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META-ANALYSIS

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Association Between Gene Polymorphisms on Chromosome 1 and Susceptibility to Pre-Eclampsia: An Updated Meta-Analysis

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Background: This meta-analysis enabled us to obtain a precise estimation of the association between gene polymorphisms on chromosome 1 (*MTHFR*, *AGT*, *F5*, *IL-10*, *LEPR*) and the susceptibility to pre-eclampsia (PE) in order to reach a uniform conclusion.

Material/Methods: Web of Science, PubMed, EMBASE, Cochran Library (CENTRAL), and Chinese databases (Chinese National Knowledge Infrastructure-CNKI and Wan Fang) were electronically searched to select relevant studies for this meta-analysis. We selected 95 case-control studies investigating 5 genes (*MTHFR*, *AGT*, *F5*, *IL-10*, and *LEPR*) with 8 SNPs. Odds ratios (OR) with their 95% confidence intervals (CI) were used for estimating the association.

Results: A total of 16 646 PE patients and 28 901 normal-pregnancy patients were included in this meta-analysis. The overall results suggested that rs1801133 of *MTHFR* (OR=1.17, 95% CI: 1.05–1.13) and rs6025 of *F5* (OR=1.53, 95%CI: 1.07–2.20) are significantly associated with PE, whereas rs1801131 of *MTHFR*, rs699 and rs4762 of *AGT*, rs1800896 and rs1800871 of *IL*-10, and rs1137101 of *LEPR* have no significant association with PE. Subgroup analysis by ethnicity revealed that, except for *MTHFR* rs1801133 and *F5* rs6025 in Caucasians, which were significantly associated with an increased risk of PE, none of these SNPs were significantly associated with PE. As suggested by a symmetric funnel plot in conjunction with the Egger's test, there was no significant publication bias in *MTHFR* rs1801133 (*P*=0.318) and rs1801131 (*P*=0.204), *F5* rs6025 (*P*=0.511), *LEPR* rs1137101 (*P*=0.511), *AGT* rs4762 (*P*=0.215) and rs699 (*P*=0.482), *IL*-10 rs1800871 (*P*=0.955), and rs1800896 (*P*=0.144).

Conclusions: This meta-analysis provides evidence that *MTHFR* rs1801133 and *F5* rs6025 are associated with an increased risk of PE, especially in Caucasians. However, we do not have sufficient evidence to conclude there is a significant association between other gene polymorphisms and PE.

MeSH Keywords: Meta-Analysis as Topic • Polymorphism, Genetic • Pre-Eclampsia

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Background

Pre-eclampsia (PE) has a cluster of symptoms, including hypertension and albuminuria, which usually appear together after 20 weeks of pregnancy. PE has an incidence rate of 2–8% in pregnant females and it is associated with lesions of the vascular (high blood pressure) and renal (albuminuria) systems [1,2]. Furthermore, PE is thought to be associated with eclampsia, HELLP syndrome (characterized by hemolysis, upregulated liver enzymes, and low levels of platelets), kidney failure, lung edema, and hemorrhagic stroke; therefore, it poses enormous threats to the health of mothers and infants [3]. Although the etiology of PE is still unclear, it is suspected that various genetic and environmental factors are associated with the susceptibility to PE [2,4]. It has been observed that females who were born from a mother with PE have an increased risk of PE during their own gestation period. In addition, females with fathers who were born of mothers with PE have an increased risk of PE. Therefore, numerous investigations have been undertaken to clarify the role of genetic factors with significant effects on the prevalence of PE [5]. As suggested by previous reports, genetic polymorphisms of interleukin (IL)-10, methylenetetrahydrofolate reductase (MTHFR), angiotensinogen (AGT), leptin receptor (LEPR), and factor V (FV) might explain the potential role of genetic factors that affect the development of PE [6–10].

There are 2 procedures which are critical to the maintenance of pregnancy: one is the inhibition of T-helper 1 (Th1) lymphocytes and the other is the stimulation of Th2 lymphocytes [11–13]. IL-10 is believed to be involved in the etiology of PE due to its role in the reduction of inflammation-mediated vascular dysfunction and the regulation of trophoblastic infiltration [6].

Hyperhomocysteinemia has been confirmed to be involved in the pathogenesis of PE [14,15]. Furthermore, a high level of serum homocysteine is likely to be followed by endothelial disorders such as coronary artery disease [16] and atherosclerosis [17]. As a key enzyme for homocysteine and folate metabolism, MTHFR transforms 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is a methyl donor in the transformation from homocysteine to methionine, and this implies a relatively negative correlation between homocysteine and folate [7,18].

AGT is converted into angiotensin II by angiotensin-converting enzyme and is a major component of the renin-angiotensin system (RAS) [19]. The RAS is also a strong regulating system that greatly affects blood pressure and water-salt balance, indicating its critical role in the development of PE [20]. Additionally, leptin, which is well known to regulate body weight, tends to be an important cytokine for the regulation of arterial blood pressure [21]. Elevated circulating leptin levels, along with the reduced soluble LEPR concentrations, are reported to be associated with susceptibility to PE [22]. The activated FV (FVa) accompanied by activated factor X (FXa) converts prothrombin into thrombin, and a connection between hypercoagulability and PE has been proposed [4].

The *IL-10* gene, *MTHFR* gene, *AGT* gene, *LEPR* gene, and *FV* gene map to 1q31-q32, 1p36.3, 1q42.2, 1p31, and 1q23, respectively. We have noticed that inconsistent conclusions still exist among meta-analyses investigating the *IL-10* gene [6,23–25]. Few studies have examined the relationship between the *LEPR* gene and PE risk, and there is no published meta-analysis focusing on the association between the *LEPR* gene and susceptibility to PE. Therefore, this study was designed to assess the association between multiple genetic polymorphisms and PE susceptibility in order to address the issue of contradictory findings resulting from heterogeneity.

Material and Methods

Search strategy

Initially, a computer-based search of the online databases Web of Science, PubMed, EMBASE, Cochran Library (CENTRAL), and Chinese databases (Chinese National Knowledge Infrastructure-CNKI and Wan Fang) was conducted with no language constraint (up to September 2015) and the following searching terms were used: ("preeclampsia" OR "pre-eclampsia") AND ("polymorphism" OR "single nucleotide polymorphism'' OR "SNP" OR "variant") AND ("factor V" OR "thrombophilia" OR "MTHFR" OR "methylenetetrahydrofolate reductase" OR "homocysteine" OR "interleukin-10" OR "IL-10" OR "angiotensinogen" OR "AGT" OR "leptin receptor" OR "LEPR"). References in the included articles containing meta-analyses were manually searched to identify additional related papers.

Inclusion criteria

Case-control studies investigating the association between genetic polymorphisms on chromosome 1 and PE susceptibility were considered. Females with new-onset high blood pressure (>140/90 mm Hg) and albuminuria (≥300 mg/24 h) at or after 20 weeks of pregnancy were diagnosed as having PE [26]. Females with a previous twin pregnancy and history of hormone therapy were excluded. Studies with genotype frequencies or adequate original data in the case and control groups were included, and genotyping was carried out using recognized methods. All included studies were done in humans. Publications with duplicate data were selected based on the sample size. Meta-analyses, editorials, or other articles irrelevant to the research subjects were excluded.

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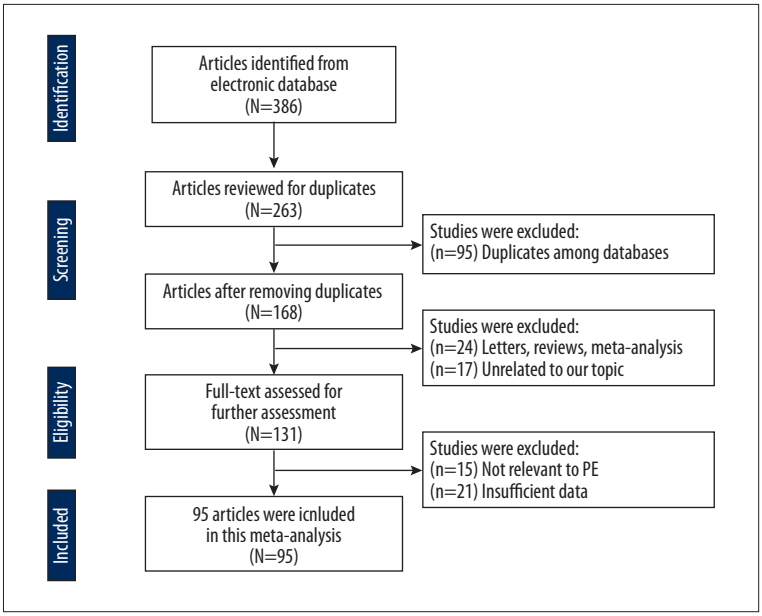

Figure 1. Literature selection flow chart.

Quality assessment

The methodological quality of the eligible studies was assessed by 2 independent researchers using the Newcastle-Ottawa Quality Assessment Scale (NOS) and any discrepancies between them were solved by discussion. The score system of NOS was based on 3 perspectives: selection, comparability, and exposure. A score of 6 or more out of 8 stars represents good quality [27].

Data extraction

Relevant information was independently obtained from all included studies by 2 researchers and any inconsistencies between them were reviewed by a third researcher. The following information was selected: name of first author, publication date, country and ethnicity, method for genotyping, and the number of cases and controls for each genotype.

Statistical analysis

The chi-squared goodness-of-fit test was used to assess whether the observed genotype frequency in the control group complied with Hardy-Weinberg equilibrium (HWE), and a *P* value of less than 0.05 suggests significant deviation from HWE. If the genotype distribution did not comply with HWE, then the corresponding study was eliminated. The strength of association between genetic polymorphisms on chromosome 1 and PE susceptibility was measured by odds ratios (ORs) along with their corresponding 95% confidence intervals (CIs). Moreover, the pooled ORs were calculated under the allele model, and the Z-test with a significance level of 0.05 was used to determine whether a significant association existed between each SNP and PE susceptibility. Study heterogeneity was measured by using the I^2 statistic and *Cochran's Q* [28,29]. The random-effects model was used to summarize the ORs if I^2 >50% and *P* value <0.1 [30]; whereas the fixed-effects model was used if there was no significant heterogeneity [28]. Potential publication bias was evaluated by a funnel plot, with a significance level of 0.05 [31]. The above analyses were all performed using R (version 3.2.1) statistical software.

Results

Literature selection

A total of 386 articles were discovered after the initial search strategy performed in Web of Science, PubMed, EMBASE, Cochran Library (CENTRAL), and Chinese databases (Chinese National Knowledge Infrastructure-CNKI and Wan Fang). By reviewing the abstracts and titles, 218 articles were excluded as not relevant to the research subject. After the exclusion of meta-analyses, reviews, studies without sufficient data, and studies with duplicate data, 95 articles with 150 eligible studies were selected (Figure 1). The methodological quality of these studies was systematically evaluated by 2 independent reviewers in accordance with the Newcastle-Ottawa Quality Assessment Scale (NOS). The NOS involves 3 main areas: study selection, comparability, and exposure. Each study was scored with answers to 8 questions, with a maximum score of 8. A total of 16 646 PE patients and 28 901 healthy mothers were included in the meta-analysis. The characteristics of the 150 included studies are summarized in Supplementary Figures 1, 2: 28 case-control studies involving *F5* polymorphisms (rs6025); 23 case-control studies involving *AGT* polymorphisms (rs699,

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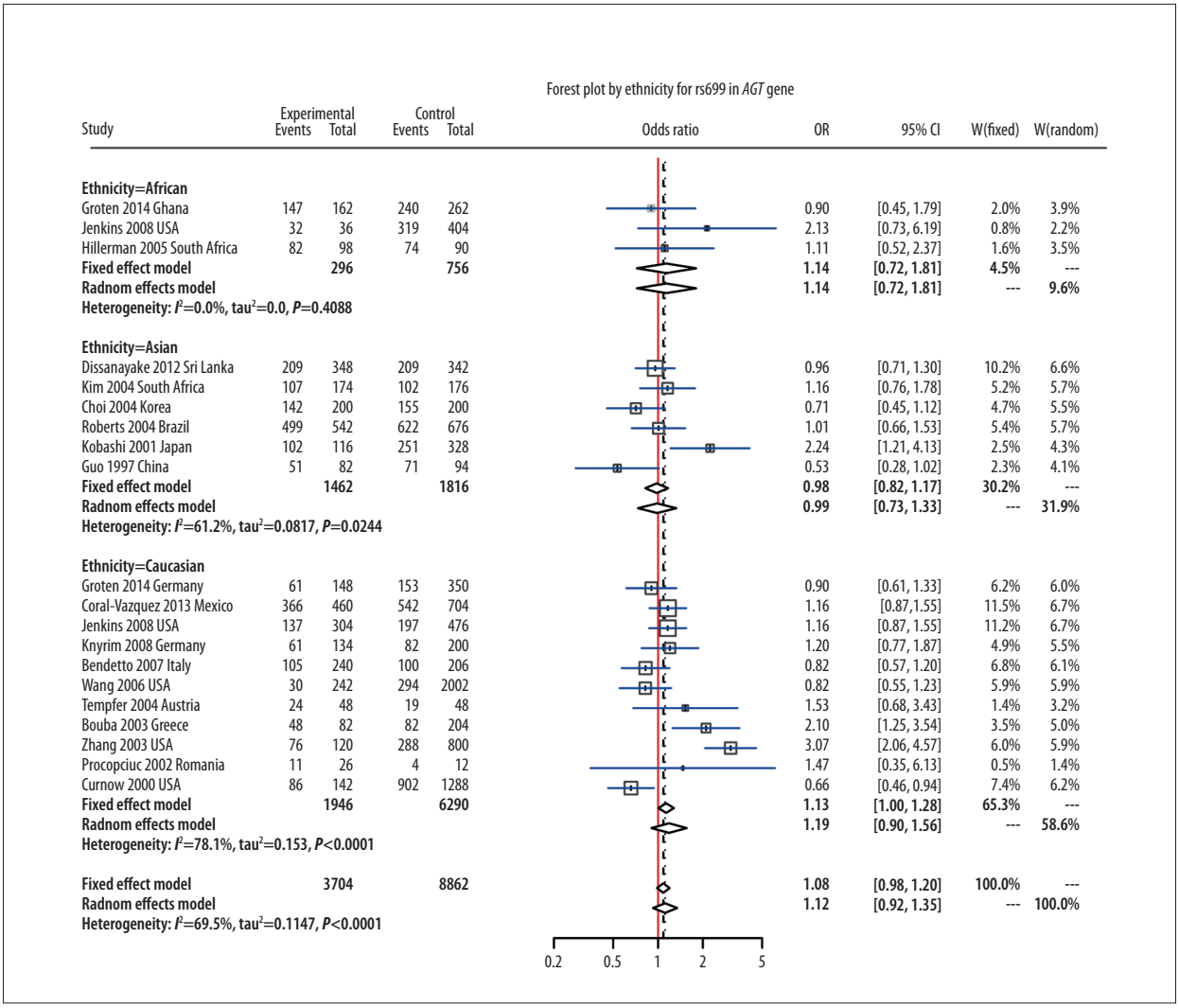
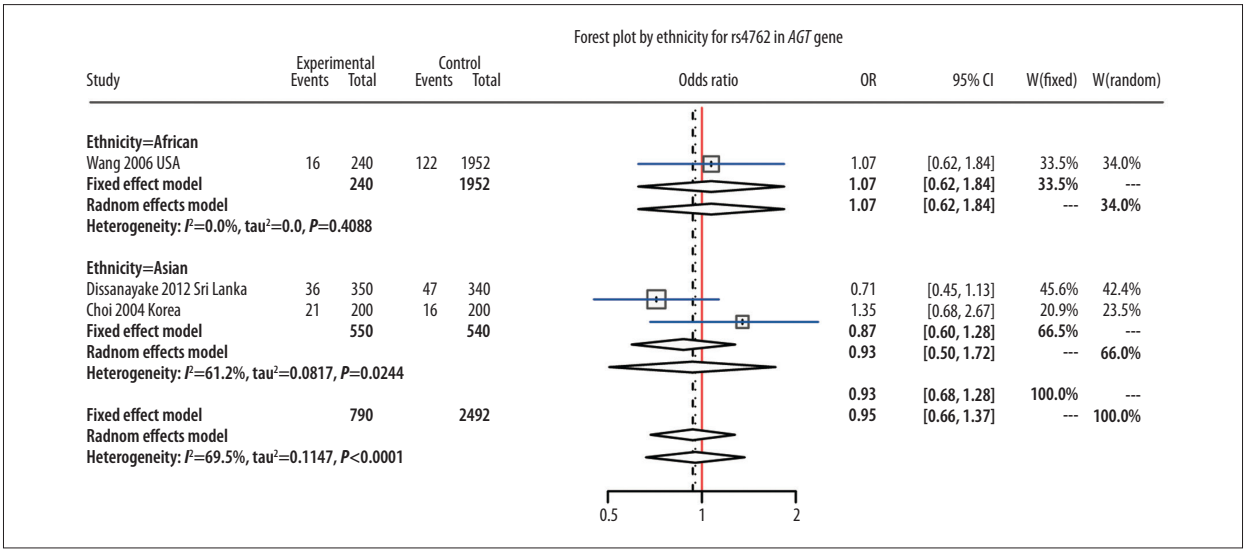


Supplementary Figure 1. Forest plot by ethnicity for rs699 in *AGT* gene.



Supplementary Figure 2. Forest plot by ethnicity for rs4762 in *AGT* gene.

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Table 1. Meta analysis of eight polymorphisms and PE susceptibility.

Gene	SNP	Genetic model	OR [95% CI]	$P_{odds\ ratio}$	Tau^2	I^2	$P_{heterogeneity}$	Ethnicity			$P_{publication\ bias}$
								Caucasians	Asian	African	
F5	rs6025	**A** *vs.* G	**1.53 [1.07,2.20]**	**0.024**	0.659	74.02%	0.000	**1.54 [1.01,2.36]**	1.35 [0.92,1.99]	–	0.511
AGT	rs699	**G** *vs.* A	1.12 [0.92,1.35]	0.266	0.129	71.97%	0.000	1.19 [0.90,1.56]	0.99 [0.73,1.33]	1.14 [0.72,1.81]	0.482
	rs4762	**T** *vs.* C	0.93 [0.68,1.28]	0.673	0.029	26.65%	0.266	–	0.93 [0.50,1.72]	1.07 [0.62.1.84]	0.215
MTHFR	rs1801131	**T** *vs.* C	1.14 [0.93,1.40]	0.196	0.054	59.61%	0.012	1.17 [0.86,1.59]	1.25 [0.98,2.18]	0.91 [0.64,1.29]	0.204
	rs1801133	**C** *vs.* A	**1.17 [1.05,1.31]**	**0.002**	0.073	67.26%	0.000	**1.16 [1.02,1.32]**	1.21 [0.95,1.54]	1.20 [0.77,1.88]	0.318
IL-10	rs1800896	**G** *vs.* A	0.91 [0.75,1.11]	0.366	0.063	72.77%	0.000	0.99 [0.90,1.10]	0.98 [0.45,2.14]	0.20 [0.07,0.58]	0.144
	rs1800871	**T** *vs.* C	0.79 [0.58,1.07]	0.655	0.166	82.99%	0.000	0.94 [0.69,1.27]	0.65 [0.41,1.03]	–	0.694
LEPR	rs1137101	**G** *vs.* A	1.41 [0.93,2.12]	0.114	0.126	69.59%	0.024	1.44 [1.05,1.98]	1.28 [0.46,3.55]	–	0.486

[1] Pooled odds ratios and 95% confidence intervals.

rs4762); 58 case-control studies involving *MTHFR* polymorphisms (rs1801131, rs1801133); 13 studies involving *IL-10* polymorphisms (rs1800896, rs1800971); and 4 studies involving *LEPR* polymorphism (rs1137101).

Association between chromosome 1 polymorphisms and PE

In this meta-analysis, we identified 8 polymorphisms on *chromosome 1* that may be associated with PE susceptibility (Table 1). The random-effects model was used to synthesize evidence for studies involving rs6025, rs699, rs1801131, rs1801133, rs1800896, rs1800871, and rs1137101, whereas the fixed-effects model was used for rs4762 (I^2=26.65%, *P*=0.266) (Table 1). Results of the meta-analysis showed that polymorphism of rs1801133 (6 678 cases/11 756 controls) was significantly associated with a 17% increase in risk of PE under the allelic model (OR=1.17, 95%CI: 1.05–1.13, *P*=0.002, Figure 2). Subgroup analysis by ethnicity revealed that this association was significant in Caucasians under the allelic model (OR=1.16, 95%CI: 1.02–1.32, Figure 2), but this association under the allelic model was not significant in Asians (OR=1.21, 95%CI: 0.95–1.54) or Africans (OR=1.20, 95%CI: 0.77–1.88, Figure 2). For rs6025 (4105 cases/4917 controls), the pooled result demonstrated that rs6025 was also significantly associated with a 53% increase in the risk of PE under the allelic model (OR=1.53, 95%CI: 1.07–2.20, *P*=0.024, Figure 3). Subgroup analysis by ethnicity suggested that this association was significant in Caucasians (OR = 1.54, 95% CI: 1.01–2.36, Figure 3) but not in Asians (OR=1.35, 95%CI: 0.92–1.99, Figure 3).

As shown in Supplementary Figures 1–6, none of the polymorphisms of rs699 (1852 cases/4431 controls), rs4762 (395 cases/1246 controls), rs1800896 (1510 cases/3393 controls), rs1800871 (489 cases/1087 controls), rs1137101 (149 cases/499 controls), or rs1801131 (1390 cases/1818 controls) were significantly associated with PE susceptibility under the allelic model (all P values >0.05). Results of subgroup analysis by ethnicity were consistent with those of the overall analysis.

Publication bias

Potential publication bias of the included studies was assessed by the funnel plot, which revealed no significant publication bias in 8 SNPs under the allelic model (all P values >0.05): rs1801133, *P*=0.318 (Figure 4A); rs6025, *P*=0.511 (Figure 4B); rs1801131, *P*=0.204; rs1137101, *P*=0.511; rs4762, *P*=0.215; rs699, *P*=0.482; rs1800871, *P*=0.955; and rs1800896, *P*=0.144 (Supplementary Figure 7A–7F).

Discussion

Pre-eclampsia (PE) is a complex disease with great phenotypic diversity. It is a serious threat to the health of females during gestation. Although the pathogenesis of preeclampsia is extremely complex, previous studies showed that thrombophilia genes are associated with hypercoagulable state [32,33], which may partly explain the development of PE. In recent years, great attention has been paid to the role of SNPs in

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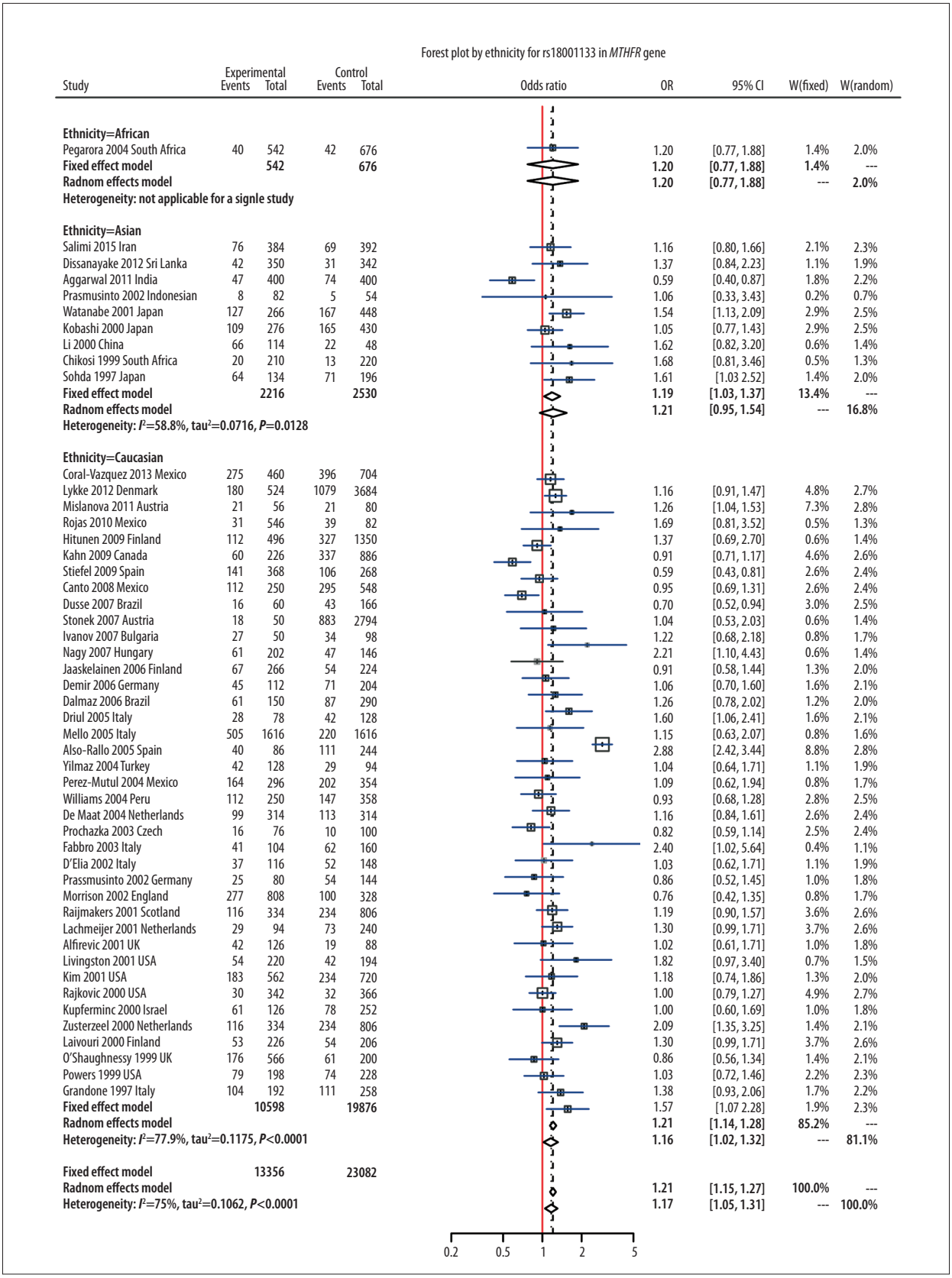

Figure 2. Forest plot by ethnicity for rs18001133 in *MTHFR* gene.

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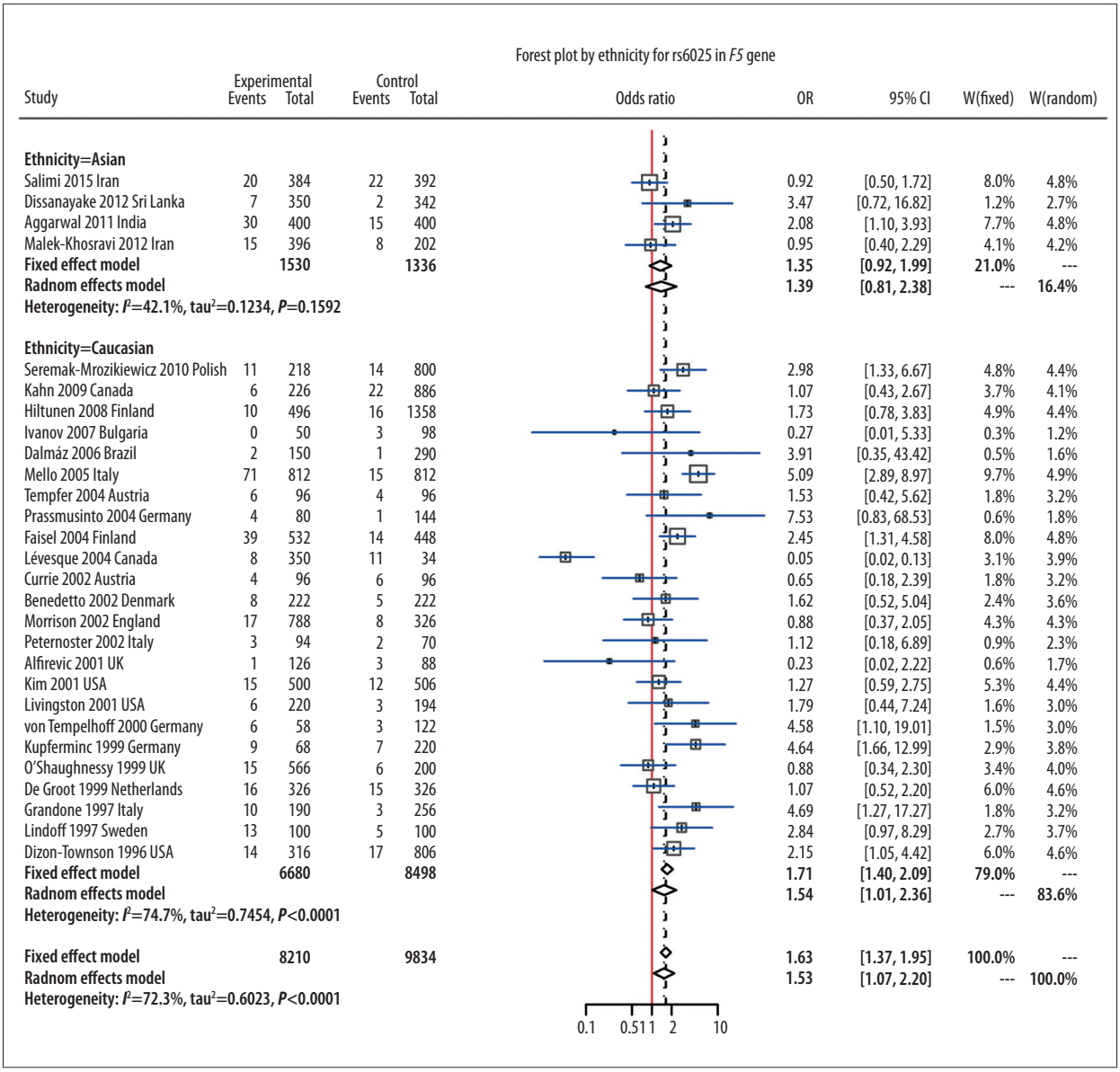

Figure 3. Forest plot by ethnicity for rs6025 in *F5* gene.

disease pathology; most of the published studies focused on the association between several SNPs and the susceptibility to PE, including *AGT* [34,35], *ACE* [36–39], *F5* [4,40–44], *MTHFR* [7,18,45–49], and *TNF-alpha* [23,24,50,51]. The present study enabled us not only to explore the relationship between gene polymorphisms on chromosome 1 (*MTHFR*, *AGT*, *F5*, *IL-10*, *LEPR*) and susceptibility to PE, but also to assess potential heterogeneity among studies.

The methylenetetrahydrofolate reductase (*MTHFR*) gene encodes the enzyme 50, 100-methylenetetrahydrofolate reductase, located on chromosomal region 1p36.3. Many studies have indicated an association between *MTHFR* SNPs and risk of PE. However, the results were inconclusive due to significant heterogeneity resulting from differences in study population, ethnicity, and genotypes. Our meta-analysis provides evidence that *MTHFR* rs1801133 is significantly associated with increased risk of PE in Caucasians under the allelic model, but this association was not significant in Asians or Africans. In contrast, a study by Wu et al. concluded that there was a significant association between SNP of rs1801133 and PE susceptibility in Asians [7]. This inconsistency may be explained by 2 factors. Firstly, the current meta-analysis had a smaller sample size for Asians, which may have restricted its ability to detect any significant association. Secondly, only the allelic genetic model was incorporated in the meta-analysis, which may lead to a biased estimation of the association. Therefore, it is necessary to design studies with large sample sizes, particularly for

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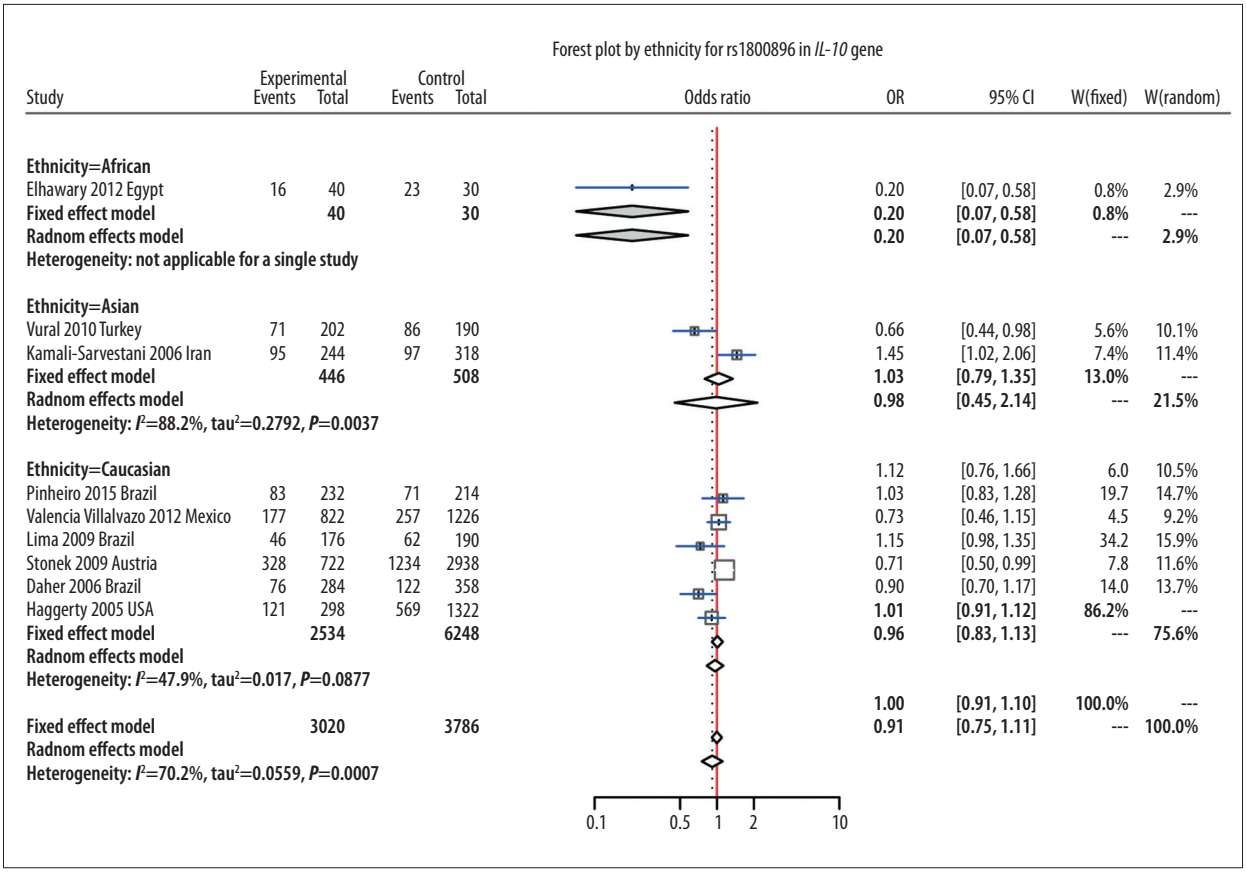
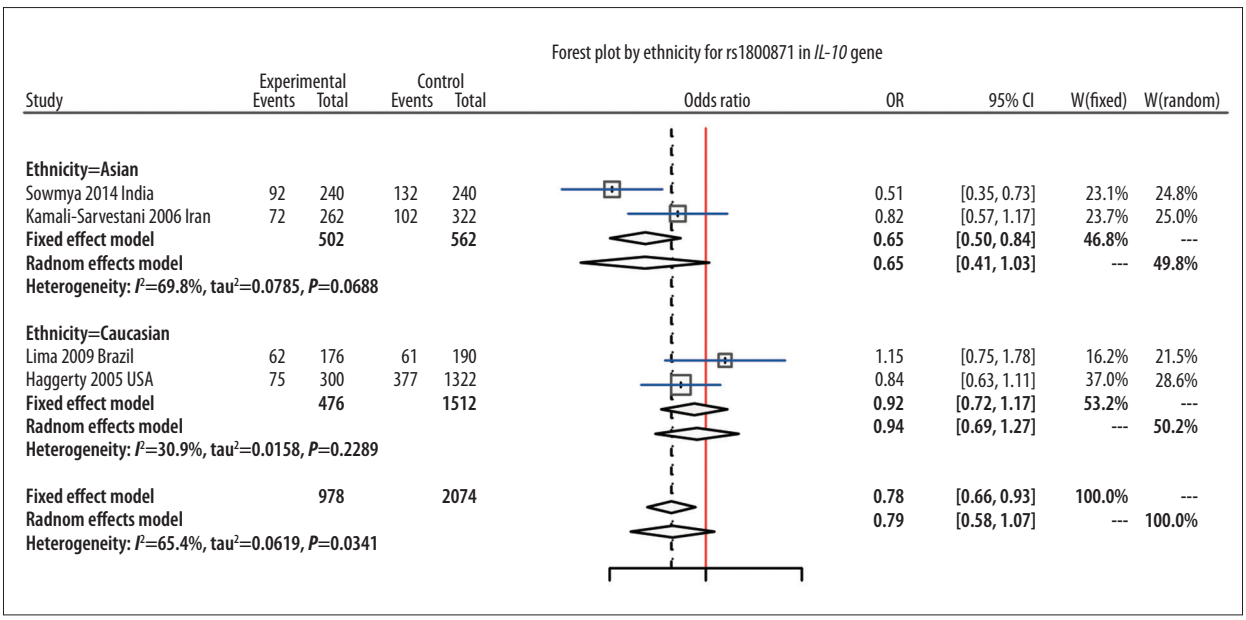


Supplementary Figure 3. Forest plot by ethnicity for rs1800896 in *IL-10* gene.



Supplementary Figure 4. Forest plot by ethnicity for rs1800871 in *IL-10* gene.

Asians and Africans. For rs1801131, the overall analysis and the subgroup analysis did not provide sufficient evidence to suggest a significant association. As of September 2015, 3 other meta-analyses had suggested that there is no significant association between rs1801131 and PE [7,18,49]. Compared to the large number of cases and controls for rs1801133, we only

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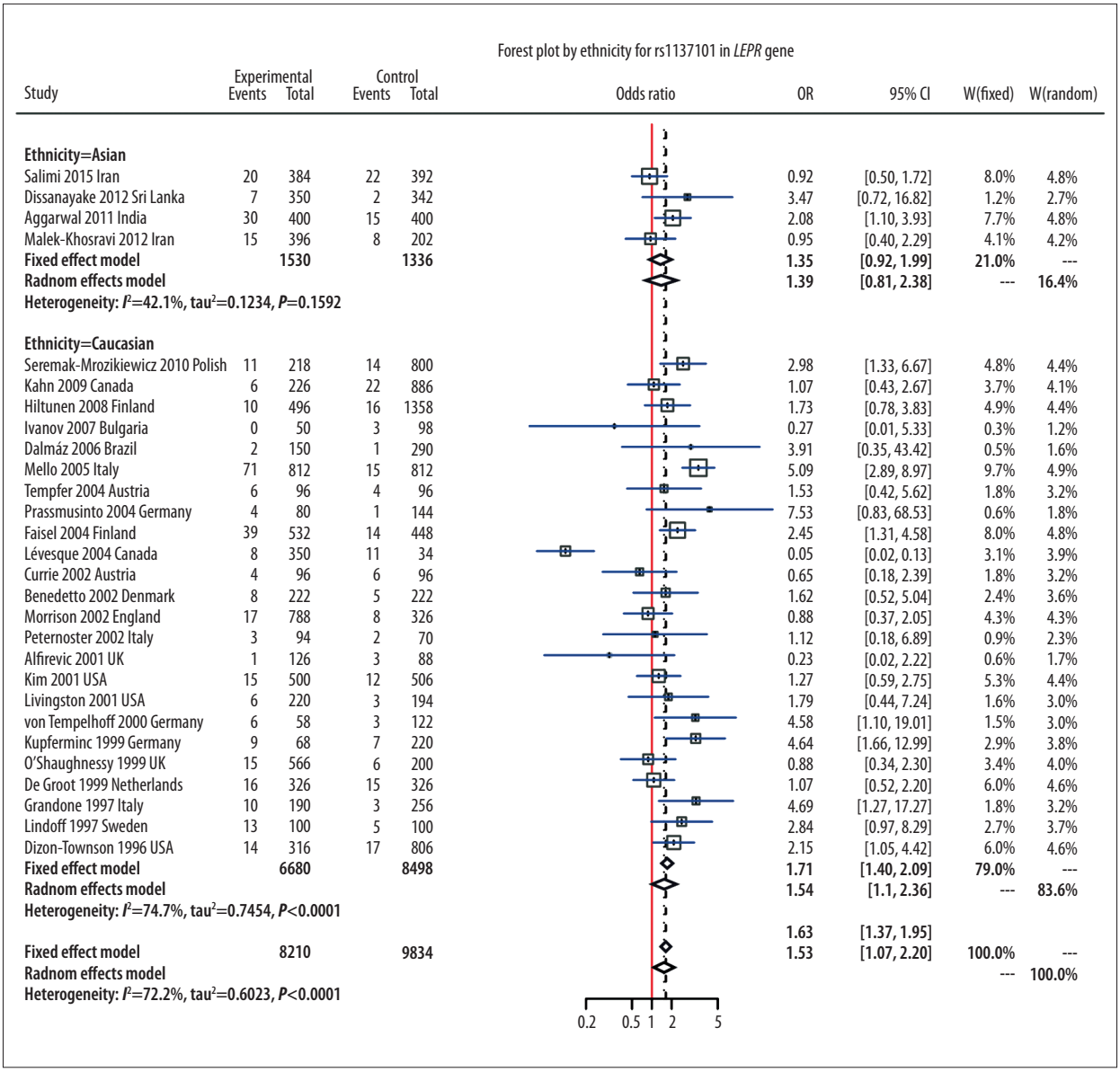

Supplementary Figure 5. Forest plot by ethnicity for rs1137101 in *LEPR* gene.

have 1390 cases/1818 controls for rs1801131, which may significantly reduce the statistical power of a meta-analysis to detect a significant association. Therefore, further studies with large sample sizes should be carried out to increase the credibility of this conclusion. Overall, we concluded that *MTHFR* rs1801133 might be an effective marker for use in PE diagnosis.

F5 is considered to be a potential genetic factor for PE because it encodes an essential cofactor of the blood coagulation cascade. *F5* has also been widely studied due to its common thrombophilic mutation [52,53]. Although the overall results suggested a significant association between polymorphism of *F5* (rs6025) and PE, other studies have not provided sufficient evidence to conclude there is a significant association [53]. Our meta-analysis indicates that *F5* rs6025 is associated with an increased risk of PE, which is contrary to the results of some other studies. This may be explained by the typical publication bias and time-lag bias inherent in smaller studies [54,55]. In addition, these smaller studies may also have failed to comply with strict standards. For example, some terms must be carefully defined, including *paternity* [56] and *gravidity* [57], because they may interact with genetic factors to affect PE susceptibility. Moreover, results from subgroup analysis may not be applicable to other ethnicities such as Africans because the included study did not involve African subjects. Thus, studies that incorporate different ethnicities, particularly Africans, should be designed to confirm the association between *F5* (rs6025) and the susceptibility to PE.

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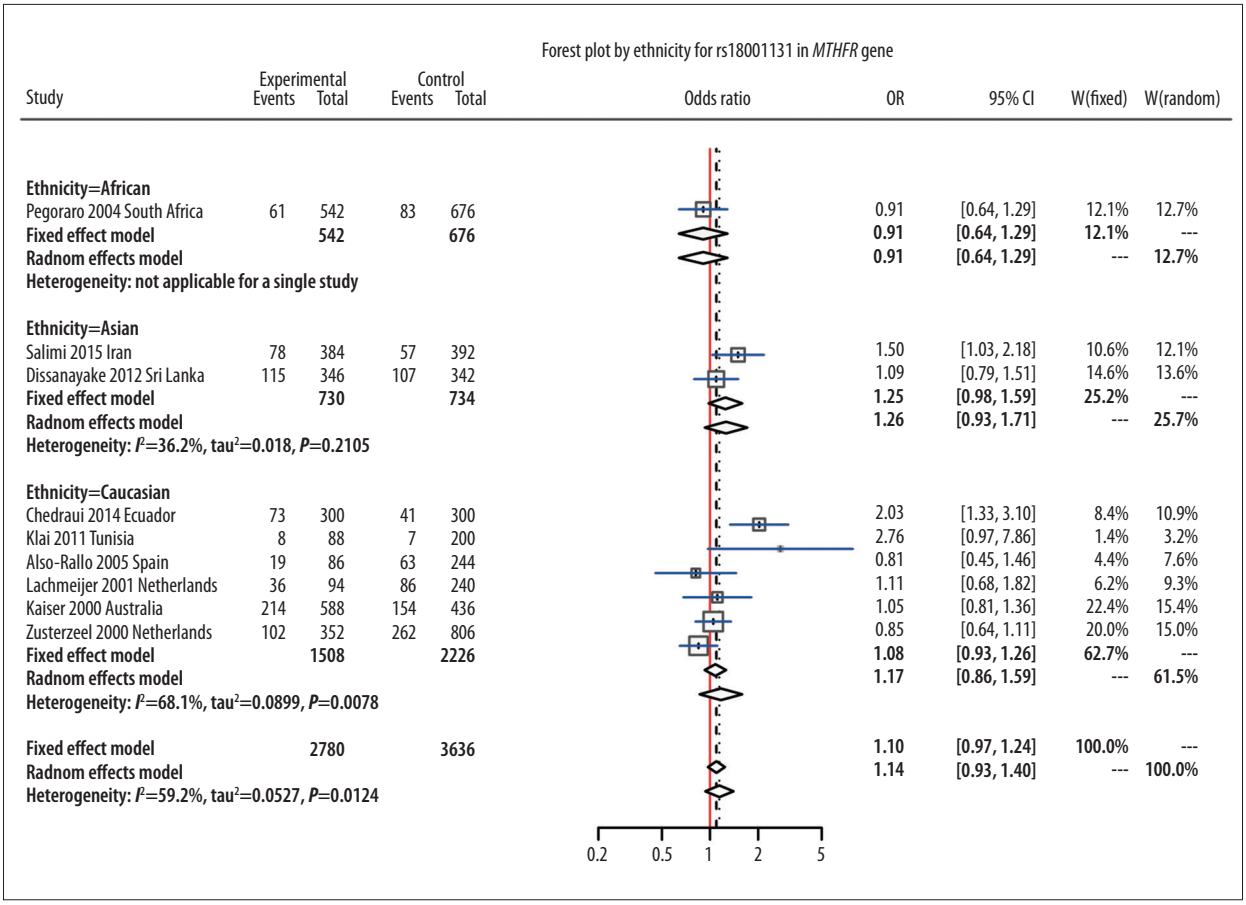

Supplementary Figure 6. Forest plot by ethnicity for rs18001131 in *MTHFR* gene.

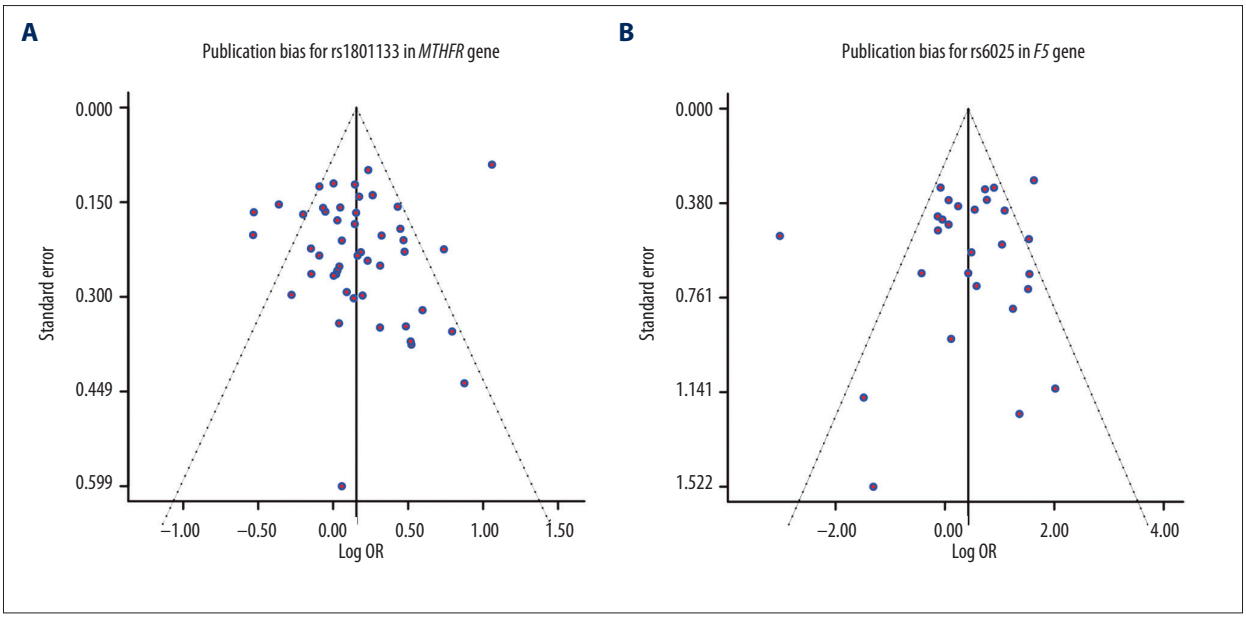

Figure 4. Publication bias for rs1801133 and rs6025.

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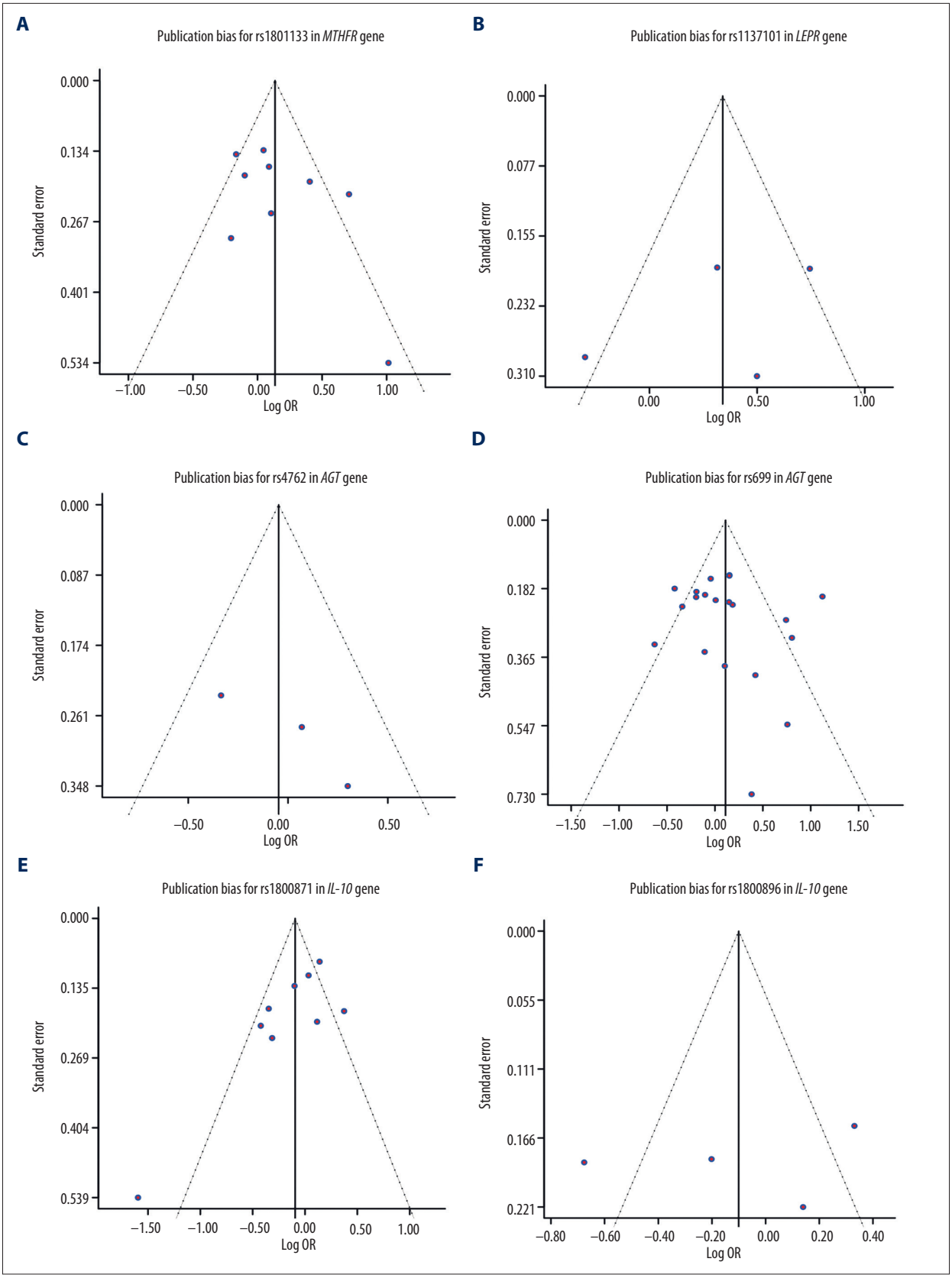

Supplementary Figure 7. Publication bias of non-significant SNPs.

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AGT is a key effector in regulating the blood pressure, and the level of *AGT* among hypertensive patients is related to the SNPs of the *AGT* gene [58]. The expression of *AGT* rs699 was elevated in decidual spiral arteries, which play a vital role in developing several events that may trigger PE [59,60]. Lin et al. indicated that *AGT* rs699 was significantly associated with PE, whereas there was no significant association between *AGT* rs4762 and PE [8]. Similar results were also found in studies conducted by Ni et al. and Zhu et al. [35,39]. On the other hand, the present meta-analysis discovered that there was no significant association between AGT polymorphism (rs699, rs4762) and PE. This inconsistency may be attributable to the limited number of studies investigating AGT polymorphisms. Although ethnicity has been taken into consideration to explain the potential source of heterogeneity, the lack of information on gene-environment interaction or the interaction between several genes could have a substantial effect on the overall conclusion.

Interleukin 10 (*IL*-10) is located on the chromosome of 1q21-32 and it is an immune-regulatory cytokine associated with different biological functions [61]. Furthermore, *IL*-10 exerts regulatory effects on the balance of Th1/ Th2 and it is a crucial cytokine for females during gestation [13,62]. This study enabled us to investigate the association between IL-10 polymorphisms (rs1800896, rs1800871) and PE. The results suggest that rs1800896 or rs1800871 is not significantly associated with PE susceptibility. Results from subgroup analysis by ethnicity were consistent with those from the overall analysis. However, we should interpret these results with great caution since all of the included studies came from different regions, which may be considered as a confounding factor that influences the conclusion. Apart from that, other confounding factors, including gestational age at the sample collection time, body mass index, and assay sensitivity, should be taken into account in order to further investigate the association between IL-10 polymorphisms and PE susceptibility.

It has been suggested that the expression of leptin receptor (*LEPR*) significantly increases when inflammation occurs and that it plays an important role in immune responses [63]. Immune response is a factor for PE [63,64] and mutations in this gene have been shown to be associated with PE. For instance, a study by Fong et al. revealed that LEPR rs1137101 was significantly associated with PE, which is contrary to the results obtained from our meta-analysis. This discrepancy may also come from our small sample size, which significantly reduces the statistical power of the present meta-analysis to detect any significant association.

Conclusions

We conclude that rs1801133 of *MTHFR* and rs6025 of *F5* are significantly associated with PE, whereas rs1801131 of *MTHFR*, rs699 and rs4762 of *AGT*, rs1800896 and rs1800871 of *IL*-10, and rs1137101 of *LEPR* have no significant association with PE. Studies with large sample sizes adjusting for various confounding factors should be designed to confirm the above conclusion. Nevertheless, our meta-analysis provides some evidence to help explain the mechanism of susceptibility to PE, which can be critical to the health of females during gestation.

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Disclosure of conflict of interest

None.

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