Association between *Vitamin D receptor (VDR)* gene polymorphisms and hypertensive disorders of pregnancy: a systematic review and meta-analysis (#80723)

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Association between *Vitamin D receptor (VDR)* gene polymorphisms and hypertensive disorders of pregnancy: a systematic review and meta-analysis

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Background. Hypertensive disorders of pregnancy (HDP) are currently one of the major causes of pregnancy-related maternal and fetal morbidity and mortality worldwide. Recent studies provide evidence that maternal *Vitamin D receptor (VDR)* gene polymorphisms probably play a key role by affecting the biological function of vitamin D in some adverse pregnancy outcomes, while the relationship between the *VDR* gene polymorphisms and the risk of HDP remains controversial in current studies. This systematic review and meta-analysis aimed to comprehensively evaluate the association of the *VDR* gene polymorphisms with HDP susceptibility.

Methods. This meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and a protocol has been registered in the PROSPERO (ID: CRD42022344383) before commencing this review. PubMed, Web of Science, Embase, and the Cochrane Library databases were searched to July 05, 2022, using terms including "*VDR* gene" and "HDP". Case-control and cohort studies that reported the association of the *VDR* gene polymorphisms with HDP were included. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for non-randomized studies. The odds ratios (ORs) with corresponding 95% confidence intervals (CIs) of the five models (allele model, dominant model, recessive model, homozygous model, heterozygous model) were pooled respectively, and subgroup analysis was performed based on ethnicity.

Results . A total of nine studies were included. The *VDR* gene *ApaI* polymorphism was associated with HDP susceptibility in the dominant model (OR: 1.44; 95% CI: 1.10, 1.88; $P = 0.007$) and the heterozygote model (OR: 1.46; 95% CI: 1.10, 1.94; $P = 0.010$). In subgroup analysis, the dominant model (1.95; 95% CI: 1.10, 3.46; $P = 0.022$) and the heterozygote model (OR: 2.14; 95% CI: 1.17, 3.92; $P = 0.014$) of the *ApaI* polymorphism were associated with HDP in Asians, but not in Caucasians.

Conclusion . The *VDR* gene *ApaI* polymorphism may be associated with HDP susceptibility. Insufficient evidence to support the existence of ethnic differences in this association.

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Abstract

Background. Hypertensive disorders of pregnancy (HDP) are currently one of the major causes of pregnancy-related maternal and fetal morbidity and mortality worldwide. Recent studies provide evidence that maternal *Vitamin D receptor (VDR)* gene polymorphisms probably play a key role by affecting the biological function of vitamin D in some adverse pregnancy outcomes, while the relationship between the *VDR* gene polymorphisms and the risk of HDP remains controversial in current studies. This systematic review and meta-analysis aimed to comprehensively evaluate the association of the *VDR* gene polymorphisms with HDP susceptibility.

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0.007) and the heterozygote model (OR: 1.46; 95% CI: 1.10, 1.94; $P = 0.010$). In subgroup analysis, the dominant model (1.95; 95% CI: 1.10, 3.46; $P = 0.022$) and the heterozygote model (OR: 2.14; 95% CI: 1.17, 3.92; $P = 0.014$) of the *ApaI* polymorphism were associated with HDP in Asians, but not in Caucasians.

Conclusion. The *VDR* gene *ApaI* polymorphism may be associated with HDP susceptibility. Insufficient evidence to support the existence of ethnic differences in this association.

Keywords. vitamin D receptor; polymorphisms; hypertensive disorders of pregnancy; gestational hypertension; preeclampsia; systematic review; meta-analysis

1 Introduction

Hypertensive disorders of pregnancy (HDP) are mainly characterized by persistently elevated blood pressure (BP) levels equal to or more than 140/90 mmHg and the resulting pathological changes, typically encompassing the following four categories: chronic hypertension (occurring before 20 weeks' gestation or persisting longer than 12 weeks after delivery), gestational hypertension (occurring after 20 weeks' gestation), preeclampsia, or preeclampsia superimposed on chronic hypertension (Metoki et al. 2022). HDP are currently one of the major causes of pregnancy-related maternal and fetal morbidity and mortality worldwide (2013). The prevalence of HDP, gestational hypertension, and preeclampsia ranges respectively from 5.2 to 8.2%, 1.8 to 4.4%, and 0.2 to 9.2% in various regions of the world (Umesawa & Kobashi 2017). In Latin America and the Caribbean, hypertensive disorders are responsible for almost 26.0% of maternal deaths, whereas in Africa and Asia they contribute to 9.0% of deaths (2019). Multiple risk

63 factors contribute to the onset of HDP, and some of them are widely recognized, such as
64 maternal age, obesity, smoking, alcohol intake, gestational diabetes mellitus (GDM), etc. (Antza
65 et al. 2018; Bartsch et al. 2016). In addition, current evidence suggested that some genetic
66 variants may also play a significant role in the development of HDP, such as the angiotensin-
67 converting enzyme (*ACE*) gene (Dmitrenko et al. 2020), methylenetetrahydrofolate reductase
68 (*MTHFR*) gene (Xia et al. 2012), tumor necrosis factor-α (*TNF-α*) gene (Lin et al. 2019),
69 catechol-O-methyltransferase gene (*COMT*) gene (Taravati et al. 2017), etc.
70 Vitamin D status has been considered another important, modifiable nutrition-related risk
71 factor for HDP in recent studies (Bodnar et al. 2014; Tabesh et al. 2013). Epidemiologic
72 investigations indicated that vitamin D deficiency or blocked utilization was associated with the
73 increased risk of HDP (Kiely et al. 2016; Serrano et al. 2018), and calcium and vitamin D
74 supplementation were confirmed to decrease the risk of preeclampsia when compared to placebo
75 by several meta-analyses (Fogacci et al. 2020; Khaing et al. 2017; Morales-Suárez-Varela et al.
76 2022; Palacios et al. 2016). The active form of vitamin D, 1,25-Dihydroxyvitamin D_3 (1,25-
77 $(OH)_2D_3$) mediates its effects of physiological by binding to the vitamin D receptor (VDR)
78 specifically (Haussler et al. 2011). The VDR is a member of the steroid receptor family in the
79 cell nucleus and is encoded by the *VDR* gene located in 12q13.11 on the chromosome, which
80 consists of two promoter regions, eight coding exons (namely, 2-9), and six untranslated exons
81 (1A-1F) (Jehan et al. 2007). Polymorphisms of the *VDR* gene have been shown to alter VDR
82 functions that affect vitamin D activities and metabolic concentrations (Maestro et al. 2016).
83 Four common single nucleotide polymorphisms (SNPs) of the *VDR* gene are most intensively

84 studied, including the *ApaI* polymorphism (rs7975232), the *BsmI* polymorphism (rs1544410), the
85 *FokI* polymorphism (rs2228570, aka rs10735810) and the *TaqI* polymorphism (rs731236).
86 Among the four SNPs, three of them occur in the intron sections (the *TaqI*, *ApaI*, and *BsmI*
87 variants), while only the *FokI* variant changes the codon (Haussler et al. 1997). Nevertheless,
88 each polymorphism of the VDR can exert different effects, for instance, the *BsmI* and *TaqI*
89 polymorphisms do not modify the VDR protein structure, but they can influence the stability
90 and/or translation efficiency of the RNA (Jurutka et al. 1997).
91 Although previous meta-analyses have found that the *VDR* gene polymorphisms could
92 increase the susceptibility to essential hypertension (EH) (Nunes et al. 2020; Zhu et al. 2019),
93 and the *VDR* gene polymorphisms were reported to be associated with plasma renin activity
94 (Vaidya et al. 2011), the relationship between the *VDR* gene polymorphisms and the risk of HDP
95 remains controversial in current studies. The results from current studies are inconsistent
96 between populations from different regions or of different ethnicities. For example, Mashhadi et
97 al. reported that the maternal *VDR* gene *FokI* variant was associated with a decreased risk of
98 preeclampsia (Farajian-Mashhadi et al. 2020); in contrast, one study conducted by Zhan et al.
99 indicated that the G allele of the *FokI* polymorphism (A>G) increased the risk of preeclampsia
100 among the Chinese population (Zhan et al. 2015), while another study conducted in China
101 showed that the association of the *FokI* polymorphism (A>G) with HDP susceptibility was not
102 statistically significant (Si et al. 2022). In fact, this association has only been intensively
103 investigated in recent years, and there has been no meta-analysis published assessing the

104 association comprehensively. Therefore, we conducted this meta-analysis to investigate the
105 association of the *VDR* polymorphisms with HDP susceptibility.
106
107 **2 Materials and methods**
108 A protocol was registered before commencing this review in the International Prospective
109 Register of Systematic Reviews PROSPERO (ID: CRD42022344383). The current meta-analysis
110 follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
111 statement (Moher et al. 2010). The PRISMA checklist for reporting the meta-analysis was shown
112 in **Table S1**.
113 **2.1 Search strategy**
114 Original articles from PubMed, Web of Science, EMBASE, and the Cochrane Library databases
115 were systematically searched from the founding date of each database to July 05, 2022. A
116 combination of the following searching terms was used: ("VDR" OR "vitamin D receptor" OR
117 "FokI" OR "rs2228570" OR "BsmI" OR "rs1544410" OR "ApaI" OR "rs7975232" OR "TaqI"
118 OR "rs731236") AND ("polymorphisms" OR "SNPs" OR "genotype" OR "variant" OR
119 "mutation") AND ("hypertensive disorders of pregnancy" OR "gestational hypertension" OR
120 "gestational hypertensive disorders" OR "pre-eclampsia"). The search strategies for each
121 database are detailed in **Table S2.** In addition, we also screened the references of relevant
122 articles to identify additional published and unpublished records. Yu Zhang and Yicong Guo
123 performed the Search Strategy. The disagreement was settled by a third reviewer (Xiangling
124 Tang)'s evaluation and discussed until a consistent result was reached.

2.2 Inclusion and exclusion criteria

The studies which met the following explicit criteria were included: (1) case-control or cohort design; (2) the relationship between the *VDR* gene polymorphisms and the risk of HDP was reported; (3) providing sufficient data about the genotype frequencies of the *VDR* gene polymorphisms for calculating the value of odds ratio (OR) and 95% confidence interval (CI); (4) the distribution of genotypes of controls were in accord with the Hardy-Weinberg equilibrium (HWE); (5) studies were published or written in English.

The exclusion criteria were: (1) reviews, case reports, letters, conference abstracts, and comments; (2) in vivo or in vitro experiments; (3) studies containing overlapping or insufficient data; (4) duplicate studies retrieved from various databases.

2.3 Data extraction and quality assessment

The following information from eligible studies was extracted or calculated based on genotype distribution: (1) the first author's name, publication year, country, ethnicity, genotyping methods, types of HDP, and the *VDR* gene variants; (2) sample size, age, and genotype distribution in both case and control groups; (3) odds ratios (ORs) and corresponding 95% confidence intervals (CIs); (4) the HWE test results for the control group. All data were extracted independently by two researchers (Yu Zhang and Yicong Guo), and if there were disagreements, questions were discussed and resolved by a third reviewer (Xiangling Tang).

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for non-randomized studies. The NOS is a rating scale in which points are awarded to studies based on selection, comparability, and exposure or outcome, where each study score ranges from

0 to 9 points (Stang 2010). A study with a total quality score of more than 7 points was considered a high-quality study. Two reviewers (Yu Zhang and Yicong Guo) independently rated the quality of the included studies, and the differences in ratings between reviewers were also resolved by discussion with a third reviewer (Xiangling Tang).

2.4 Statistical analysis

The HWE of genotypes in each control group was determined using the Chi-square test. The pooled ORs and corresponding 95% CIs of the five models (allele model, homozygous model, heterozygous model, dominant model, and recessive model) were calculated respectively, to evaluate the association between the *VDR* gene polymorphisms (*ApaI*, *BsmI*, *TaqI*, and *FokI*) and the risk of HDP. The heterogeneity was evaluated by Cochran's Q-statistic test and I-squared (I^2) (Chen & Benedetti 2017; Higgins et al. 2003). If $I^2 > 50\%$ and $P < 0.10$, the random effect model was used, otherwise the fixed effect model was applied (DerSimonian & Laird 1986). Subgroup analysis grouped by ethnicity (Caucasian and Asian) was performed to investigate the ethnic differences of this association. Sensitivity analysis was performed to evaluate the effect of a particular study on the overall results by deleting one study at a time and combining the effect values of the remaining studies. In addition, we assessed the publication bias by Egger's test (Hayashino et al. 2005) and Begg's test (Begg & Mazumdar 1994).

All statistical analyses were performed using Stata v16.0 (Stata Corp LP, College Station, TX, USA). A two-sided $P < 0.05$ was considered statistically significant except for Cochran's Q test. In our study, all analyses were based on previously published research; thus, no ethical approval or patient consent was required.

3 Results

3.1 Study selection

Figure 1 provided the flowchart of the literature search process. Our study yielded 173 potentially relevant articles in four electronic databases: 43 from PubMed, 66 from Embase, 62 from Web of Science, and 2 from the Cochrane Library. After excluding duplicate studies, 141 articles were retained. Of the 141 studies initially identified, 118 were excluded because they failed to meet the inclusion criteria based on title and abstract review. The full texts of the remaining 23 articles were reviewed for eligibility, and 14 articles were excluded for various reasons, such as irrelevant studies, absence of detailed data, and other outcomes. We finally selected a total of 9 qualified articles (Caccamo et al. 2020; Farajian-Mashhadi et al. 2020; Ghorbani et al. 2021; Magiełda-Stola et al. 2021; Rezavand et al. 2019; Rezende et al. 2012; Setiarsih et al. 2022; Si et al. 2022; Zhan et al. 2015), including 1, 518 cases and 5, 079 controls in the meta-analysis.

3.2 Characteristics and quality of the included studies

The characteristics and genotype frequencies of all the included studies were summarized in **Table 1** and **Table 2**. Among the nine studies, five studies (Farajian-Mashhadi et al. 2020; Ghorbani et al. 2021; Magiełda-Stola et al. 2021; Rezende et al. 2012; Si et al. 2022) were analyzed for the *ApaI* polymorphism, six studies (Caccamo et al. 2020; Farajian-Mashhadi et al. 2020; Magiełda-Stola et al. 2021; Rezavand et al. 2019; Rezende et al. 2012; Zhan et al. 2015) for the *BsmI* polymorphism, eight studies (Caccamo et al. 2020; Farajian-Mashhadi et al. 2020;

Magiełda-Stola et al. 2021; Rezavand et al. 2019; Rezende et al. 2012; Setiarsih et al. 2022; Si et al. 2022; Zhan et al. 2015) for the *FokI* polymorphism and four studies (Farajian-Mashhadi et al. 2020; Magiełda-Stola et al. 2021; Rezavand et al. 2019; Setiarsih et al. 2022) for the *TaqI* polymorphism. Regarding the subjects' ethnicity, there were six studies (Farajian-Mashhadi et al. 2020; Ghorbani et al. 2021; Rezavand et al. 2019; Setiarsih et al. 2022; Si et al. 2022; Zhan et al. 2015) on Asians and three studies (Caccamo et al. 2020; Magiełda-Stola et al. 2021; Rezende et al. 2012) on Caucasians. Five studies (Farajian-Mashhadi et al. 2020; Ghorbani et al. 2021; Magiełda-Stola et al. 2021; Rezavand et al. 2019; Zhan et al. 2015) included only patients with preeclampsia as case groups, and patients with both gestational hypertension and preeclampsia were involved in the remaining four studies (Caccamo et al. 2020; Rezende et al. 2012; Setiarsih et al. 2022; Si et al. 2022). The distribution of genotypes in controls from two studies (Farajian-Mashhadi et al. 2020; Rezavand et al. 2019) was not completely in accordance with HWE, thus they were excluded in the subsequent meta-analysis.

Of the nine studies included, four studies (Caccamo et al. 2020; Magiełda-Stola et al. 2021; Si et al. 2022; Zhan et al. 2015) scored 7 or higher and were considered high quality, four studies (Farajian-Mashhadi et al. 2020; Ghorbani et al. 2021; Rezende et al. 2012; Setiarsih et al. 2022) were rated 6, and one study (Rezavand et al. 2019) with a score of 5, indicating that the overall quality was acceptable **(see Table S3)**.

3.3 *VDR* gene polymorphisms and the risk of HDP

Table 3 showed the pooled results of the four SNPs based on the five models. For the *VDR* gene *ApaI* polymorphism, statistically significant associations with HDP susceptibility were

found in the overall population in the dominant model (aa + Aa vs. AA: OR: 1.44; 95% CI: 1.10, 1.88; $P = 0.007$) and the heterozygote model (Aa vs. AA: OR: 1.46; 95% CI: 1.10, 1.94; $P = 0.010$). Subgroup analysis based on ethnicity showed that the dominant model (aa + Aa vs. AA: OR: 1.95; 95% CI: 1.10, 3.46; $P = 0.022$) **(Fig. 2A)** and the heterozygote model (Aa vs. AA: OR: 2.14; 95% CI: 1.17, 3.92; $P = 0.014$) **(Fig. 2B)** of the *ApaI* polymorphism were associated with an increased risk of HDP in Asians but not in Caucasians.

A statistically significant association was observed between the *VDR* gene *Bmsl* polymorphism and the risk of HDP in the overall population in the homozygote model (bb vs. BB: OR: 0.72; 95% CI: 0.56, 0.99; $P = 0.042$) **(Fig. 3)**. Besides, no statistically significant associations were found between the *BsmI* polymorphism and HDP when stratified by ethnicity.

The *VDR* gene *FokI* polymorphism was only found statistically associated with the risk of HDP in Caucasians based on the recessive model (ff vs. Ff + FF: OR: 1.43; 95% CI: 1.01, 2.03; $P = 0.041$) **(Fig. 4A)**. In the overall population, no statistically significant associations were observed between the *FokI* polymorphism and HDP in the recessive model (ff vs. Ff + FF: OR: 1.23; 95% CI: 0.88, 1.73; $P = 0.228$) **(Fig. 4B)**.

The *VDR* gene *TaqI* polymorphism had no significant associations with the risk of HDP in both the overall and Asian populations according to the five models. In addition, in subgroup analysis, only one study investigated this relationship among Caucasians and reported a statistically significant association between the *TaqI* polymorphism and HDP susceptibility in the allele model (t vs. T: OR: 1.42; 95% CI: 1.02, 1.98; $P = 0.040$).

3.4 Sensitivity analyses and publication bias

Sensitivity analyses were conducted by removing each study included from the meta-analysis at a time. After the included studies were successively removed, the estimates were statistically significant with OR ranging from 1.39 (95% CI: 1.05, 1.84) to 1.77 (95% CI: 1.20, 2.60) in the dominant model (aa + Aa vs. AA) **(Fig. 5A)** and from 1.37 (95% CI: 1.01,1.85) to 1.77 (95% CI: 1.18, 2.65) in the heterozygote model (Aa vs. AA) **(Fig. 5B)**, indicating that the overall results were relatively stable.

Begg's test did not show any evidence of publication bias among the included studies, while Egger's test showed that there was a publication bias in the heterozygote model of the *ApaI* polymorphism in the overall population ($P = 0.030$) **(Table 3)**.

4 Discussion

To provide a better understanding of the relationship between the *VDR* gene polymorphisms and HDP susceptibility, we conducted this systematic review and meta-analysis. As far as we know, this is the first meta-analysis to comprehensively investigate the associations between the four common SNPs of the *VDR* gene and HDP susceptibility by pooling ORs and the corresponding 95% CIs.

The results of our meta-analysis showed that the *VDR* gene *ApaI* polymorphism was associated with HDP susceptibility in the overall population without heterogeneity, especially in Asian populations. Pregnant women with the *ApaI* Aa polymorphism had a 46% increased risk of HDP compared with AA carriers, and a 2.14-fold increased risk was observed in Asians. However, no association between the *ApaI* polymorphism and the risk of HDP was observed

among Caucasians in the subgroup analysis. This study also found the *VDR* gene *BsmI* polymorphism had an association with HDP susceptibility in the homozygote model. The *BsmI* bb variant provided 28% more protection against HDP compared with the BB genotype. Besides, the association between the *VDR* gene *FokI* polymorphism and HDP was only found statistically significant in Caucasians, but not in the overall population. This may be due to a single study that reported a relatively stronger association, rather than a common high frequency of susceptible genotype in the Caucasian population. For the *VDR* gene *TaqI* polymorphism, only one study reported a statistically significant association in the Caucasian population. Thus, the results of our current study still cannot sufficiently clarify the role of the *VDR* gene *FokI* and *TaqI* polymorphisms in the occurrence of HDP, and the positive findings observed should be only considered exploratory, and future studies with larger sample sizes still need to confirm these findings.

The following points are worth noting when interpreting our integrated findings. First, differences in ethnicity may contribute to the variability in our findings on the relationship between the *VDR* gene *ApaI* polymorphism and HDP. The *VDR* gene is highly polymorphic, and the frequencies of its alleles were highly variable among different ethnicities (Valdivielso & Fernandez 2006). Thus, the VDR affinity for vitamin D metabolites may also vary by ethnicity, which alters individual susceptibility to 1,25-$(OH)_2$ D_3 (Haussler et al. 1998). In this sense, our results can be supported by previous studies, e.g., Ghorbani et al. reported that the *ApaI* (G>T) GT variant was associated with preeclampsia in Iran pregnant women (GT vs. GG: OR: 2.55; 95% CI:1.04, 6.22; $P = 0.04$) (Ghorbani et al. 2021), while another study conducted among the

Polish did not found the such association in the heterozygous model (OR: 1.51; 95% CI: 0.87, 2.61) (Magiełda-Stola et al. 2021). Besides, this explanation can be supported by previous studies on the concentrations of vitamin D. One study conducted in Egypt reported women carrying mutant alleles for the *ApaI* polymorphism showed significantly lower serum 25-(OH) D_3 levels than those with the wild genotypes (aa + Aa vs. AA:13.5 ± 1.4 vs. 17.4 ± 1.5; $P < 0.05$) (Zaki et al. 2017), while another study indicated the *ApaI* (C>A) CA variant was not correlated with maternal 25-hydroxyvitamin D_3 (25-(OH) D_3) levels (β = -2.65; 95% CI: -10.83, 5.51; P = 0.52) for women in Brazil (Pereira-Santos et al. 2019). However, the insufficient number of current studies included could not rule out the possibility of sampling error and publication bias, which can also affect the results. Second, since the *FokI* polymorphism has consequences for both VDR protein structure and transcriptional activity (Whitfield et al. 2001), most studies have examined the association of the *VDR* gene *FokI* polymorphism with HDP susceptibility. Our meta-analysis failed to provide adequate evidence to support the association between the *FokI* polymorphism and the risk of HDP. This finding is consistent with most prior studies (Caccamo et al. 2020; Magiełda-Stola et al. 2021; Rezavand et al. 2019; Rezende et al. 2012; Si et al. 2022), while there were also studies that had contrary results (Farajian-Mashhadi et al. 2020; Setiarsih et al. 2022; Zhan et al. 2015), e.g. Mashhadi et al. (Farajian-Mashhadi et al. 2020) and Zhan et al.(Zhan et al. 2015) reported the f allele of the *FokI* polymorphism as the protective factor and risk factor for HDP, respectively. On the other hand, given the potential mediating role of vitamin D status in this association (Caccamo et al. 2020), the exact role played by the *VDR* gene *FokI* polymorphism in vitamin D concentrations remains obscure as well. Monticielo

et al. reported significantly higher concentrations of 1,25-$(OH)_2D_3$ in Brazil subjects with the *FokI* f/f genotype than those with the F/F genotype (31.6 ± 14.1 ng/ml vs. 23.0 ± 9.2 ng/ml; P = 0.004) (Monticielo et al. 2012). On the contrary, another study conducted by Karras et al. in Greece suggested that mothers with the *FokI* F/F polymorphism had a 70% lower risk of vitamin D deficiency compared with f/f ones (OR: 0.30; 95 % CI: 0.09, 0.92; P = 0.03) (Karras et al. 2020), however, there was also a study revealing that the *FokI* f/f genotype was not associated with vitamin D levels and deficiency of vitamin D among a Greek rural population (OR: 0.56; 95 % CI: 0.29, 1.10; P = 0.09) (Divanoglou et al. 2021). Third, the heterogeneity did not decrease in parallel after subgroup analysis based on ethnic groups, indicating that the inconsistent results of current studies and the heterogeneity of this meta-analysis might not only be derived from the differences in the sample sizes, populations, or ethnicities of the subjects, but gene-environment interactions that need to be considered. One study conducted by Serrano et al. preliminarily displayed the interaction between alcohol consumption and family history in preeclampsia patients (Serrano et al. 2020), but the available evidence is absent for the existence of interaction effects between the *VDR* gene SNPs and environmental risk factors on HDP. Further studies are needed to clarify the complex gene-gene, gene-environment, and gene-nutrient interactions.

Although the mechanisms through how the *VDR* gene polymorphisms affect the risk of HDP are still not entirely clear, it is rational in biology. Evidence for the association of the *VDR* gene polymorphisms with common risk factors for HDP has been reported in previous studies, such as obesity (Chen et al. 2019), GDM (Zeng et al. 2022), hypertension susceptibility (Zhu et al. 2019), chronic kidney disease (CKD) susceptibility (Santoro et al. 2015), etc. Furthermore,

the *VDR* gene polymorphisms might be involved in target organ damage in hypertensive patients (Kulah et al. 2006). On the other hand, vitamin D deficiency was found associated with endothelial dysfunction and vascular damage (Kim et al. 2020). Vitamin D has been proven to downregulate the renin-angiotensin-aldosterone system (RAAS), which is one of the essential mechanisms of blood pressure regulation (Giménez et al. 2020). Since the VDR is extensively expressed in cardiomyocytes and vascular endothelial cells, and the 1,25-$(OH)_2D_3$ may suppress the RAAS to maintain stable BP by binding to the VDR (Giménez et al. 2020). Based on that, vitamin D supplementation during pregnancy was regarded to be protective against preeclampsia (Khaing et al. 2017), and the response to vitamin D supplementation can also be regulated by the *VDR* gene (Usategui-Martín et al. 2022).

The present meta-analysis has several limitations that should be considered. First, the number of eligible studies included in this meta-analysis was relatively small. This limited the strength of evidence for our findings and further investigation in the meta-analysis. We did not conduct the subgroup analysis based on the subtypes of HDP since the grouping status for gestational hypertension and preeclampsia was not available in most studies included. In addition, data provided by current studies on stratification by ethnicity was limited, thus constraining our further elucidation of ethnic differences. Second, the existence of potential confounding factors could not be ruled out, including obesity, smoking, alcohol intake, etc., and these possible confounding factors might bias the results of our meta-analysis when pooling the unadjusted results. Third, an obvious heterogeneity was observed among these studies, indicating that the results from current studies are still characterized by considerable uncertainty and

335 controversy and the pooled results should be interpreted with caution.

336

337 **5 Conclusions**

338 In conclusion, our current meta-analysis provides evidence that the *VDR* gene *ApaI* and
339 *BsmI* polymorphisms may be associated with the susceptibility risk of HDP. The existing
340 evidence is insufficient to conclude that there are ethnic differences in the association of the *VDR*
341 gene polymorphisms with HDP. Therefore, more case-control studies of high quality with larger
342 sample sizes from multiple ethnic groups deserve to be launched to further confirm our findings.

343

344 **Abbreviations**

345 VDR: vitamin D receptor; HDP: hypertensive disorders of pregnancy; OR: odds ratios; CI:
346 confidence intervals; BP: blood pressure; GDM: gestational diabetes mellitus; ACE: angiotensin-
347 converting enzyme; MTHFR: methylenetetrahydrofolate reductase; TNF-α: tumor necrosis
348 factor-α; COMT: catechol-O-methyltransferase; RAAS: renin-angiotensin-aldosterone system;
349 1,25-(OH)2D3: 1,25-Dihydroxyvitamin D3; SNP: single nucleotide polymorphism; PRISMA:
350 Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO:
351 International Prospective Register of Systematic Reviews; HWE: Hardy-Weinberg equilibrium;
352 NOS: Newcastle-Ottawa Scale; GH: gestational hypertension; PE: pre-eclampsia; PCR-RFLP:
353 polymerase chain reaction-restriction fragment length polymorphism; TaqMan qPCR: TaqMan-
354 Based real-time polymerase chain reaction; MALDI-TOF MS PCR: matrix-assisted laser
355 desorption ionization time-of-flight mass spectrometry coupled with single-base extension

polymerase chain reaction.

Data availability

The data described in this article can be freely and openly accessed from the original published articles in the database.

Conflicts of Interest

The authors declare that they have no competing interests.

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None.

Author Contributions

Z-Y, GY-C, XH-L, and L-XH contributed to the conception and design of this study.

Z-Y, GY-C, and T-XL performed the critical appraisal and data extraction.

Z-Y and G-YC were equally responsible for the subsequent data analysis, interpretation of the results, and drafting of the manuscript.

XH-L and L-XH revised the manuscript critically for important intellectual content.

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Table 1(on next page)

Characteristics of included studies in the meta-analysis

Table 1 Characteristics of included studies in the meta-analysis

Table 1 Characteristics of included studies in the meta-analysis

					Age, y		Sample size, n				
Authors	Year	Country	Ethnicity	Disease	Case	Control	Case	Control	Genotyping methods	SNPs	NOS
Rezende et al.	2012	Brazil	Caucasian	GH, PE	28.1 ± 6.8	26.6 ± 6.1	316	213	PCR-RFLP	*ApaI, BsmI, FokI*	6
Zhan et al.	2015	China	Asian	PE	30.7 ± 5.7	30.7 ± 4.5	402	554	TaqMan qPCR	*BsmI, FokI*	7
Rezavand et al.	2019	Iran	Asian	PE	31.4 ± 6.4	29.0 ± 6.0	100	100	PCR-RFLP	*BsmI, FokI, TaqI*	5
Caccamo et al.	2020	Italy	Caucasian	GH, PE	33.0 ± 6.2	33.0 ± 5.9	116	69	TaqMan qPCR	*BsmI, FokI*	7
Farajian-Mashhadi et al.	2020	Iran	Asian	PE	27.6 ± 6.4	28.1 ± 6.4	152	160	PCR-RFLP	*ApaI, BsmI, FokI, TaqI*	6
Magielda-Stola et al.	2021	Poland	Caucasian	PE	30.1 ± 5.5	30.6 ± 4.4	122	184	PCR-RFLP	*ApaI, BsmI, FokI, TaqI*	7
Ghorbani et al.	2021	Iran	Asian	PE	31.4 ± 6.4	29.0 ± 6.0	100	100	PCR-RFLP	*ApaI*	6
Si et al.	2022	China	Asian	GH, PE	29.3 ± 4.0	28.7 ± 3.6	105	3594	MALDI-TOF MS PCR	*ApaI, FokI*	8
Setiarsih et al.	2022	Indonesia	Asian	GH, PE	29.1 ± 6.9	27.1 ± 6.0	105	105	PCR-RFLP	*FokI, TaqI*	6

Abbreviations: GH, gestational hypertension; PE, pre-eclampsia; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; TaqMan qPCR, TaqMan-Based real-time polymerase chain reaction; MALDI-TOF MS PCR, matrix-assisted laser desorption ionization time-of-flight mass spectrometry coupled with single-base extension polymerase chain reaction; SNP, single nucleotide polymorphism; NOS, Newcastle-Ottawa Scale.

Table 2(on next page)

Genotype frequencies of vitamin D receptor gene polymorphisms in HDP patients and matched controls

Table 2 Genotype frequencies of vitamin D receptor gene polymorphisms in HDP patients and matched controls

Table 2 Genotype frequencies of vitamin D receptor gene polymorphisms in HDP patients and matched controls

SNP	Authors	Genotype						HWE
		Case			Control			
								P value
ApaI (rs7975232)		AA	Aa	aa	AA	Aa	aa	
	Rezende et al.	92	156	68	70	98	45	0.329
	Farajian-Mashhadi et al.	36	95	21	45	91	24	**0.046**
	Magielda-Stola et al.	38	61	23	40	97	47	0.449
	Ghorbani et al.	9	62	29	17	46	37	0.677
	Si et al.	11	15	3	371	270	57	0.427
BsmI (rs1544410)		BB	Bb	bb	BB	Bb	bb	
	Rezende et al.	52	159	105	36	107	70	0.651
	Zhan et al.	313	84	5	456	89	9	0.062
	Rezavand et al.	20	72	8	28	65	7	**<0.001**
	Caccamo et al.	23	65	28	11	36	22	0.557
	Farajian-Mashhadi et al.	39	86	27	40	90	30	0.102
	Magielda-Stola et al.	41	48	33	82	74	28	0.104
FokI (rs2228570)		FF	Ff	ff	FF	Ff	ff	
	Rezende et al.	121	145	50	90	104	19	0.150
	Zhan et al.	63	176	163	101	292	161	0.117
	Rezavand et al.	6	22	72	7	38	55	0.900
	Caccamo et al.	55	43	18	31	27	11	0.227
	Farajian-Mashhadi et al.	106	38	8	89	54	17	0.052
	Magielda-Stola et al.	30	58	34	40	102	42	0.140
	Si et al.	3	15	10	145	349	202	0.799
	Setiarsih et al.	16	53	36	7	50	48	0.205
TaqI (rs731236)		TT	Tt	tt	TT	Tt	tt	
	Rezavand et al.	40	51	9	40	55	5	**0.011**
	Farajian-Mashhadi et al.	59	71	22	65	70	25	0.399
	Magielda-Stola et al.	42	59	21	84	78	22	0.554
	Setiarsih et al.	98	7	0	97	8	0	0.685

Abbreviations: HDP, Hypertensive Disorders of Pregnancy; HWE, Hardy–Weinberg equilibrium; SNP, single nucleotide polymorphism.

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Table 3(on next page)

Meta-analysis of associations between VDR *ApaI* (rs7975232), *BsmI* (rs1544410), *FokI* (rs2228570) and *TaqI* (rs731236) polymorphisms and HDP

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				Test of association			Tests of heterogeneity				Begg test for publication test		Egger test for publication bias	
SNP	Comparison	Subgroup	No. of studies	OR	95% CI	*P*-value	Model	Q	*P*-value	I^2, %	*z*	*P*-value	*t*	*P*-value
ApaI														
	a vs A	Overall	4	0.98	0.82, 1.16	0.799	F	5.67	0.129	47.1	0.34	0.734	0.36	0.753
		Asian	2	1.11	0.79, 1.57	0.550	F	1.02	0.312	2.3				
		Caucasian	2	0.90	0.60, 1.35	0.606	R	3.95	0.047	74.7				
	aa + Aa vs AA	Overall	4	1.44	1.10, 1.88	**0.007**	F	2.34	0.506	0.0	1.70	0.089	4.27	0.051
		Asian	2	1.95	1.10, 3.46	**0.022**	F	0.03	0.856	0.0				
		Caucasian	2	1.32	0.98, 1.79	0.069	F	0.93	0.335	0.0				
	aa vs Aa + AA	Overall	4	1.04	0.78, 1.39	0.767	F	3.32	0.345	9.6	-0.34	1.000	0.18	0.874
		Asian	2	0.79	0.46, 1.35	0.388	F	0.79	0.374	0.0				
		Caucasian	2	1.17	0.83, 1.64	0.370	F	1.07	0.301	6.4				
	aa vs AA	Overall	4	1.42	0.99, 2.01	0.051	F	1.68	0.641	0.0	0.34	0.734	0.97	0.435
		Asian	2	1.57	0.73, 3.39	0.252	F	0.05	0.831	0.0				
		Caucasian	2	1.38	0.93, 2.04	0.109	F	1.55	0.213	35.4				
	Aa vs AA	Overall	4	1.46	1.10, 1.94	**0.010**	F	2.65	0.449	0.0	1.70	0.089	5.64	**0.030**
		Asian	2	2.14	1.17, 3.92	**0.014**	F	0.28	0.599	0.0				
		Caucasian	2	1.31	0.95, 1.81	0.106	F	0.41	0.524	0.0				
BsmI														
	b vs B	Overall	5	1.02	0.80, 1.28	0.604	R	11.08	0.026	63.9	-0.24	1.000	-0.09	0.937

	Asian	2	0.90	0.72, 1.11	0.308	F	0.94	0.333	0.0				
	Caucasian	3	1.10	0.76, 1.61	0.604	R	7.78	0.020	74.3				
bb + Bb vs BB	Overall	5	1.03	0.84, 1.26	0.777	F	6.99	0.136	42.8	0.73	0.462	-1.33	0.277
	Asian	2	1.26	0.96, 1.66	0.101	F	0.32	0.574	0.0				
	Caucasian	3	0.80	0.59, 1.09	0.162	F	2.11	0.349	5.1				
bb vs Bb + BB	Overall	5	0.81	0.64, 1.04	0.103	F	5.22	0.266	23.3	0.24	0.806	-0.95	0.413
	Asian	2	0.90	0.54, 1.50	0.681	F	0.11	0.738	0.0				
	Caucasian	3	0.72	0.45, 1.17	0.184	R	4.92	0.085	59.3				
bb vs BB	Overall	5	0.72	0.56, 0.99	**0.042**	F	5.11	0.276	21.7	0.24	0.806	-0.33	0.765
	Asian	2	0.80	0.43, 1.49	0.489	F	0.00	0.985	0.0				
	Caucasian	3	0.66	0.36, 1.20	0.176	R	4.96	0.084	59.7				
Bb vs BB	Overall	5	1.11	0.89, 1.37	0.361	F	4.02	0.404	0.4	0.73	0.462	-1.93	0.149
	Asian	2	1.30	0.98, 1.74	0.070	F	0.45	0.504	0.0				
	Caucasian	3	0.89	0.64, 1.24	0.494	F	0.65	0.724	0.0				
FokI													
f vs F	Overall	8	1.08	0.88, 1.34	0.459	R	28.55	<0.001	75.5	0.12	0.902	0.52	0.623
	Asian	5	1.08	0.78, 1.50	0.631	R	25.90	<0.001	84.6				
	Caucasian	3	1.13	0.94, 1.36	0.177	F	1.65	0.438	0.0				
ff + Ff vs FF	Overall	8	0.91	0.67, 1.23	0.531	R	15.33	0.032	54.3	0.12	0.902	-0.53	0.613
	Asian	5	0.85	0.48, 1.51	0.579	R	13.46	0.009	70.3				
	Caucasian	3	1.04	0.80, 1.35	0.795	F	1.23	0.541	0.0				
ff vs Ff + FF	Overall	8	1.23	0.88, 1.73	0.228	R	20.14	0.005	65.2	1.11	0.266	-1.44	0.201

		Asian	5	1.12	0.66, 1.91	0.671	R	18.06	0.001	77.9				
		Caucasian	3	1.43	1.01, 2.03	**0.041**	F	2.01	0.366	0.6				
	ff vs FF	Overall	8	1.11	0.73, 1.70	0.615	R	17.00	0.017	58.8	0.87	0.386	-1.24	0.262
		Asian	5	0.98	0.48, 2.02	0.957	R	14.12	0.007	71.7				
		Caucasian	3	1.35	0.91, 2.01	0.130	F	2.71	0.258	26.1				
	Ff vs FF	Overall	8	0.86	0.71, 1.04	0.127	F	9.08	0.247	22.9	0.12	0.902	-0.60	0.573
		Asian	5	0.79	0.60, 1.04	0.087	F	7.45	0.114	46.3				
		Caucasian	3	0.94	0.71, 1.24	0.659	F	0.85	0.655	0.0				
TaqI	t vs T	Overall	3	1.18	0.93, 1.49	0.167	F	2.39	0.303	16.3	0.00	1.000	-0.46	0.724
		Asian	2	0.99	0.71, 1.37	0.933	F	0.06	0.802	0.0				
		Caucasian	1	1.42	1.02, 1.98	**0.040**								
	tt + Tt vs TT	Overall	3	0.85	0.62, 1.16	0.296	F	2.85	0.240	29.9	0.00	1.000	-0.05	0.969
		Asian	2	1.06	0.71, 1.60	0.773	F	0.16	0.688	0.0				
		Caucasian	1	0.63	0.39, 1.01	0.054								
	tt vs Tt + TT	Overall	3	0.78	0.50, 1.22	0.270	F	0.55	0.759	0.0	0.00	1.000	0.13	0.916
		Asian	2	0.91	0.49, 1.69	0.769	F	0.00	0.963	0.0				
		Caucasian	1	0.65	0.34, 1.25	0.195								
	tt vs TT	Overall	3	0.71	0.44, 1.13	0.145	F	1.31	0.520	0.0	0.00	1.000	0.07	0.955
		Asian	2	0.90	0.48, 1.70	0.750	F	0.00	0.962	0.0				
		Caucasian	1	0.52	0.26, 1.05	0.068								
	Tt vs TT	Overall	3	0.87	0.62, 1.20	0.387	F	2.11	0.348	5.4	0.00	1.000	-0.08	0.952
		Asian	2	1.06	0.69, 1.63	0.798	F	0.16	0.691	0.0				
		Caucasian	1	0.66	0.40, 1.09	0.104								

Abbreviations: VDR, Vitamin D receptor; HDP, Hypertensive Disorders of Pregnancy; SNP, single nucleotide polymorphism; OR odds ratio; 95% CI, 95% confidence interval; F fixed effect model; R random effect model.

Figure 1

Figure 1. Flow chart of the included studies of meta-analysis.

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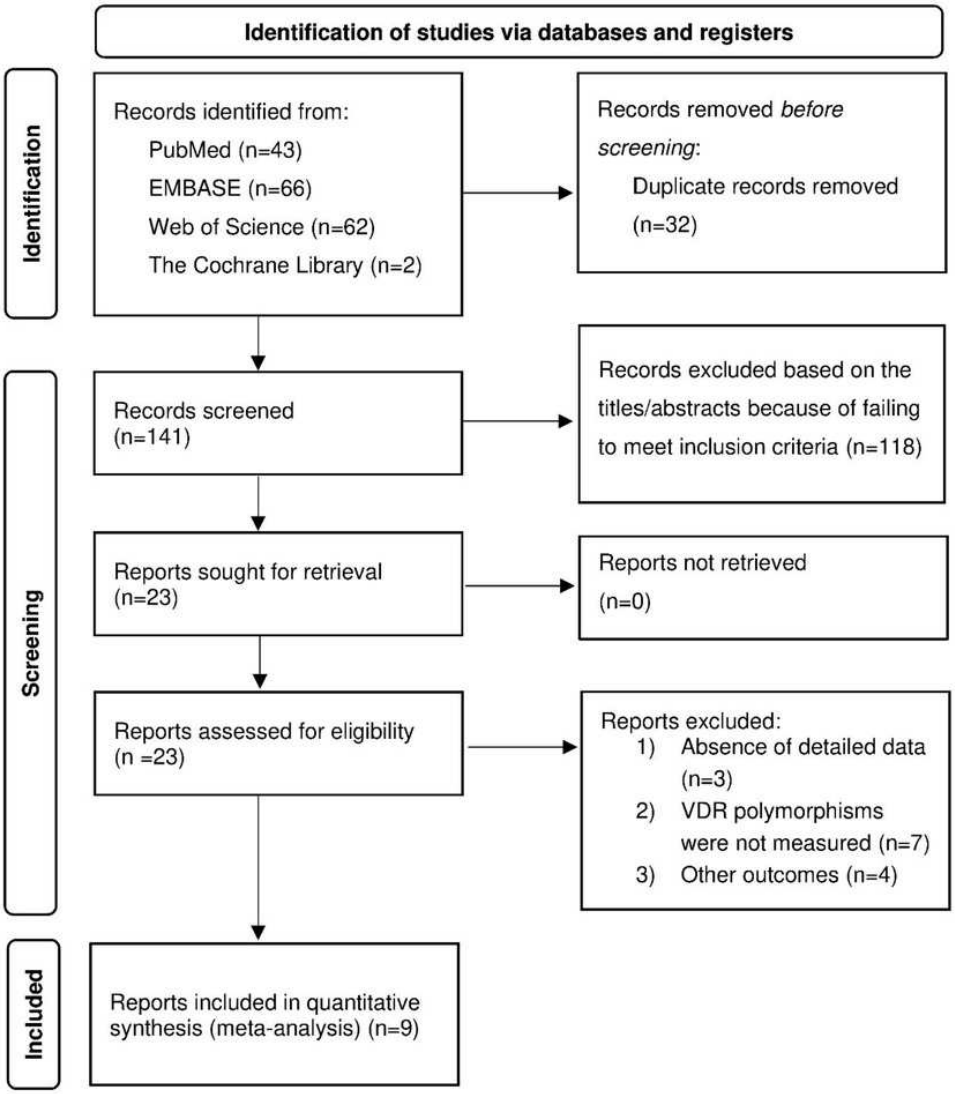


Figure 1. Flow chart of the included studies of meta-analysis.

Figure 2

Association between the *VDR* gene *ApaI* polymorphism and hypertensive disorders of pregnancy.

Figure 2. Forest plot for pooled odds ratio (OR) and the corresponding 95% confidence interval (CI) of the association between the *ApaI* polymorphism and hypertensive disorders of pregnancy (HDP); (A) Dominant model (aa + Aa vs. AA); (B) Heterozygote model (Aa vs. AA).

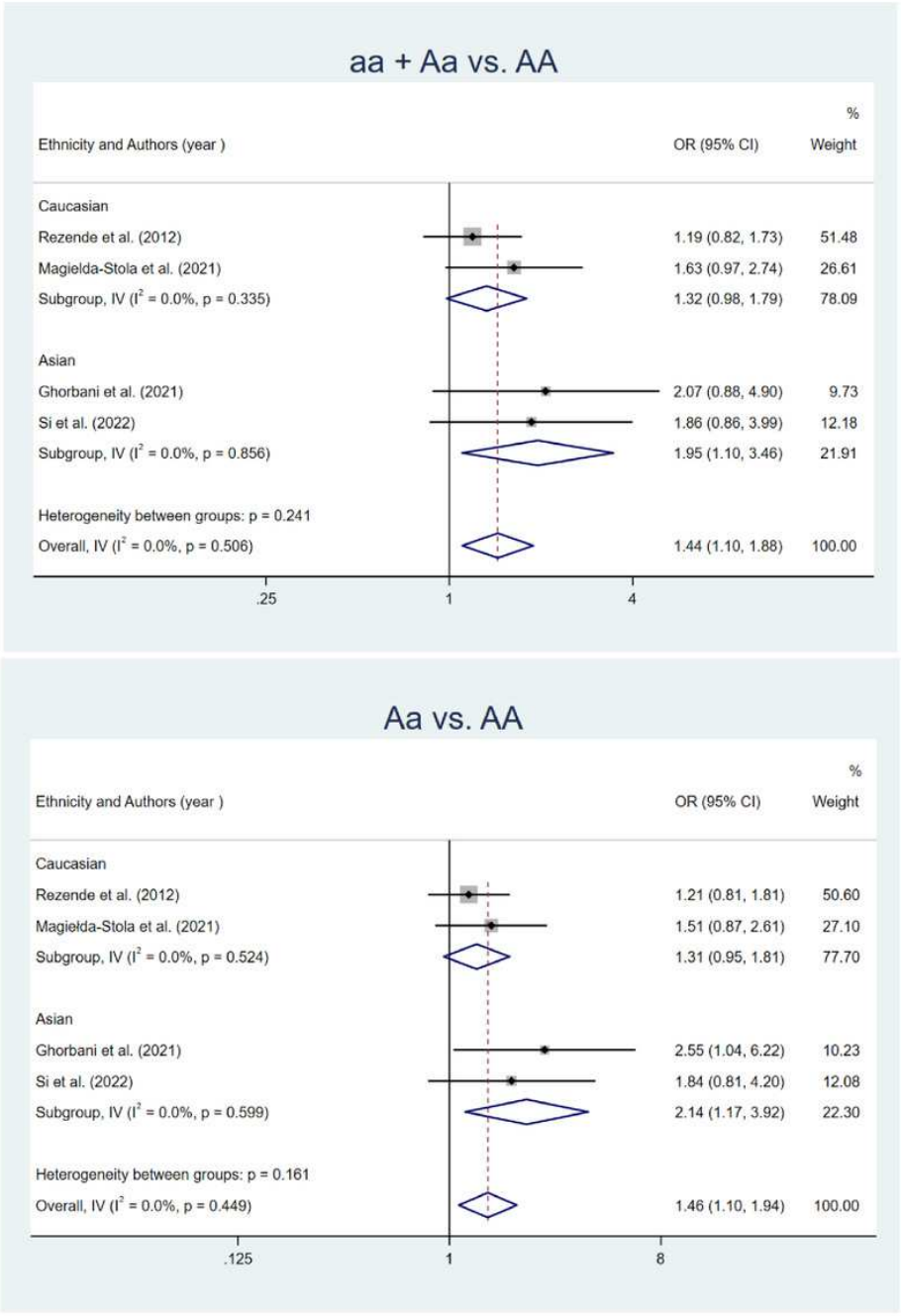


Figure 2. Forest plot for pooled odds ratio (OR) and the corresponding 95% confidence interval (CI) of the association between the *ApaI* polymorphism and hypertensive disorders of pregnancy (HDP); (A) Dominant model (aa + Aa vs. AA); (B) Heterozygote model (Aa vs. AA).

Figure 3

Association between the *VDR* gene *BsmI* polymorphism and hypertensive disorders of pregnancy.

Figure 3. Forest plot for pooled odds ratio (OR) and the corresponding 95% confidence interval (CI) of the association between the *BsmI* polymorphism and hypertensive disorders of pregnancy (HDP) in the homozygote model (bb vs. BB).

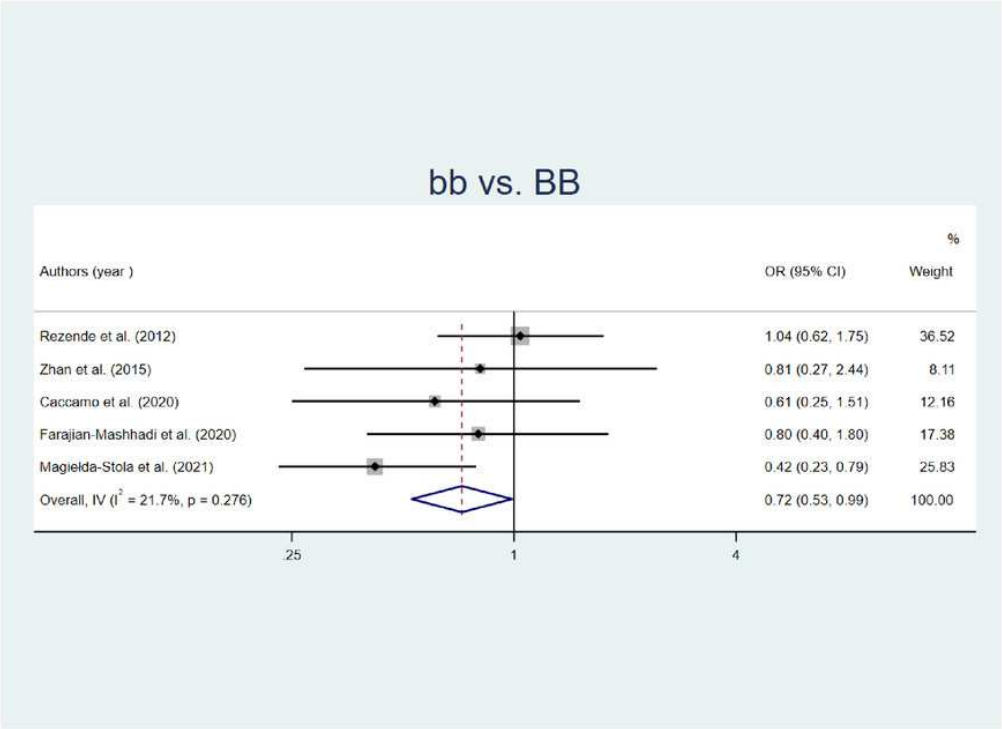
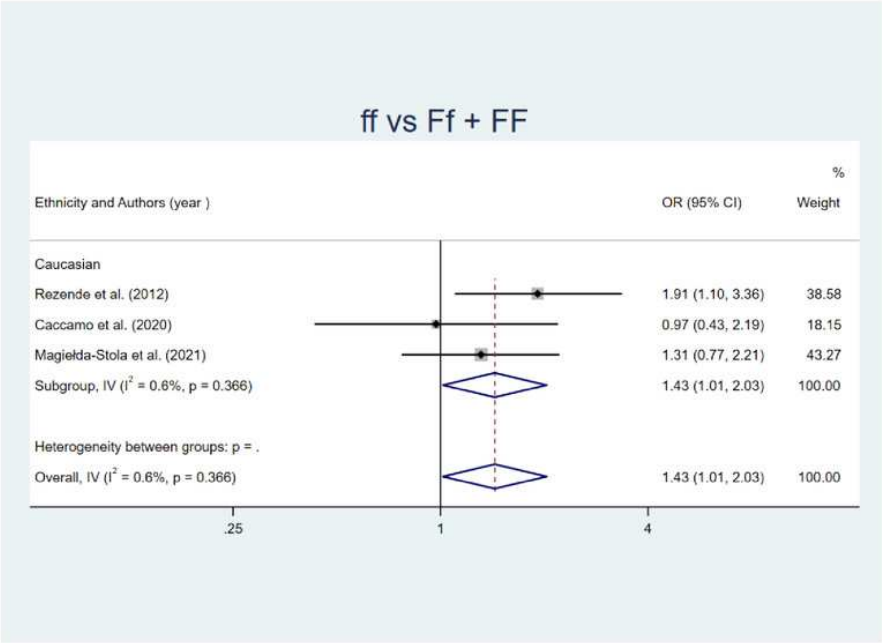


Figure 3. Forest plot for pooled odds ratio (OR) and the corresponding 95% confidence interval (CI) of the association between the *BsmI* polymorphism and hypertensive disorders of pregnancy (HDP) in the homozygote model (bb vs. BB).

Figure 4

Association between the *VDR* gene *FokI* polymorphism and hypertensive disorders of pregnancy.

Figure 4. Forest plot for pooled odds ratio (OR) and the corresponding 95% confidence interval (CI) of the association between the *FokI* polymorphism and hypertensive disorders of pregnancy (HDP); (A) Recessive model (ff + Ff vs. FF) in Caucasians; (B) Recessive model (ff vs. Ff + FF) in the overall population.



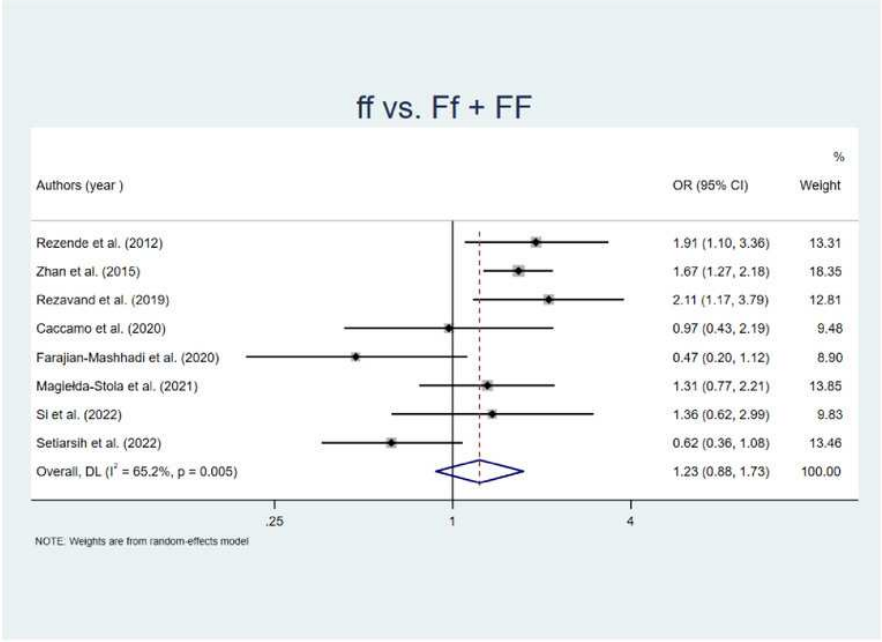


Figure 4. Forest plot for pooled odds ratio (OR) and the corresponding 95% confidence interval (CI) of the association between the *FokI* polymorphism and hypertensive disorders of pregnancy (HDP); (A) Recessive model (ff + Ff vs. FF) in Caucasians; (B) Recessive model (ff vs. Ff + FF) in the overall population.

Figure 5

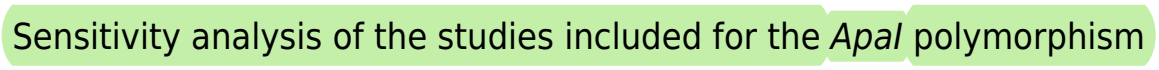


Figure 5. Sensitivity analysis of the studies included for the *ApaI* polymorphism; (A) Dominant model (aa + Aa vs. AA); (B) Heterozygote model (Aa vs. AA).

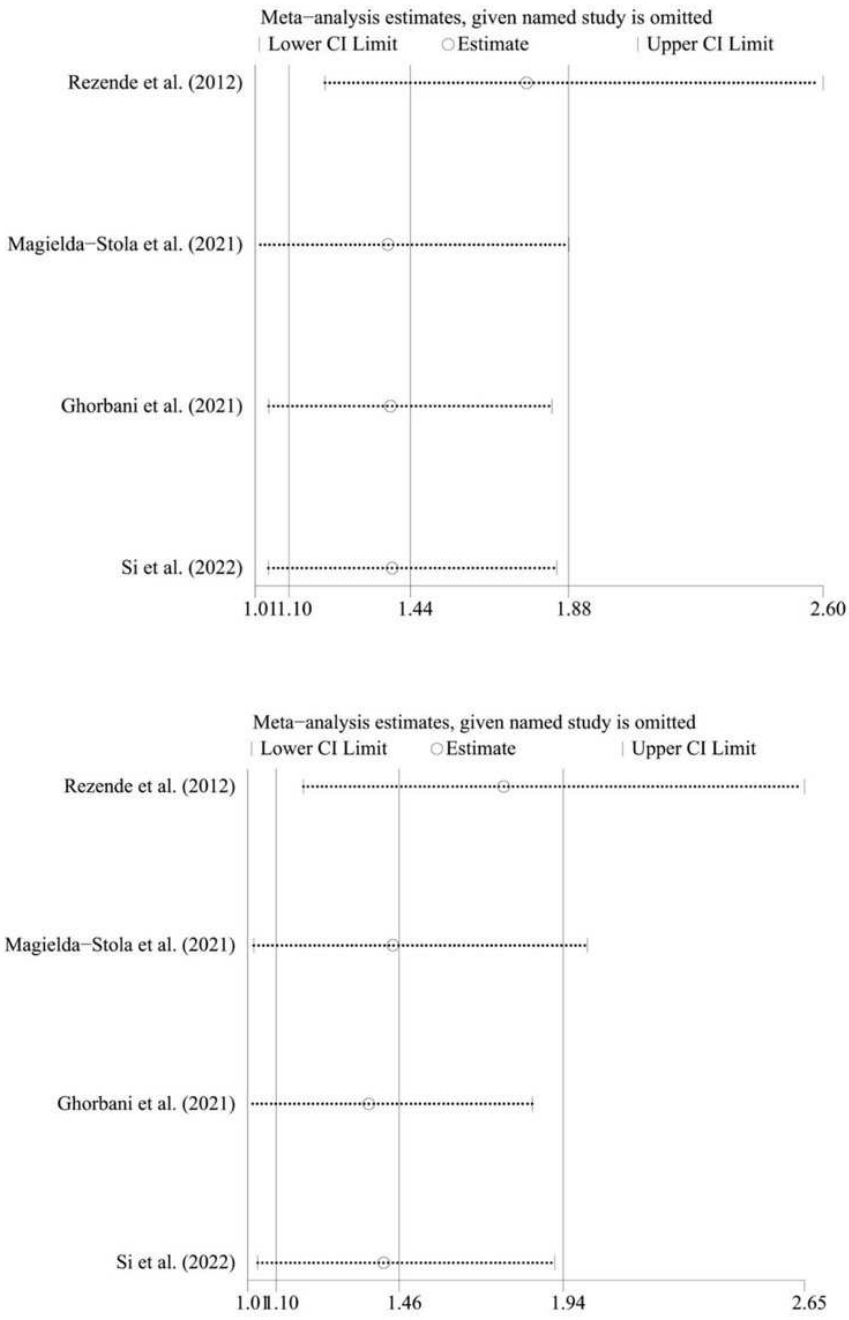


Figure 5. Sensitivity analysis of the studies included for the *ApaI* polymorphism; (A) Dominant model (aa + Aa vs. AA); (B) Heterozygote model (Aa vs. AA).