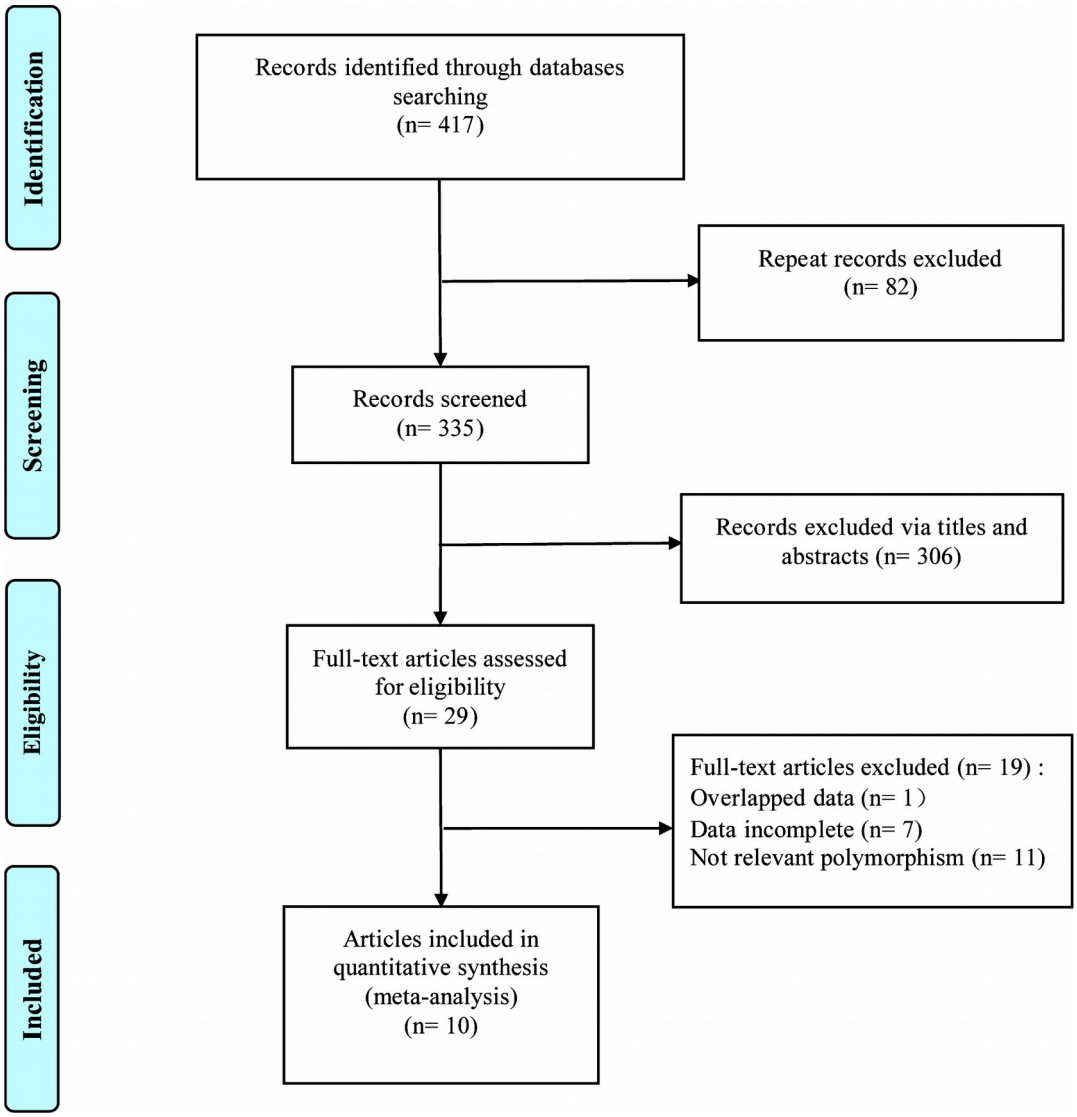


Figure 2. Forest plots of MMP-9-C1562T polymorphism with preeclampsia risk. A — allele model; B — homozygous model; C — heterozygous model; D — dominant model; E — recessive model

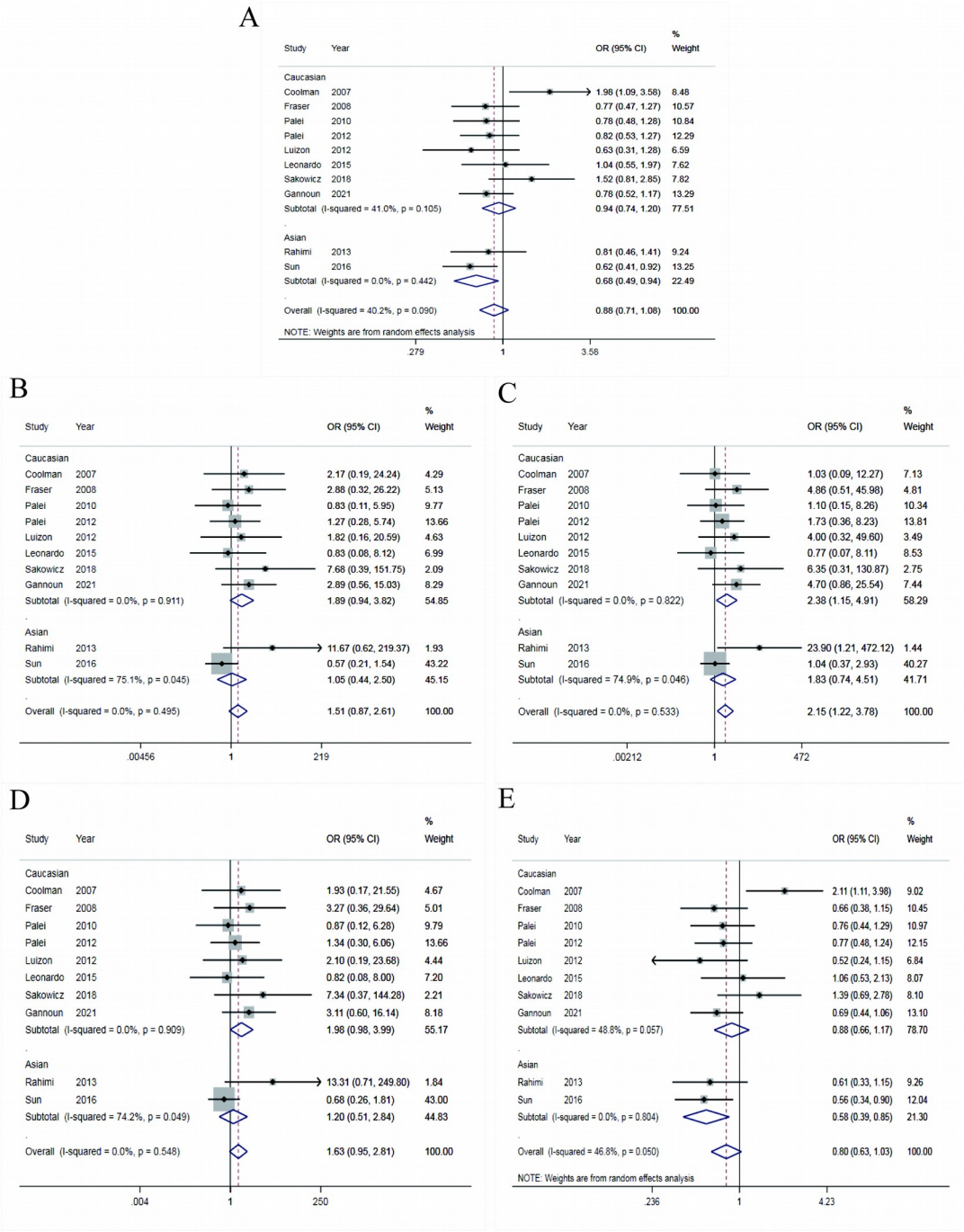


Figure 3. Funnel plot of MMP-9-C1562T allelic model with preeclampsia risk

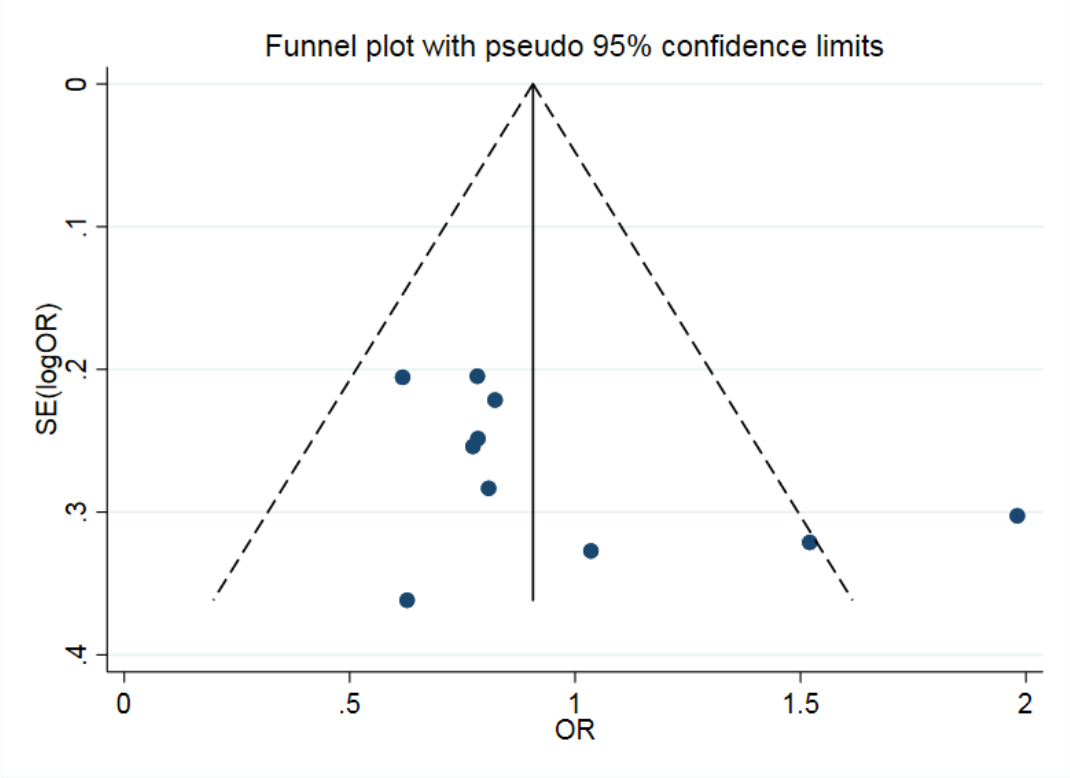
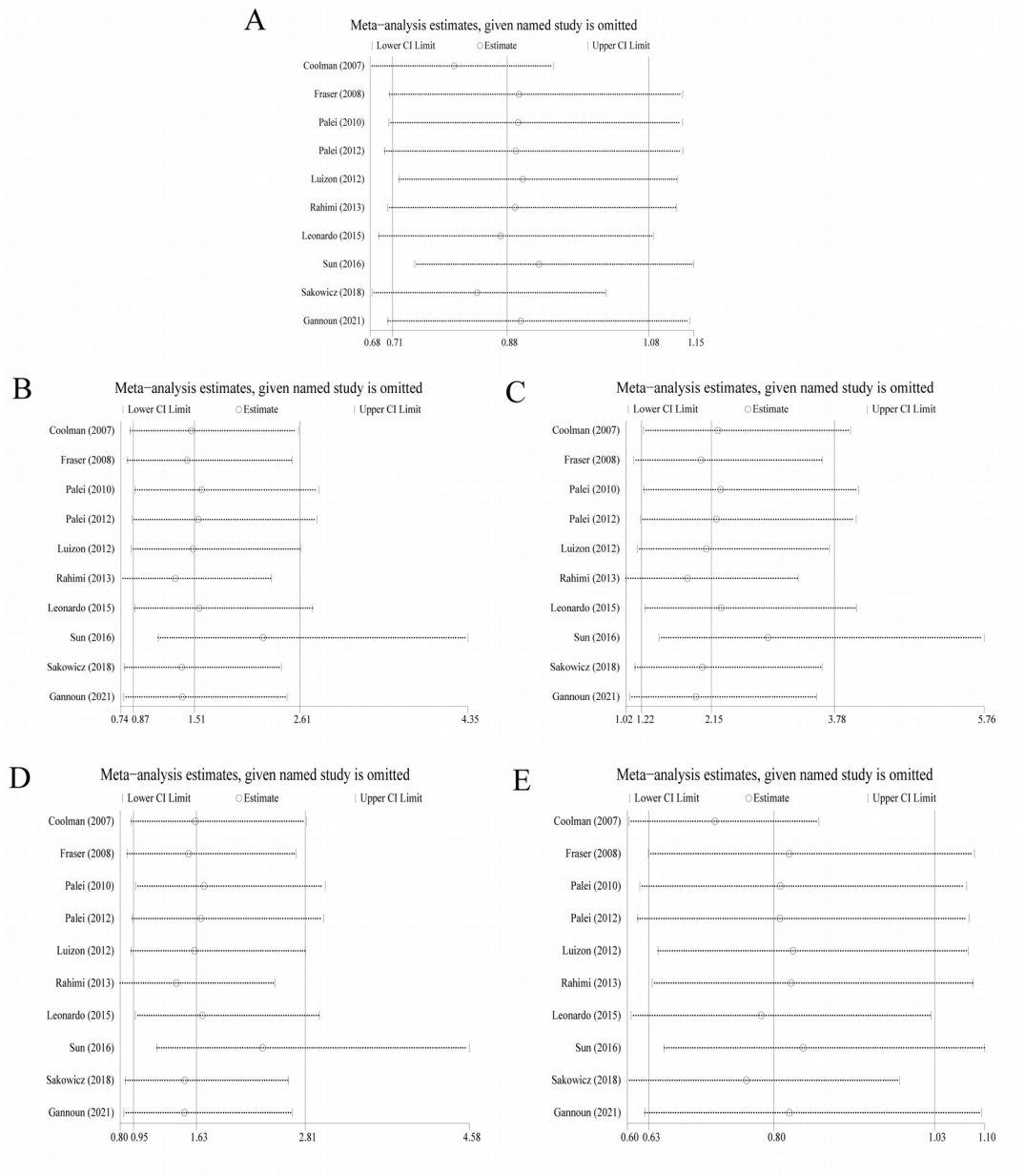


Figure 4. Sensitivity analysis of MMP-9-C1562T polymorphism with preeclampsia risk. A — comparison of allele model; B — comparison of homozygous model; C — comparison of heterozygous model; D — comparison of dominant model; E — comparison of recessive model


A
Meta−analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Coolman (2007)
Fraser (2008)
Palei (2010)
Palei (2012)
Luizon (2012)
Rahimi (2013)
Leonardo (2015)
Sun (2016)
Sakowicz (2018)
Gannoun (2021)
0.68 0.71 0.88 1.08 1.15
B
Meta−analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Coolman (2007)
Fraser (2008)
Palei (2010)
Palei (2012)
Luizon (2012)
Rahimi (2013)
Leonardo (2015)
Sun (2016)
Sakowicz (2018)
Gannoun (2021)
0.74 0.87 1.51 2.61 4.35
C
Meta−analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Coolman (2007)
Fraser (2008)
Palei (2010)
Palei (2012)
Luizon (2012)
Rahimi (2013)
Leonardo (2015)
Sun (2016)
Sakowicz (2018)
Gannoun (2021)
1.02 1.22 2.15 3.78 5.76
D
Meta−analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Coolman (2007)
Fraser (2008)
Palei (2010)
Palei (2012)
Luizon (2012)
Rahimi (2013)
Leonardo (2015)
Sun (2016)
Sakowicz (2018)
Gannoun (2021)
0.80 0.95 1.63 2.81 4.58
E
Meta−analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Coolman (2007)
Fraser (2008)
Palei (2010)
Palei (2012)
Luizon (2012)
Rahimi (2013)
Leonardo (2015)
Sun (2016)
Sakowicz (2018)
Gannoun (2021)
0.60 0.63 0.80 1.03 1.10