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The effect of AT1R-1166A/C and AT2R-1675A/G polymorphisms on susceptibility to preeclampsia

A systematic review and meta-analysis

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Abstract

Background: The aim of this meta-analysis is to investigate the association between Angiotensin II type 1 receptor (AT1R)-1166A/C, Angiotensin II type 2 receptor (AT2R)-1675A/G polymorphisms and susceptibility to preeclampsia (PE).

Methods: Online databases, including Web of Science, PubMed, EMBASE, CINAHL, CENTRAL, Scopus, Lilacs/SciELO, and Chinese National Knowledge Infrastructure, China Wan Fang, China Science and Technology Journal Database, were used to perform the literature search up to April 2022. The odds ratio (OR) and 95% confidence interval (CI) were used as effect size. The data was analyzed by Stata 15.0 software.

Results: According to the inclusion and exclusion criteria, a total of 22 case-control studies were identified, including 3524 cases and 6308 controls. Our meta-analysis showed that the *AT1R* -1166 A/C allele was significantly associated with susceptibility to PE (A vs C: OR = 0.82, 95% CI: 0.69-0.96, *P* = .013), and there was significant difference in recessive gene model (AA vs AC + CC: OR = 0.81, 95% CI: 0.67-0.97, *P* = .021). However, no association was found between *AT2R*-1675A/G polymorphism and susceptibility to PE.

Conclusion: our meta-analysis suggested that *AT1R*-1166A/C polymorphism had an association with susceptibility to PE, but *AT2R*-1675A/G polymorphism had no association with susceptibility to PE.

Abbreviations: ANG = angiotensin, AT1R = angiotensin II type 1 receptor, CI = confidence interval, NOS = Newcastle-Ottawa scale, OR = odds ratio, PE = preeclampsia, RAS = renin-angiotensin system, SNP = single nucleotide polymorphisms.

Keywords: *AT1R*, *AT2R*, meta-analysis, polymorphism, *p*reeclampsia, susceptibility

1. Introduction

Preeclampsia (PE) is a pregnancy-specific syndrome, a type of hypertensive disorder in pregnancy, characterized by new-onset hypertension and proteinuria after 20 weeks of gestation.[1] Seriously, it will cause renal dysfunction, liver injury, pulmonary edema, heart failure and multisystem dysfunction, endangering the life and health of pregnant women and perinatal children.[2] Approximately 2% to 8% of pregnancies worldwide suffer from PE, a leading cause of maternal and perinatal morbidity and mortality.[3] However, the etiology and pathogenic mechanisms of PE have yet been poorly elucidated. Thereby, there are still no effective measures for prevention and treatment.[4] It is considered that PE is an accessory of suitable interactions among immunity, inflammation, diet, and genetic factors, leading to a decrease in trophoblast invasiveness and abnormal remodeling of uterine spiral artery.[5,6] Increasing evidences suggest that genetic factors, including gene polymorphisms, contribute to the etiology, development and complexity of PE.[7] Copy number variations have also been reported to be associated with the susceptibility to PE.[8–10] In addition, more and more studies have identified that single nucleotide polymorphisms (SNP) are closely related to susceptibility to PE.[11–13]

The circulating renin-angiotensin system (RAS), composed of a series of peptide hormones and corresponding enzymes, is an important humoral regulation system, which is involved in regulating the balance of blood pressure, water and electrolyte, and maintaining the relative stability of the human body environments.[14–16] Angiotensin (ANG) II is a major bioactive peptide produced by the hydrolysis of ANG I by ANG-converting enzyme. The ANG II is involved in regulating blood pressure, vascular growth promotion, aldosterone synthesis, and release

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by binding ANG receptors, mainly found in vascular smooth cells, glomerular zone cells, and some parts of the brain, heart and kidney organs.[17,18]

ANG receptors, a member of the G protein-coupled receptor family mainly, consist of ANG II type 1 receptor (*AT1R*) and ANG II type 2 receptor (*AT2R*).[19,20] Studies have reported that the expression of AT1R significantly increased in the placenta of PE pregnant women than normal pregnant women, which suggested that *AT1R* may participate in the pathogenesis of PE and restricted fetal growth.[21–23] Besides, previous studies showed that the abnormal expression of *AT2R* in the placenta during pregnancy would lead to shallow placenta implantation and participate in the pathophysiology of pregnancy-induced hypertension.[24,25] However, the exact mechanism of *AT1R* and *AT2R* on the pathogenesis of PE has still not been elucidated. A growing numbers of evidence suggest that the different polymorphisms in the *AT1R* gene, located on chromosome 3q21-q25, and the *AT2R* gene, located on X chromosome q22-23, have closely related to the susceptibility of PE. In particular, it has been defined that a single nucleotide polymorphism (SNP) in the 3' untranslated region of the *AT1R* gene (-1166A/C; rs5186) and an SNP of the *AT2R* gene (-1675A/G; rs5194) have a significant association with susceptibility to PE. However, it is controversial for different ethnic groups about the association between the SNPs and the susceptibility to PE.[26–29] In order to attenuate the limitations of distinct epidemic genetic characteristics and insufficient sample size of individual study, we performed a systemic review and a meta-analysis of all eligible studies to discuss whether the *AT1R* -1166A/C, *AT2R*-1675A/G polymorphisms are correlated to susceptibility to PE.

2. Methods

2.1. Search strategy

Online databases, including Web of Science, PubMed, EMBASE, CINAHL, CENTRAL, Scopus, Lilacs/SciELO, Chinese National Knowledge Infrastructure, China Wan Fang, China Science and Technology Journal Database, were comprehensively searched for literature about *AT1R* -1166A/C and *AT2R*-1675A/G polymorphisms associated with Susceptibility to PE until April 2022. The searching keywords were used as follows: ("preeclampsia" OR "pre-eclampsia" OR "pregnancy hypertension") AND ("polymorphism" OR "single nucleotide polymorphism" OR "SNP" OR "variant" OR "gene polymorphism" OR "genetic polymorphism") AND ("angiotensin II receptor type 1" OR "*AT1R*" OR "angiotensin II type 1 receptor" OR "Ang II receptor type 1" OR "Ang II type 1 receptor" OR "angiotensin II receptor type 2" OR "*AT2R*" OR "angiotensin II type 2 receptor" OR "Ang II receptor type 2" OR "Ang II type 2 receptor"). Each database was searched independently by 2 researchers and finally cross-checked. There were no restrictions on language.

2.2. Inclusion and exclusion criteria

All studies were included in this meta-analysis according to the following criteria: Case-control study or cohort study focused on associations between *AT1R* -1166A/C and *AT2R*-1675A/G polymorphisms and susceptibility to PE; The studies provided

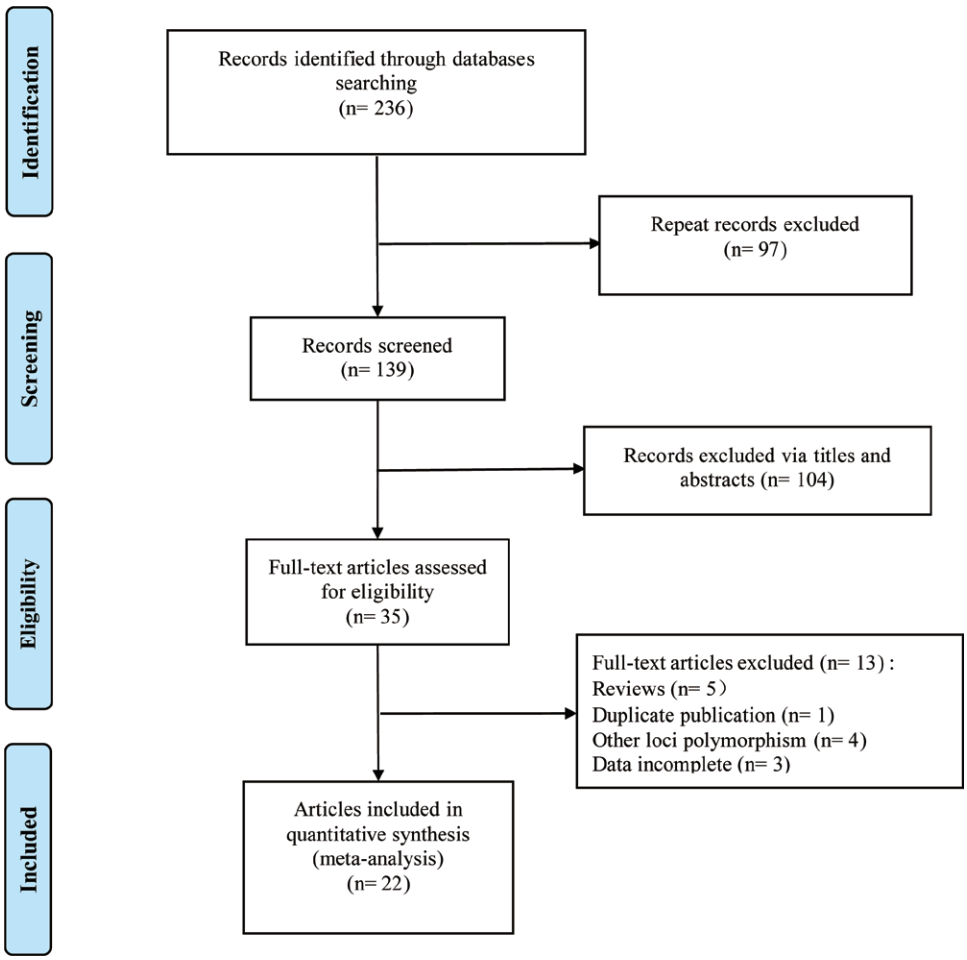

Figure 1. Flow diagram of the selection of included studies.

Table 1

The baseline characteristics of the eligible studies included in this meta-analysis.

Study	Yr	Country	Methods	Ages (yrs) (Case/Control)	Case selection	Source of control	Sample size case/control	Polymorphisms studied	NOS
Nalogowska[26]	2000	Poland	PCR-RFLP	20-48/18-42	SBP/DBP >140/90 mm Hg after 20 wks of pregnancy in a previously normotensive woman	Consecutive healthy normotensive pregnant women with median age 27 yrs recruited from the same centers	122/144	AT1R -1166A/C	8
Bouba[27]	2003	Greece	PCR-ASO	21-45/17-48	1.SBP/DBP >140/90 mm Hg 2.Proteinuria >300 mg/L or 300 mg/24 h	Normotensive pregnant women had undergone at least 2 pregnancies	41/102	AT1R -1166A/C	8
Plummer[28]	2004	UK	PCR-ASO	28.4 ± 5.76/27.6 ± 5.14	SBP/DBP >140/90 mm Hg after 20 wks of pregnancy in a previously normotensive woman	Normotensive pregnant women	98/118	AT1R -1166A/C	8
Roberts[31]	2004	South Africa	PCR-ASO	Mean:26.3/25.0	SBP/DBP ≥140/90 mm Hg	Healthy pregnant normotensive participants who had delivered normally	204/338	AT1R -1166A/C	7
Seremak-Mrozikiewicz[34]	2005	Poland	PCR-RFLP	29.3 ± 5.6/27.6 ± 5.6	The American College of Obstetricians and Gynecologists	Healthy pregnant women	47/113	AT1R -1166A/C	8
Benedetto[32]	2007	Italy	PCR-RFLP	30 ± 4/30 ± 4	1.SBP/DBP >140/90 mm Hg 2.Proteinuria >300 mg/24 h	Normotensive pregnant women	120/103	AT1R -1166A/C	8
Li H[33]	2007	China	PCR-RFLP	22-40/23-38	1.SBP/DBP >140/90 mm Hg 2.Proteinuria > 300 mg/L	Eligible subjects who were not affected by preeclampsia in the pregnancy progressing to >20 wks gestation	133/105	AT1R -1166A/C	7
Huang Y[48]	2007	China	PCR-RFLP	29 ± 4; 29 ± 3	1.SBP/DBP ≥140/90 mm Hg 2.Proteinuria >300 mg/24 h	Normal pregnant women in hospital during the same period	58/102	AT1R -1166A/C	7
Jiang MQ[47]	2008	China	PCR-RFLP	26.42 ± 4.10/NR	1.SBP/DBP ≥140/90 mm Hg 2.Proteinuria >300 mg/24 h	Normal delivery in hospital at the same time	55/70	AT1R -1166A/C	7
Akbar[29]	2009	Afro-Caribbean Asian-Pakistani Caucasian	PCR-RFLP	31.88 ± 5.72/28.92 ± 6.51; 27.26 ± 4.91/26.45 ± 4.37; 31.85 ± 5.79; 29.72 ± 5.61	International society for study of hypertension in pregnancy	Normal pregnancy	67/119 122/189 47/118	AT1R -1166A/C, AT2R-1675A/G	8
Deng J[45]	2010	China	PCR-RFLP	30.82 ± 5.16/29.64 ± 3.25	1. SBP/DBP ≥140/90 mm Hg 2. Proteinuria >300 mg/24 h	Normal delivery women	50/100	AT1R -1166A/C	7
Procopciuc[36]	2011	Romania	PCR-RFLP	28.19 ± 4.6/28.55 ± 5.09	1. SBP/DBP ≥140/90 mm Hg 2. Proteinuria >300 mg/24 h	Normal pregnant women	21/71	AT1R -1166A/C	8
Salimi[35]	2011	Iran	PCR-RFLP	27.2 ± 7.8/26.2 ± 6.2	1.SBP/DBP ≥140/90 mm Hg 2.Proteinuria ≥0.3g/24 h or + 1 on a urine dipstick	Healthy pregnant women	125/132	AT1R -1166A/C	8

(Continued)

Table 1

(Continued)

Study	Yr	Country	Methods	Ages (yrs) (Case/Control)	Case selection	Source of control	Sample size case/control	Polymorphisms studied	NOS
Zhou A[38]	2013	Australia and New Zealand	Mass	26.8 ± 5.4/28.2 ± 5.6	SBP/DBP ≥140/90 mm Hg before the onset of labor or postpartum	Normotensive pregnancies with delivery of a healthy and appropriately grown infant at 37 wks' gestation	115/1068	AT1R -1166A/C, AT2R-1675A/G	8
Rahimi[37]	2013	Iran	PCR-RFLP	29.3 ± 6.4/27.4 ± 6.4	1.SBP/DBP ≥140/90 mm Hg 2.Proteinuria ≥0.3 g/24 h	Age- and parity-matched controls	181/92	AT1R -1166A/C	8
Kvehaugen[39]	2013	Norway	Taqman	26.6 ± 5.57/29.6 ± 5.07	The American College of Obstetricians and Gynecologist criteria	Any woman with a DNA sample in HUNT2 registered in MBRN without a diagnosis of preeclampsia in any of their pregnancies	1142/2309	AT1R -1166A/C	8
Alkanli[46]	2014	Turkey	PCR-RFLP	27.87 ± 6.44/27.39 ± 6.87	The World Health Organization Detecting Pre-eclampsia	Eligible subjects who were not affected by PE	75/75	AT1R -1166A/C	8
Zhang H[40]	2017	China	Taqman	28.77 ± 5.39/28.33 ± 4.86	SBP/DBP ≥140/90 mm Hg, with or without convulsions or seizures	Healthy normotensive pregnant women delivering at the same hospital	235/347	AT1R -1166A/C	7
Andrea[41]	2018	Slovakia	TaqMan	28.6 ± 4.4/28.8 ± 6.5	1.SBP/DBP ≥140/90 mm Hg 2.Proteinuria ≥300 mg/24 h	Healthy pregnant women delivering at term	50/42	AT1R -1166A/C	8
Soltani-Zangbar[42]	2018	Iran	PCR-RFLP	28.3 ± 4.1/27.3 ± 3.7	1.SBP/DBP ≥140/90 mm Hg 2.Proteinuria ≥0.3 g/24 h or + 1 on a urine dipstick	Volunteer pregnant women without any history of autoimmunity, malignancy, hypertension or family history for PE	212/218	AT1R -1166A/C, AT2R-1675A/G	8
Procopciuc[43]	2019	Romania	PCR-RFLP	28.7 ± 5.1/28.4 ± 4.7	International Society for the Study of Hypertension in Pregnancy	Normal pregnant women	87/130	AT1R -1166A/C	8
Azimi-Nezhad[44]	2020	Iran	ASO	20-37/NR	1.SBP/DBP >140/90 mm Hg 2.Proteinuria >300 mg/24 h	Normotensive women with at least one normal pregnancy without history of PE	117/103	AT1R -1166A/C, AT2R-1675A/G	8

ASO = allele-specific oligonucleotide hybridization, AT1R = Angiotensin II type 1 receptor, AT2R = Angiotensin II type 2 receptor, DBP = diastolic blood pressure, HUNT2 = phase 2 of the Nord-Trondelag Health Study, MBRN = medical birth registry of Norway, NOS = Newcastle-Ottawa Scale, NR = not reported, PCR = polymerase chain reaction, PE = preeclampsia, RFLP = restriction fragment length polymorphism, SBP = systolic blood pressure.

adequate original and complete data in the case and control groups for genotype frequencies; The study participants were pregnant women with PE.

Criteria for inclusion were as follows: Meeting abstract or patent application; Editorial, review, abstract, etc; Repeated publication; the defective and incomplete data reported in the study.

2.3. Risk assessment of bias

Two researchers separately evaluated the bias risk of the included literature according to the Newcastle-Ottawa Scale (NOS),[30] and finally cross-checked. The total NOS scores were 9, with 7 to 9 as high-quality research, 5 to 6 as medium-quality research, and less than 5 as low-quality research.

2.4. Data extraction

The relevant data extraction was carefully performed from all the eligible publications by 2 independent researchers. Any divergences between the 2 researchers were resolved by discussion. The information extracted from each included study was as follows: first author, publication year, country, age of PE and controls, genotyping methods, case inclusion criteria, source of controls, total number of cases and controls group, number of cases and controls of each studied genotype frequencies.

2.5. Statistical analysis

The odds ratio (OR) and its 95% confidence interval (CI) were calculated to estimate the association between *AT1R* -1166A/C, *AT2R*-1675A/G polymorphisms and susceptibility to PE. In our meta-analysis, allele gene model, homozygous model, heterozygous, dominant, and recessive gene model were used to evaluate the association between *AT1R* -1166A/C, *AT2R*-1675A/G polymorphisms and susceptibility to PE, respectively. If P value <.05 of the heterogeneity test or $I^2 > 50\%$, the random-effects model was applied to calculate the pooled ORs; otherwise, the fixed-effects model was used. Whether the meta-analysis was significant was determined by Z test, in which $P < .05$ was considered that there was a statistically significant correlation between each SNP and susceptibility to PE. Begg' s funnel plot was performed to assess potential publication bias. Stata 15.0 software (Stata Corporation) was used to perform all statistical data analysis.

3. Results

3.1. The characteristics of studies included in the meta-analysis

According to inclusion and exclusion criteria, a total of 22 case-control studies were included in our meta-analysis, in which the correlation research of *AT1R* -1166A/C and *AT2R*-1675A/G polymorphisms and susceptibility to PE were both involved in 4 studies.[26–29,31–48] The flow diagram of the included studies selection is shown in Figure 1. At first, a total of 81 articles were retrieved. Then, 35 duplicate studies among databases were excluded. By reviewing the title and abstract, 11 irrelevant articles were deleted. A total of 3524 cases and 6308 controls, composed of Caucasians, Asians and Africans, were included. Besides, Akbar et al' study[29] included 3 populations. The general characteristics and NOS scores of 22 eligible studies in the meta-analysis are summarized in Table 1.

3.2. Association between AT1R -1166 A/C and AT2R-1675 A/G polymorphisms and susceptibility to PE

In this meta-analysis, we evaluated the association between 2 polymorphisms of *AT1R* -1166 A/C and *AT2R*-1675 A/G and susceptibility to PE. A summary of the detailed results of the meta-analysis was provided in Table 2. The pooled analysis of *AT1R* -1166A/C polymorphism revealed that *AT1R* -1166 A/C polymorphism was significantly associated with PE under allele model analysis (OR = 0.82, 95% CI: 0.69-0.96, P = .013) (Fig. 2A). Stratification analysis by ethnicity showed that there was a significant correlation between *AT1R* -1166 C allele and PE in Caucasians (OR = 0.81, 95% CI: 0.68-0.96, P = .014). Nevertheless, the results of AT1R -1166 A/C locus homozygous, dominant, and heterozygous models illustrated no significant association with susceptibility to PE (AA vs CC: OR = 0.89, 95% CI: 0.75-1.06, P = .131; AA + AC vs CC: OR = 0.89, 95% CI: 0.75-1.05, P = .166; AC vs CC: OR = 0.91, 95%CI: 0.75-1.10, P = .322). Similarly, no significant differences were observed by using stratification analysis based on ethnicity in homozygote and dominant models. Interestingly, there was an association between AT1R -1166 A/C polymorphism and susceptibility to PE in the analysis of the recessive gene model (AA vs AC + CC: OR = 0.81, 95% CI: 0.67-0.97, P = .021) (Fig. 2B).

According to overall genetic model analysis, no significant associations were discovered between AT2R-1675 A/G polymorphisms and susceptibility to PE (A vs G: OR = 0.96, 95% CI: 0.68-1.439, P = .798; AA vs GG: OR = 0.95, 95% CI: 0.48-1.86, P = .87; AA + AG vs GG: OR = 1.10, 95% CI: 0.78-1.55, P = .592; AA vs AG + GG: OR = 0.83, 95% CI: 0.44-1.59, P = .580; AG vs GG: OR = 0.80, 95%CI: 0.42-1.51, P = .484) (Fig. 3 and Table 2). Owing to few cases and control groups, stratified Analysis was not carried out.

Table 2

Meta-analysis of the relationship between *AT1R* -1166 A/C and *AT2R*-1675 A/G polymorphisms and susceptibility to PE.

			Number		Study of association			Heterogeneity of study design		
Polymorphism studied		Ethnicity	Cases	Controls	OR	95%CI	Z (*P* value)	*P*	I^2 (%)	Model
AT1R -1166 A/C	A vs C	Overall	3524	6308	0.82	0.69-0.96	2.48 (**.013**)	<.001	64.4	REM
		Caucasian	2600	4938	0.81	0.68-0.96	2.26(**.014**)	<.001	64.9	REM
		Asian	653	913	0.73	0.48-1.13	1.42(.155)	.030	59.7	REM
	AA + AC vs CC	Overall	3524	6308	0.89	0.75-1.05	1.38(.166)	.191	20.5	FEM
		Caucasian	2600	4938	0.87	0.73-1.03	1.58(.113)	.078	35.6	FEM
		Asian	653	913	1.25	0.47-3.30	0.45(.652)	.804	0.0	FEM
	AA vs AC + CC	Overall	3524	6308	0.81	0.67-0.97	2.30(**.021**)	<.001	58.1	REM
		Caucasian	2600	4938	0.81	0.67-0.98	2.18(**.029**)	.005	53.9	REM
		Asian	653	913	0.69	0.42-1.13	1.49(.136)	.018	63.4	REM
	AA vs CC	Overall	3524	6308	0.89	0.75-1.06	1.51(.131)	.062	33.8	FEM
		Caucasian	2600	4938	0.87	0.73-1.04	0.52(.604)	.021	46.6	REM
		Asian	653	913	1.29	0.49-3.43	1.29(.199)	.752	0.0	FEM
	AC vs CC	Overall	3524	6308	0.91	0.75-1.10	0.99(.322)	.614	0.0	FEM
		Caucasian	2600	4938	0.89	0.73-1.08	1.19(.232)	.435	1.5	FEM
		Asian	653	913	1.45	0.54-3.93	0.74(.461)	.685	0.0	FEM
AT2R-1675 A/G	A vs G	Overall	684	1831	0.96	0.68-1.35	0.26(.798)	<.001	83.20	REM
	AA vs AG + GG	Overall	684	1831	1.10	0.78-1.55	0.54(.592)	.073	50.40	REM
	AA + AG vs GG	Overall	684	1831	0.83	0.44-1.59	0.55(.580)	<.001	86.90	REM
	AA vs GG	Overall	684	1831	0.95	0.48-1.86	0.16(.874)	<.001	80.80	REM
	AG vs GG	Overall	684	1831	0.80	0.42-1.51	0.70(.484)	<.001	85.2	REM

AT1R = angiotensin II type 1 receptor, AT2R = angiotensin II type 2 receptor, FEM = fixed-effects model, OR = odds ratio, PE = preeclampsia, REM = random-effects model.

3.3. Publication bias

Begg' s funnel plot was applied to assess potential publication bias, revealing no significant asymmetry in AT1R -1166 A/C (P = .113, Fig. 4A) and AT2R-1675 A/G (P = .707, Fig. 4B) polymorphisms in the allele contrast.

3.4. Sensitivity analysis

The robustness of the conclusions obtained was verified by excluding each study and then performing a meta-analysis again. In the analyses of the *AT1R* -1166 A/C (Fig. 5A) and *AT2R*-1675 A/G (Fig. 5B) locus allele models, the original

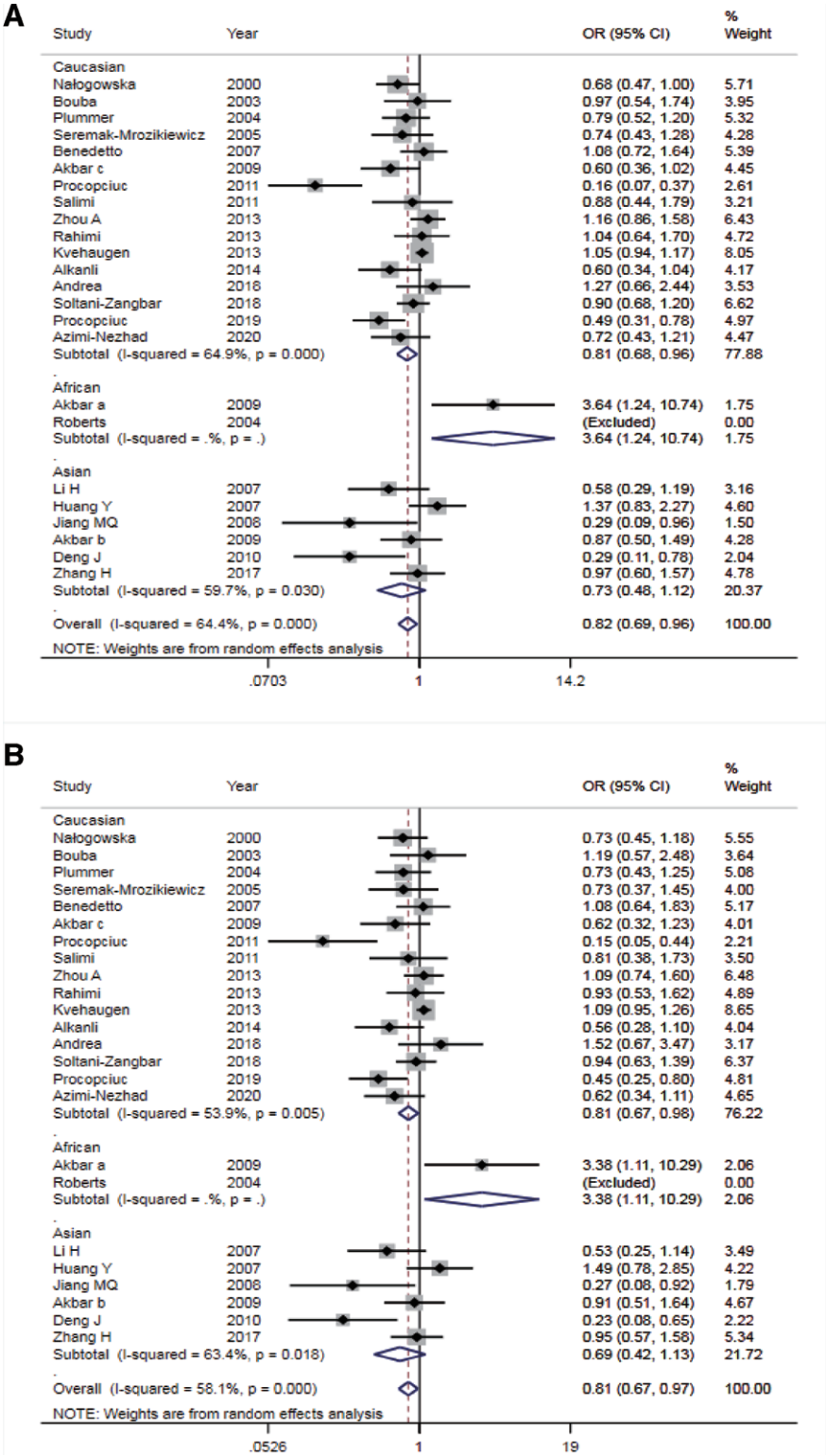

Figure 2. Forest plots of the *AT1R* -1166 A/C polymorphisms associated with susceptibility to preeclampsia. A: allele gene model; B: recessive model. AT1R = angiotensin II type 1 receptor.

conclusions were not significantly altered by omitting any study. In *AT1R* -1166A/A locus recessive gene model, when 1 study was removed,[43] the original conclusion was significantly altered (Fig. S1B, http://links.lww.com/MD/H549). When omitting any of the studies, *AT1R* -1166 A/C (Dominant, homozygous, and heterozygous model) and *AT2R*-1675 A/G (Dominant, recessive, homozygous, and heterozygous model) other gene models had no significant changes in their original findings (Fig. S1A, C, D, http://links.lww.com/MD/H549; Supplemental Fig. S2A-D, http://links.lww.com/MD/H550). This indicates that the findings of this meta-analysis are robust.

4. Discussion

PE, a pregnancy-specific hypertension disease, seriously endangers the life and health of pregnancies and perinatal infants. However, the etiology and pathogenesis of PE have not yet been interpreted clearly. A growing numbers of evidence show that the occurrence and development of PE are caused by the interaction of multiple variables including heredity, among which genetic polymorphism has been paid more and more attention. RAS is an important humoral regulatory system composed of a series of peptide hormones and corresponding enzymes, involved in regulating the balance of blood pressure, water and electrolyte to maintain the stability of the human body environment. Under the pathological conditions, The RAS is an important mechanism involved in the pathogenesis of hypertension.[14] Meanwhile, it has been demonstrated that almost all components of the RAS are up-regulated in normal pregnancy, but renin activity, ANG II, and aldosterone in PE decrease.[49] The underlying mechanisms remain unexplored. AT1R, a major ANG II- 1 receptor, has been reported to be involved in the occurrence of PE, which activates the RAS through the stimulation of autoantibody AT1-AA.[49,50] Several studies have demonstrated that *AT1R* gene polymorphism, mainly focusing on 1166 A/C polymorphism, is associated with PE.[29,51] In addition, another ANG receptor *AT2R* gene polymorphism has also been reported to be associated with the susceptibility to PE.[24,51] However, the conclusions of the association between AT1R and AT2R gene polymorphisms and susceptibility to PE are contradictory. Therefore, in the present study, we synthesized the data based on previous studies to investigate the correlation between *AT1R* and *AT2R* gene polymorphisms and susceptibility to PE.

AT1R is a heterologous G protein-coupled receptor, which plays a role by activating phospholipase C, tyrosine kinase, or non-receptor tyrosine kinase.[52,53] In addition, the genetic variation in the *AT1R* gene can promote its structural abnormalities and expression changes, thus affecting its regulatory response. The *AT1R* gene is located at position 24 on the long arm of chromosome 3. It has been reported that the SNPs of *AT1R* gene are associated with an increased risk of hypertension,[54,55] heart disease,[56,57] or diabetic nephropathy.[58] Notably, a substantial number of correlative researches have elucidated that a variation in 3' untranslated region of the *AT1R* gene at 1166 position that *AT1R* -1166 A/C was closely related to essential hypertension and can be used as a predictor of screening hypertension susceptible families.[59] Furthermore, a growing number of studies have explored whether *AT1R* -1166 A/C was also associated with PE, a special hypertension disease. Nałogowska Głośnicka et al showed that *AT1R* -1166 A/C polymorphism was associated with the increased risk of pregnancy-induced hypertension.[26] It was also reported that the interaction between *AT1R* 1166 C allele and *AT2R* 1332 G allele was relevant to the risk of mild PE.[60] Interestingly, *AT1R* 1166 C allele was revealed to play a significant role in PE development among Chinese pregnant women.[40] On the contrary, in some studies, there were no correlation between *AT1R* -1166 A/C polymorphism and susceptibility to PE.[29,35,51] In 2015, a systematic review and meta-analysis by Li et al showed the *AT1R* -1166 A/C polymorphism was not associated with PIH or PE among a pooled analysis of overall genetic models,[61] which was consistent with previous results of Zhao et al' s study.[62] Five years have passed, we updated the systematic analysis because of the new progress in studying the association between PE and *AT1R* -1166 A/C polymorphism. The present study shows that *AT1R* 1166 C allele can increase susceptibility to PE and promote the occurrence of PE in comprehensive population, as well as in Caucasians, which is inconsistent with the results of previous meta-analysis, owing to the larger sample size and changing proportion of ethnic groups. Surprisingly, no significant connection between *AT1R* -1166 A/C polymorphism and susceptibility to PE was found by homozygous model, dominant and heterozygous model analysis in our meta-analysis. More likely, the

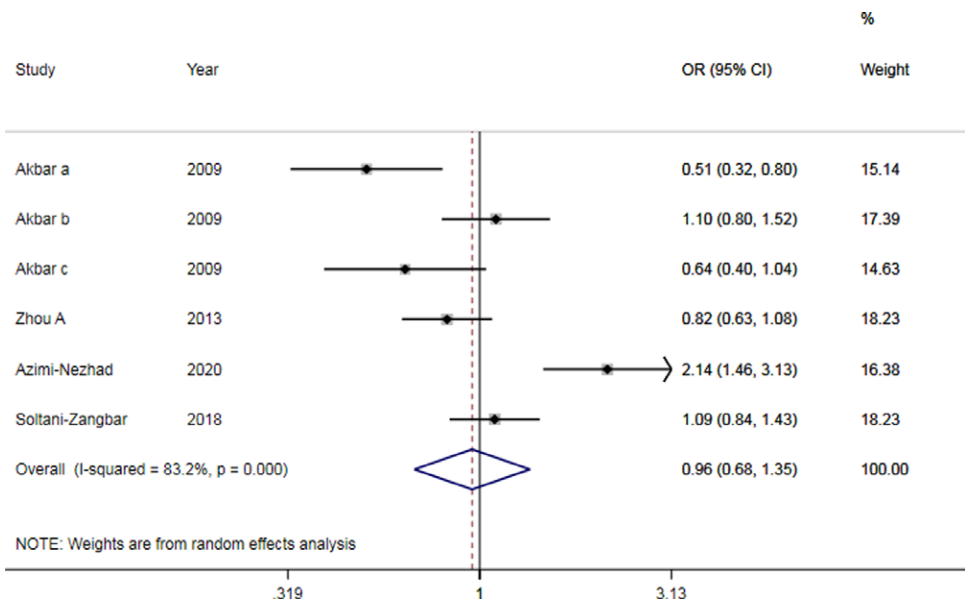

Figure 3. Forest plots of the *AT2R*-1675 A/G allele gene model associated with susceptibility to preeclampsia.

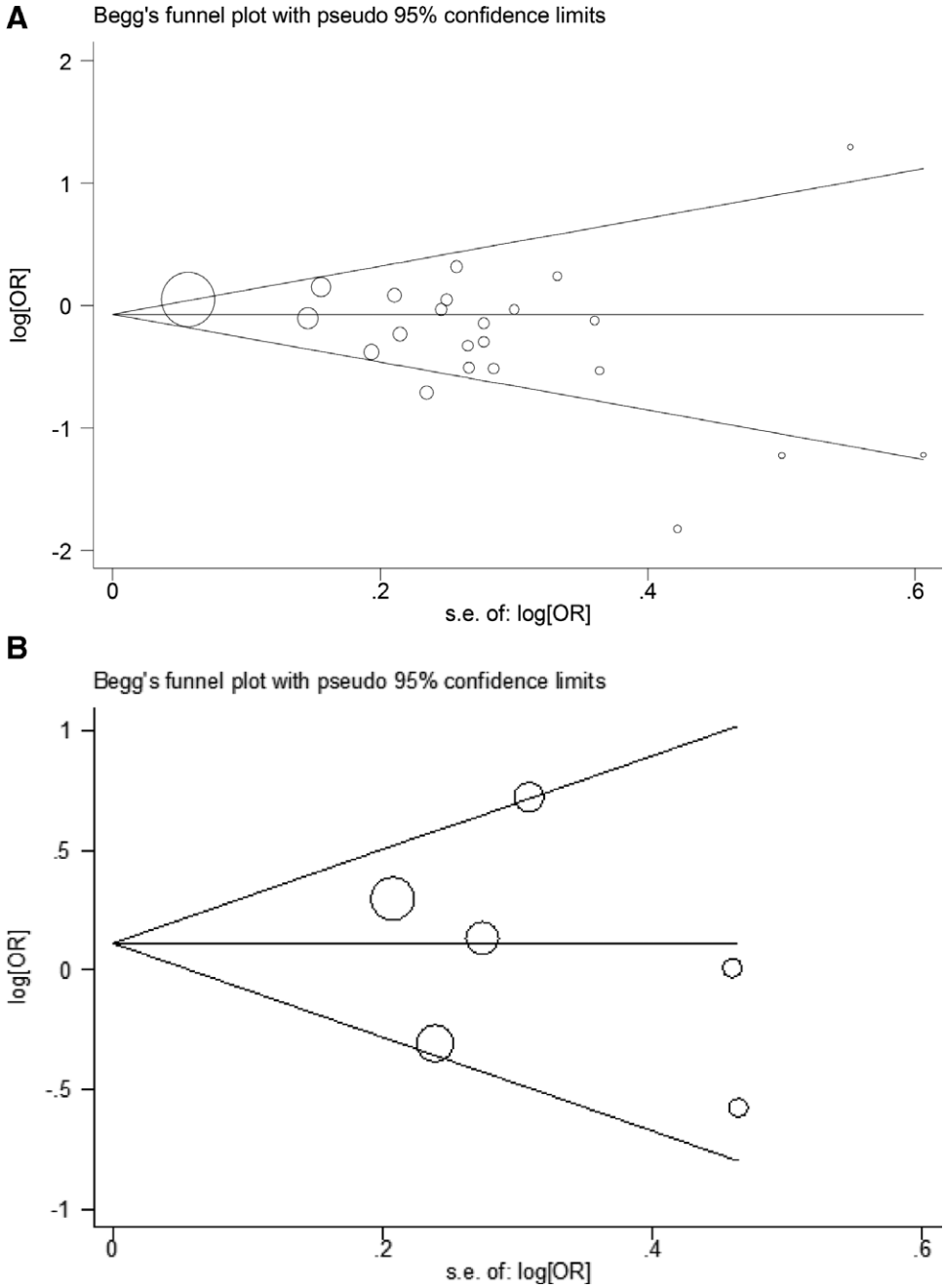

Figure 4. Begg's funnel plot for assessing publication bias of allele gene model in (A) *AT1R* -1166 A/C locus and (B) *AT2R*-1675 A/G locus related to susceptibility to preeclampsia. AT1R = angiotensin II type 1 receptor, AT2R = angiotensin II type 2 receptor.

random-effects model analysis was performed to evaluate the correlation between *AT1R* -1166 A/C polymorphism and PE under allele control model and recessive contrast model.

AT2R gene is located on the X chromosome and a single nucleotide gene polymorphism (+1675G/A; rs5194) within the coding region at position + 1675 has been defined that is related to gene transcription and translation start point. *AT2R* gene, which consists of 3 exons and 2 introns, is located on the X chromosome and a single nucleotide polymorphism related to the transcription and translation starting point was found at + 1675 in the coding region, which has also been defined to be associated with hypertensive diseases.[63–65] Meanwhile, it was reported that *AT2R*-1675 A/G polymorphism was involved in PE or eclampsia in Afro-Caribbean pregnant women.[29] Mohammad et al demonstrated that *AT2R*-1675 A/G polymorphism was associated with PE alone but was related to susceptibility to PE in Iranian women when combined with *AT1R* polymorphism.[42] In 2015, a meta-analysis by Li et al[61] showed that *AT2R*-1675 A/G polymorphism was associated with PE. In the present study, we updated the meta-analysis including 2 new studies. The results illustrated that *AT2R*-1675 A/G polymorphism was not associated with susceptibility to PE. On the one hand, the previous sample size is too small to attenuate the test efficiency. On the other hand, genetic differences caused by different ethnic groups caused inconsistent results. Moreover, we found that the previous meta-analysis included the wrong literature, 2 of which studied the association between *AT2R*–1332A/G gene polymorphism and PE.[28,60]

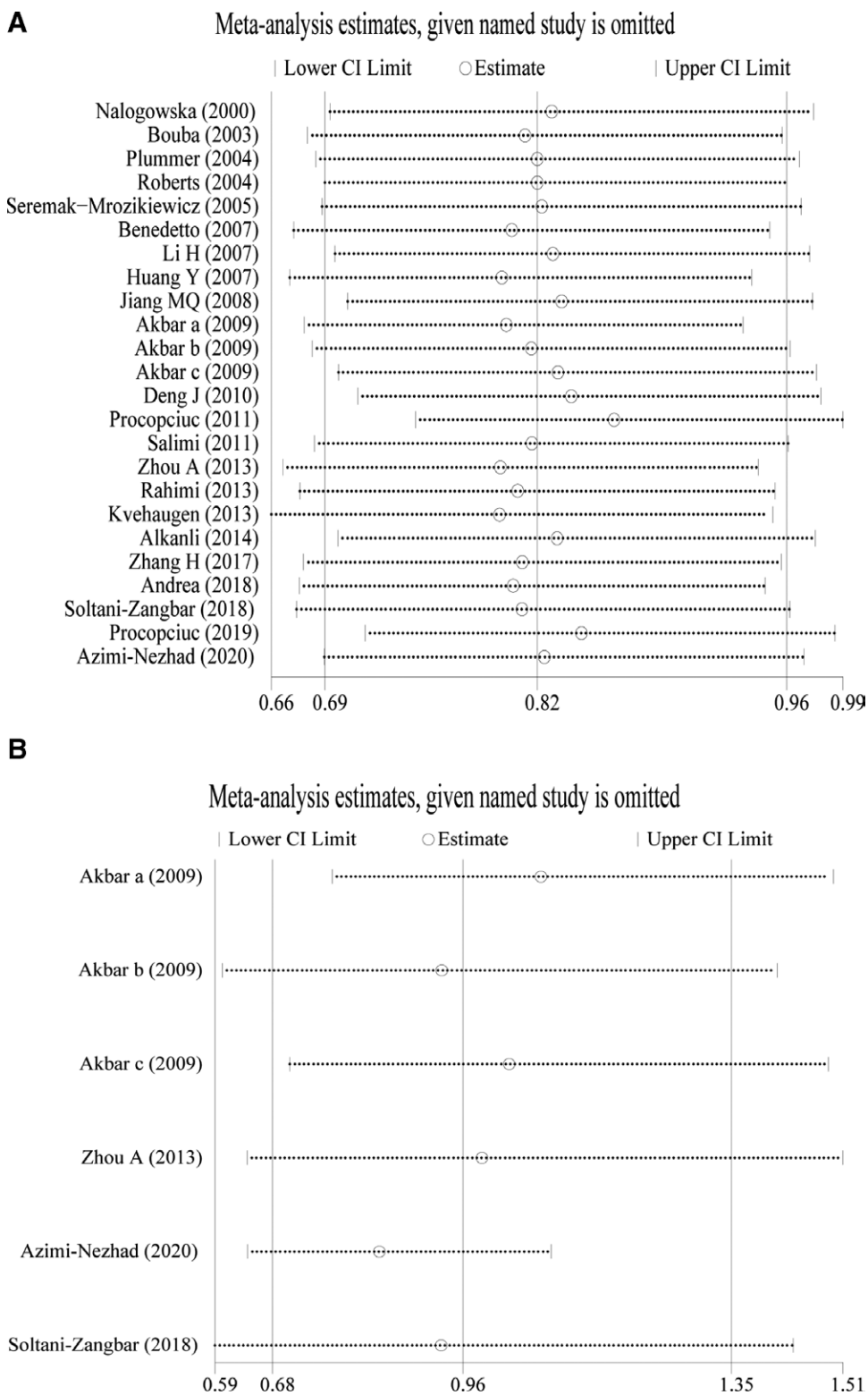

Figure 5. Sensitivity analysis of allele gene model in (A) *AT1R* -1166 A/C locus and (B) *AT2R*-1675 A/G locus related to susceptibility to preeclampsia. AT1R = angiotensin II type 1 receptor, AT2R = angiotensin II type 2 receptor.

Begg's Test and funnel plot showed no significant publication bias in the analyses of AT1R -1166 A/C and AT2R -1332A/G polymorphisms associated with susceptibility to PE. Moreover, sensitivity analysis showed good robustness of the findings in our meta-analysis. Therefore, the conclusions obtained in this study are reliable.

However, there were some limitations in this meta-analysis. Firstly, the literature and sample size included in this study were limited, which might have a certain impact on the robustness of the conclusions. Secondly, Asian and Caucasian populations were mainly enrolled in our meta-analysis, while there were few studies on African populations. Among the analysis of

AT1R-1166A/C locus polymorphism, the results, only including 1 study[29] of African population, showed that allele A and genotype AA significantly increased susceptibility to PE, which was inconsistent with the conclusions of Caucasian population. Limited by the number of studies, no firm conclusions can be drawn at present. Thirdly, in the study of AT2R-1675 A/G polymorphism, the 5 gene models analyzed all have significant heterogeneity. Due to the limited number of included literature, as well as the limited information provided by the original literature, it was difficult to determine the source of heterogeneity further.

In conclusion, our meta-analysis suggested that AT1R 1166 C allele had a significant association with susceptibility to PE, but AT2R-1675 A/G polymorphism had no effect on susceptibility to PE. Considering the limitations of this study, such as a limited sample size, more studies with more rigorous design and larger scope are needed to verify the findings of this meta-analysis in the future.

Author contributions

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Investigation: Junliang Guo.
Methodology: Ping Liu, Junliang Guo.
Project administration: Junliang Guo.
Resources: Yi Quan, Ping Liu, Long Zhang.
Software: Long Zhang.
Supervision: Long Zhang.
Validation: Long Zhang.
Visualization: Long Zhang.
Writing – original draft: Yi Quan, Junliang Guo.
Writing – review & editing: Yi Quan.

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