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Association of *IL-10* -819C/T, -592A/C polymorphisms with the risk of preeclampsia

An updated meta-analysis

Guanglu Che, MM, Fang Liu, MM, Li Chang, MM*, Yongmei Jiang, MD

Abstract

Objective: The purpose of our study was to investigate whether *IL-10* -819C/T, -592A/C polymorphisms were associated with preeclampsia (PE) susceptibility.

Methods: A comprehensive and systematic literature search was performed through online databases, including Web of Science, PubMed, EMBASE, and Chinese databases. Then eligible literatures were included according to inclusion criteria and exclusion criteria. Statistical data analysis was performed using Stata 10.0 software. Odds ratios (OR) and 95% confidence interval were applied to evaluated the association between *IL-10* -819C/T, -592A/C polymorphisms and PE susceptibility.

Results: According to inclusion and exclusion criteria, 9 case-control studies, including 1423 cases and 2031 controls, were included in this meta-analysis. Our meta-analysis revealed that no association was found between *IL-10* -819C/T, -592A/C polymorphisms and the risk of PE in our study.

Conclusion: Our meta-analysis suggested that *IL-10* -819C/T and -592A/C polymorphisms had no association with PE susceptibility, but had a significant association with PE susceptibility in Asian and Caucasian.

Abbreviations: IL = interleukin, OR = odds ratios, PE = preeclampsia, SNP = single nucleotide polymorphism.

Keywords: IL10 -592A/C polymorphism, IL-10 -819C/T polymorphism, meta-analysis, preeclampsia, susceptibility

1. Introduction

Preeclampsia (PE) is a pregnancycomplicated hypertensive disorder, characterized by new onset hypertension and proteinuria after 20 weeks of gestation and accompanied by renal dysfunction, liver injury, pulmonary edema and multisystem dysfunction.[1,2] Currently, 2% to 8% pregnancies throughout the world are suffered from PE, a leading cause of maternal and perinatal mortality.[3] However, the etiology and pathogenesis of PE have not yet been fully elucidated. PE is thought to be an accessory of suitable interactions among immunity, inflammation, diet, and genetic factors,[4,5] leading to a decrease in trophoblast invasiveness and abnormal remodeling of uterine spiral artery. Particularly, increasing evidence suggests that genetic factors contribute to the etiology, development and complexity of PE. Copy number variations have been reported to be associated with the risk of PE.[6–8] In addition, several studies have identified that single nucleotide polymorphisms (SNPs) have been involved in the pathogenesis of PE, such as cytokines genes SNPs.[9–11]

Inflammation has been increasingly recognized as an important factor to contribute to endothelial dysfunction and to the pathology of PE.[12–14] For example, pro-inflammatory cytokine tumor necrosis factor α, by a mechanism depending on influencing the invasiveness of trophoblast cells and remodeling of the uterine spiral artery,[15] and interleukin (IL) 6, contributing to the systemic endothelial activation and vascular damage,[16,17] play an important role in the development of PE. Contrarily, IL-10, as an important anti-inflammatory factor, maintains the function of trophoblast by regulating the balance of anti-inflammatory signals, which leads to appropriate pregnancy outcomes.[18] It has reported that dysregulation of IL-10 was involved in the pathophysiology of PE.[19] Meanwhile, IL-10 is involved in regulating secretion of matrix metalloproteinases and invasiveness of trophoblast cells.[20] Taking into account the inheritable nature of PE and crucial function of IL-10 in PE, the influence of the *IL-10* gene polymorphisms on PE are not negligible.

The *IL-10* gene, located on chromosome 1q31-32, exhibits high polymorphisms, such as *IL-10* -1082A/G (rs1800896), *IL-10* -819C/T (rs1800871), *IL-10* -592A/C (rs1800872), which

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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have been investigated to be correlated with the risk of PE, but the results remained controversial. Mehrnaz's meta-analysis identified that IL-10 -1082 G > A polymorphism was significantly associated with an increased risk of PE. However, there are several studies examining the association between *IL-10* polymorphisms and PE including *IL-10* -819C/T (rs1800871), *IL-10* -592A/C (rs1800872), which are exhibited to be relevant to the risk of PE, characterized by deranged angiogenesis and trophoblast invasion by altering gene expression and protein production. But the results of different races and groups are contradictory and controversial.[21–29] In order to attenuate the limitations of individual study, we performed a systemic review and a meta-analysis of all eligible case control studies including 1423 pregnant women with PE and 2031 normotensive pregnant women to determine whether the *IL-10* -819C/T, -592A/C polymorphisms are associated with the susceptibility to PE. However, there were unknown significance referring the relationship between *IL-10* -819C/T, -592A/C polymorphisms and PE susceptibility, it had a significant association with PE susceptibility in Asian and Caucasian.

2. Methods

2.1. Search strategy

The literature, whose publication date is up to June 2020, was searched from online databases, including Web of Science, PubMed, EMBASE, and Chinese databases (Chinese National Knowledge Infrastructure and Wan Fang). The searching terms were used as following: ("preeclampsia" OR "pre-eclampsia") AND ("polymorphism" OR "single nucleotide polymorphism" OR "SNP" OR "variant") AND ("interleukin-10" OR "*IL-10*").

2.2. Inclusion and exclusion criteria

Overall, the inclusion criteria for eligible studies in this meta-analysis were:

1. case-control studies focused on associations between *IL-10* -819C/T, -592A/C polymorphisms and risk of PE;
2. cases were strictly included and excluded;
3. the studies provided adequate original data in the case and control groups for various genotypes.

Except for English and Chinese, language constraint was applied in the selection of articles. The exclusion criteria were as follows:

1. prospective study;
2. meeting abstract;
3. editorial;
4. meta-analysis and review;
5. repeated publication.

2.3. Data extraction

The relevant data was carefully extracted from all the eligible publications by 2 independent researchers for this meta-analysis. Any divergences between the 2 reviewers were resolved by consensus. The information collected from each study was as follows: first author's name, publication date, country, ethnicity, genotyping methods, case inclusion criteria, source of controls, total number of case and control group, the number of cases and controls of each studied polymorphism.

2.4. Ethical statement

Because this is a literature-based meta-analysis, ethical approval is not required.

2.5. Statistical analysis

Stata 10.0 software (Stata Corporation, USA) was carried out to perform statistical data analysis. The association between *IL-10* -819C/T, -592A/C polymorphisms and PE susceptibility was evaluated by calculating odds ratios (OR) and 95% confidence interval. An allele contrast model, homozygote model, dominant and recessive model were used for evaluation of association between *IL-10* -819C/T, -592A/C polymorphisms and PE susceptibility, respectively. When the heterogeneity test of P value is $<.1$ and the I^2 is $>50\%$, the random effect model is applied, whereas the fixed effect model is used instead. The significance of the OR was determined by the Z-test, in which $P<.05$ was considered that there was statistically significant correlation between each SNP and PE susceptibility. Begg funnel plot was performed to evaluate potential publication bias.

3. Results

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

The flow chart of study selection shown in Figure 1 exhibits the process, of which the studies were searched and screened. Totally, 122 studies were searched online from 5 databases. And then 46 duplicate studies among databases were excluded. Fifty one irrelevant articles were removed by reviewing titles and abstracts. According to inclusion and exclusion criteria, 6 of them were prospective study, conference abstracts, reviews or meta-analysis, which were excluded. Ten records were deleted owing to duplicate publication, no data, referring to other loci polymorphism or language constraint. Finally, 9 case-control studies were included in this meta-analysis,[21–29] of which 8 studies in *IL-10* -819 C/T polymorphism, 7 in *IL10* -592 A/C polymorphism. A total of 1423 cases and 2031 controls, which were from 3 Caucasians, 4 Asian populations, 2 African populations, and 1 Mulatto, mixed white and black ancestry, were included in this meta-analysis. Besides, the study by Haggerty[21] included African population and Caucasian. However, because of the insufficient population of some ethnic groups, we selectively conducted ethnicity-specific meta-analysis of 2 SNPs. The general characteristics of 9 eligible studies with respect to associations between the *IL-10* -819C/T, -592A/C polymorphisms and PE are summarized in Table 1.

3.2. Association between IL-10 -819C/T, -592A/C polymorphisms and PE

In this meta-analysis, we evaluated the association between *IL-10* -819C/T, -592A/C polymorphisms and the susceptibility of PE (data shown in Table 2). Meta-analysis of *IL-10* -819C/T polymorphism revealed that *IL-10* -819 C allele was not significantly associated with the risk of PE (OR = 1.188, 95% CI: 0.958-1.472, $P = 0.116$) (Table 2 and Fig. 2A). Stratification analysis by ethnicity showed that the association between *IL-10* -819 C allele and PE was significant in Caucasians (OR = 1.270, 95% CI: 1.024–1.576, $P = .039$) and in Asians (OR = 1.410, 95% CI: 1.054–1.886, $P = .021$) (Table 2). On the contrary, *IL-10* -819 C allele was found to be associated with the risk of PE in

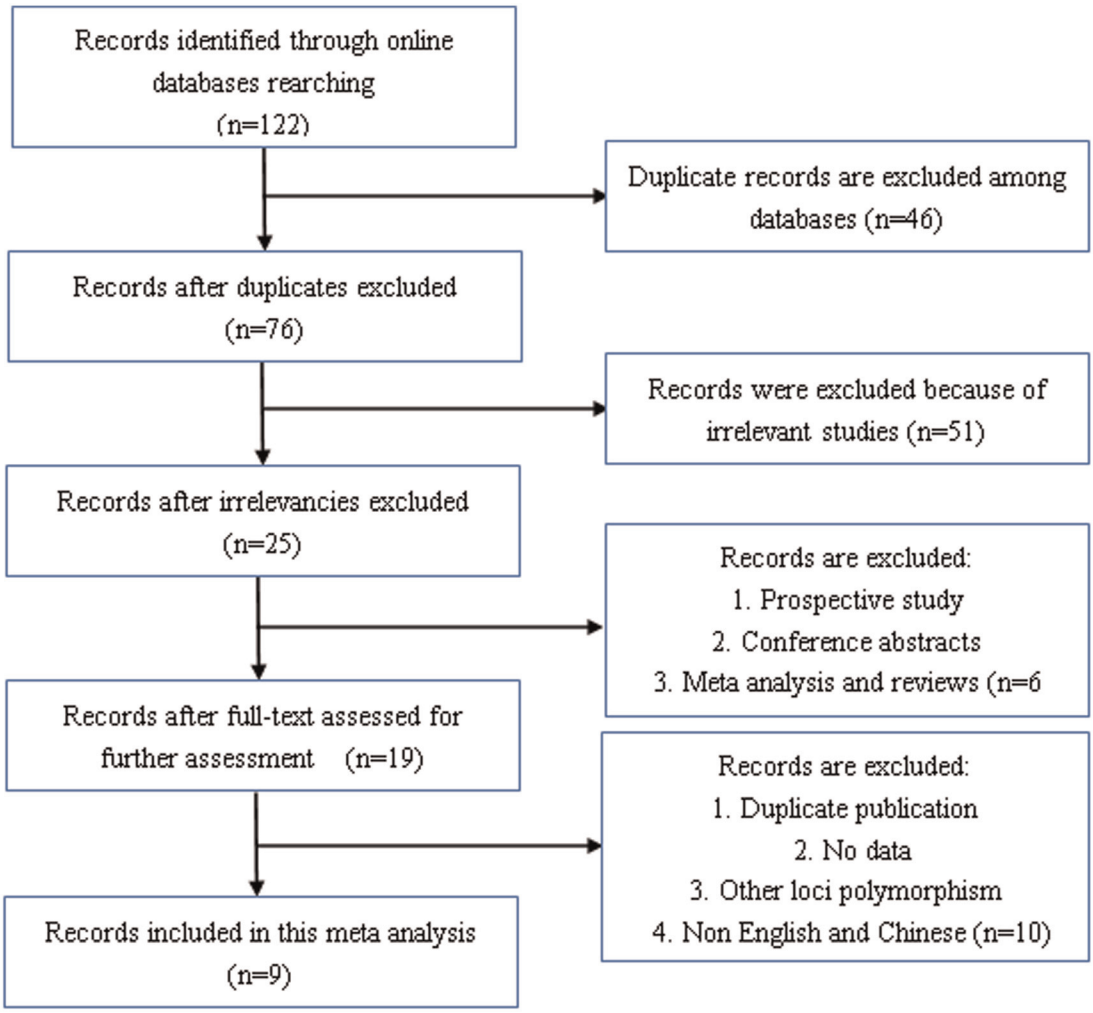

Figure 1. The study selection flow chart in our study.

Africans (OR = 0.791, 95% CI: 0.628–0.996, $P = .046$). The strong association between PE and the *IL-10* -819C/T polymorphism was recorded using the recessive model (OR = 1.316, 95% CI: 1.002–1.728, $P = .048$) or a homozygote contrast in Asians (OR = 1.755, 95% CI: 1.236–2.492, $P = .002$), other than overall or in Caucasians and Africans (Table 2 and Fig. 2B and 2D). However, no association was found between *IL-10* -819C/T polymorphism and PE under the dominant model analysis (Table 2 and Fig. 2C).

Besides, the meta-analysis indicated that no association was found between *IL10* -592 A/C polymorphism and the risk of PE in overall under an allele contrast (OR = 0.786, 95% CI: 0.617–1.001, $P = .051$) (Fig. 3A), the recessive model contrast (OR = 0.855, 95% CI: 0.537–1.361, $P = .508$) (Fig. 3B) or a homozygote contrast (OR = 0.784, 95% CI: 0.459–1.341, $P = .374$) (Fig. 3D). Analysis by a dominant model contrast showed a significant association between the *IL10* -592 A/C polymorphism and PE (OR = 0.716, 95% CI: 0.526–0.975, $P = .034$) (Table 2 and Fig. 3C). Stratification by ethnic divisions displayed *IL-10* -592A/C polymorphism was significantly related to a risk of PE in Asians under an allele contrast (OR = 0.635, 95% CI: 0.530–0.762, $P < .001$) (Table 2), homozygote contrast (OR = 0.441, 95% CI: 0.308–0.633, $P < .001$) (Table 2), recessive (OR = 0.536, 95% CI: 0.408–0.704, $P < .001$) (Table 2), and dominant contrast models (OR = 0.609, 95% CI: 0.444–0.836, $P = .002$) (Table 2). Moreover, ethnic stratification analysis revealed a significant association between the *IL-10* -592A/C polymorphism and PE in Caucasians under an allele contrast (OR = 0.725, 95% CI: 0.554–0.948, $P = .019$) and dominant contrast model (OR = 0.700, 95% CI: 0.404–0.836, $P = .001$), rather than recessive contrast model (OR = 1.170, 95% CI: 0.585–2.338, $P = .658$) or homozygous contrast (OR = 0.952, 95% CI: 0.463–1.959, $P = .894$) (Table 2).

3.3. Publication bias

Begg funnel plot was performed to assess potential publication bias of the included studies, which revealed no significant publication bias in 2 SNPs in the allele contrast (*IL-10* -819C/T, $P = .271$; *IL-10* -592A/C, $P = .368$) (Fig. 4A and 4B).

4. Discussion

PE is a pregnancy-specific complication with undefined etiology and pathogenesis. Increasing evidence indicates that the occurrence and development of PE were caused by multivariate

Table 1

General characteristics of 9 eligible studies contained in this meta-analysis.

Study name	Country	Ethnicity	Methods	Case selection	Source of control	Sample Size Case/Control	Polymorphisms studied
Haggerty, 2005	USA	European African American	TaqMan	1. SBP/DBP > 140/90 mmHg 2. Proteinuria > 300 mg/24 h or protein/creatinine ratio >0.3 3. Hyperuricemia	1. Normotensive 2. No proteinuria or hyperuricemia during pregnancy	130/462 20/199	IL-10 -819 C/T
Kamali, 2006	Iran	Asian	ASO-PCR/ PCR-RFLP	National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy National High Blood Pressure	1. At least two successful deliveries 2. Without any history of PE	134/164	IL-10 -819 C/T, IL-10 -592A/C
Mirahmadian, 2008	Iran	Asian	PCR-SSP	National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy	1. Normal laboratory examination 2. No clinical signs and symptoms of PE	260/100	IL-10 -819 C/T, IL-10 -592A/C
de Lima, 2009	Brazil	South American	PCR-SSP	National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy	1. Normotensive in previous pregnancy 2. At least one successful pregnancy without any maternal or fetal disorder	92/101	IL-10 -819 C/T, IL-10 -592A/C
Sowmya, 2014	India	South-Asian	ARMS-PCR	1. SBP/DBP >130/90 mm Hg 2. New onset of proteinuria > 2+ dipstick	More than 20 weeks pregnancy with normal blood pressure, fetal growth and physiological normalities	120/120	IL-10 -819 C/T, IL-10 -592A/C
Song, 2015	China	Asian	PCR-RFLP	1. SBP/DBP ≥ 140/90 mm Hg 2. Proteinuria ≥ 300 mg/24 h or 2+	1. More than 20 wks pregnant women 2. No history of chronic hypertension, renal, autoimmune, metabolic or cardiovascular disease	155/201	IL-10 -819 C/T, IL-10 -592A/C
Liu, 2015	China	Asian	PCR-RFLP	1. SBP/DBP ≥ 140/90 mm Hg 2. Proteinuria	Normal pregnant women in the same period	177/182	IL-10 -819 C/T
Fan, 2017	China	Asian	PCR-RFLP	1. SBP/DBP ≥140/90 mm Hg 2. Proteinuria ≥300 mg/24 h	1. More than 20 wks pregnant women 2. No history of chronic hypertension, cardiovascular disease, end-stage liver or renal diseases, or diabetes	142/260	IL-10 -592A/C
Raguema, 2018	Tunisia	African	TaqMan	1. SBP/DBP ≥140/90 mm Hg 2. Proteinuria ≥300 mg/24 h or 2+	1. Age-matched with cases and from the same region 2. No personal or family history of hypertension and PE	345/300	IL-10 -819 C/T, IL-10 -592A/C

ARMS = amplification refractory mutation system, ASO = antisense oligonucleotide, DBP = diastolic blood pressure, IL = interleukin, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism, SBP = systolic blood pressure, SSP = sequence specific primer.

Table 2

Meta analysis of the association of *IL-10* -819C/T, -592A/C polymorphisms and PE susceptibility.

Polymorphism studied		Ethnicity	Number		Study of association			Heterogeneity of study design		
			Cases	Controls	OR	95% CI	Z (*P* value)	*P*	I^2	Model
IL-10 -819	C vs T	Overall	1281	1771	1.188	0.958–1.472	1.57 (.116)	.001	69.10%	Random
		African	356	478	0.791	0.628–0.996	2.00 (.46)	.139	54.40%	Fixed
		Caucasian	385	695	1.270	1.024–1.576	2.17 (.039)	.313	13.90%	Fixed
		Asian	452	506	1.410	1.054–1.886	2.31 (.021)	.082	60.00%	Random
	CC + CT vs TT (recessive)	Overall	1281	1771	1.065	0.858–1.322	0.57 (.569)	.107	39.20%	Fixed
		African	356	478	0.662	0.391–1.121	1.54 (.125)	.107	61.50%	Fixed
		Caucasian	385	695	1.046	0.581–1.883	0.15 (.880)	.702	0.00%	Fixed
		Asian	452	506	1.316	1.002–1.728	1.98 (.048)	.925	0.00%	Fixed
	CC vs CT + TT (dominant)	Overall	1281	1771	1.361	0.984–1.883	1.86 (.063)	<.001	72.90%	Random
		African	356	478	0.774	0.576–1.041	1.69 (.091)	.408	0.00%	Fixed
		Caucasian	385	695	1.487	0.953–2.321	1.75 (.081)	.073	61.80%	Random
		Asian	452	506	1.770	0.948–3.303	1.79 (.073)	.017	75.40%	Random
	CC vs. TT	Overall	1281	1771	1.175	0.743–1.859	0.69 (.491)	.010	60.40%	Random
		African	356	478	0.600	0.347–1.037	1.83 (.067)	.107	61.60%	Fixed
		Caucasian	385	695	1.188	0.645–2.189	0.55 (.58)	.858	0.00%	Fixed
		Asian	452	506	1.755	1.236–2.492	3.14 (.002)	.216	34.60%	Fixed
IL-10 -592	A vs C	Overall	1133	1238	0.786	0.617–1.001	1.95 (.051)	.001	73.30%	Random
		Caucasian	288	261	0.725	0.554–0.948	2.35 (.019)	.448	0.00%	Fixed
		Asian	417	582	0.635	0.530–0.762	4.88 (<.001)	.862	0.00%	Fixed
	AA vs AC + CC (recessive)	Overall	1133	1238	0.855	0.537–1.361	0.66 (.508)	.001	72.70%	Random
		Caucasian	288	261	1.170	0.585–2.338	0.44 (.658)	.242	27.00%	Fixed
		Asian	417	582	0.536	0.408–0.703	4.50 (<.001)	.427	0.00%	Fixed
	AA + AC vs CC (dominant)	Overall	1133	1238	0.716	0.526–0.975	2.12 (.034)	.010	64.10%	Random
		Caucasian	288	261	0.700	0.404–0.804	3.21 (.001)	.233	29.80%	Fixed
		Asian	417	582	0.609	0.444–0.836	3.07 (.002)	.638	0.00%	Fixed
	AA vs CC	Overall	1133	1238	0.784	0.459–1.341	0.89 (.374)	.002	70.90%	Random
		Caucasian	288	261	0.952	0.463–1.959	0.13 (.894)	.342	0.00%	Fixed
		Asian	417	582	0.441	0.308–0.633	4.45 (<.001)	.935	0.00%	Fixed

CI = confidence interval, OR = odds ratios.

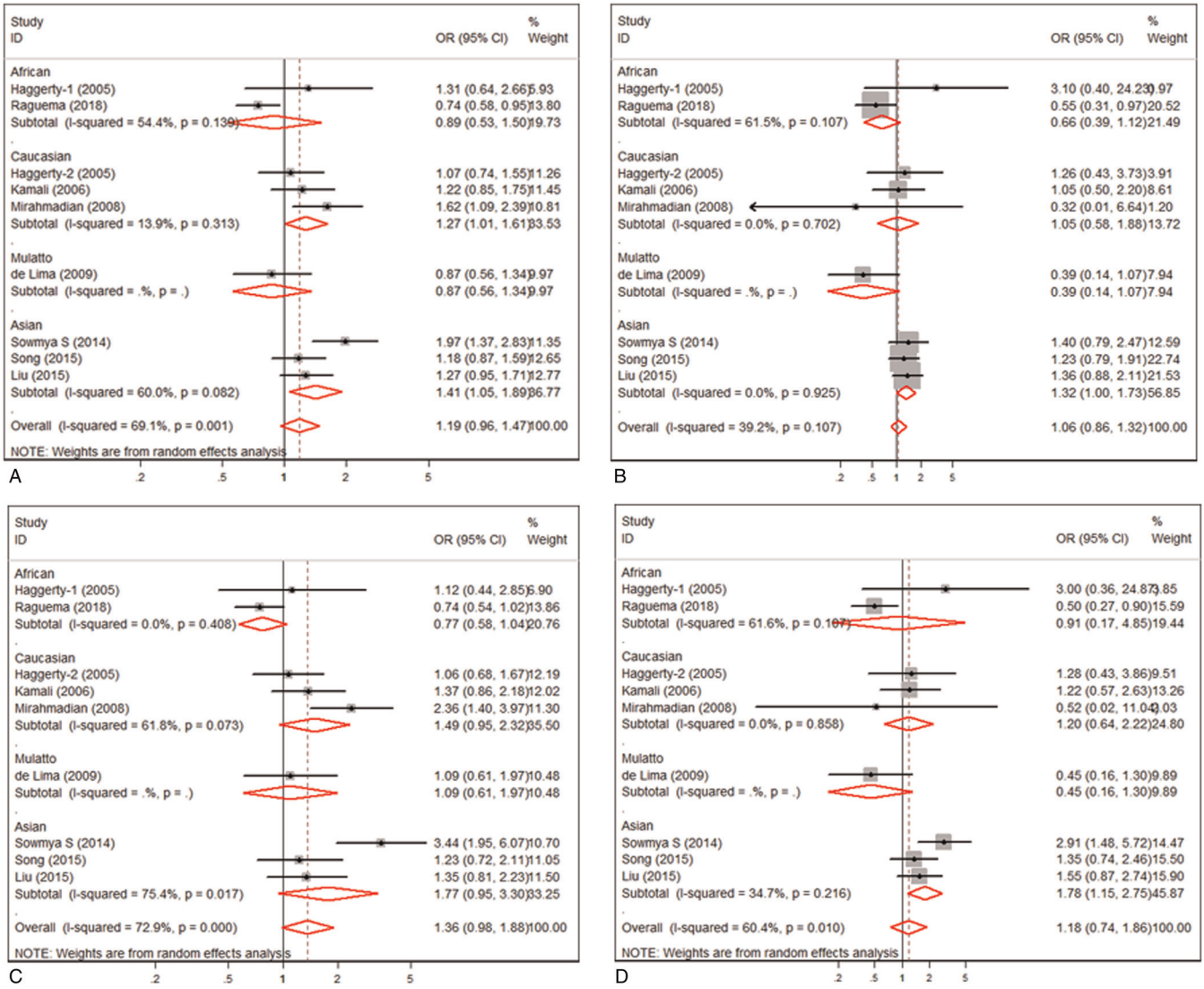

Figure 2. Meta-analysis of the association between the *IL10* -819 C/T polymorphism and PE. (A). allele control model; (B). recessive genotype model; (C). dominant genotype model; (D). homozygous genotype model.

interaction including heredity, among which genetic polymorphisms have caught increasingly attention.[30,31] Meanwhile, inflammation is also an accomplice in the development of PE, in which inflammatory factors make a crucial contribution.[19,32,33] Considering the importance of inflammation and genetic polymorphisms in the etiology and progression of PE, a growing number of studies have been performed to explore the associations between inflammatory gene polymorphisms and susceptibility to PE.[21–23,34–42] More and more meta-analysis have been conducted on the relationship between inflammatory factors IL-6,[43] TNF – α[44] and anti-inflammatory factors IL-10[45] gene polymorphism and PE, which further indicates that gene polymorphism is closely related to the susceptibility of PE. In the present study, we synthesized data from published studies to explore the relationship between the risk of PE and other commonly studied polymorphisms of the *IL-10* -819C/T and -592A/C.

IL-10 gene, located on chromosome 13q13, encodes an anti-inflammatory cytokine IL-10. During PE, decreased IL-10 was present in the plasma and placenta.[46,47] It was found that IL-10 treatment in PE pregnant mice significantly increasing Treg cells and decreased hypertension.[48] Hence, the decrease of IL-10 contributes to the pathogenesis of PE. So more and more studies are now investigating the relationship between *IL-10* gene polymorphisms and the risk of PE. It was reported that several polymorphisms in the IL-10 gene were associated with IL-10 production, including *IL-10* -819C/T,[49] and -592A/C[50,51] polymorphisms. Increasing studies are involved in investigating the relationship between *IL-10* -819C/T and -592A/C polymorphisms and PE susceptibility. Fan et al have revealed that *IL-10* -592A/C polymorphism was associated with PE susceptibility.[28] Moreover, it was reported that *IL-10* -819C/T are associated with PE in different populations.[25,29] On the contrary, some studies have demonstrated that there was no correlation between

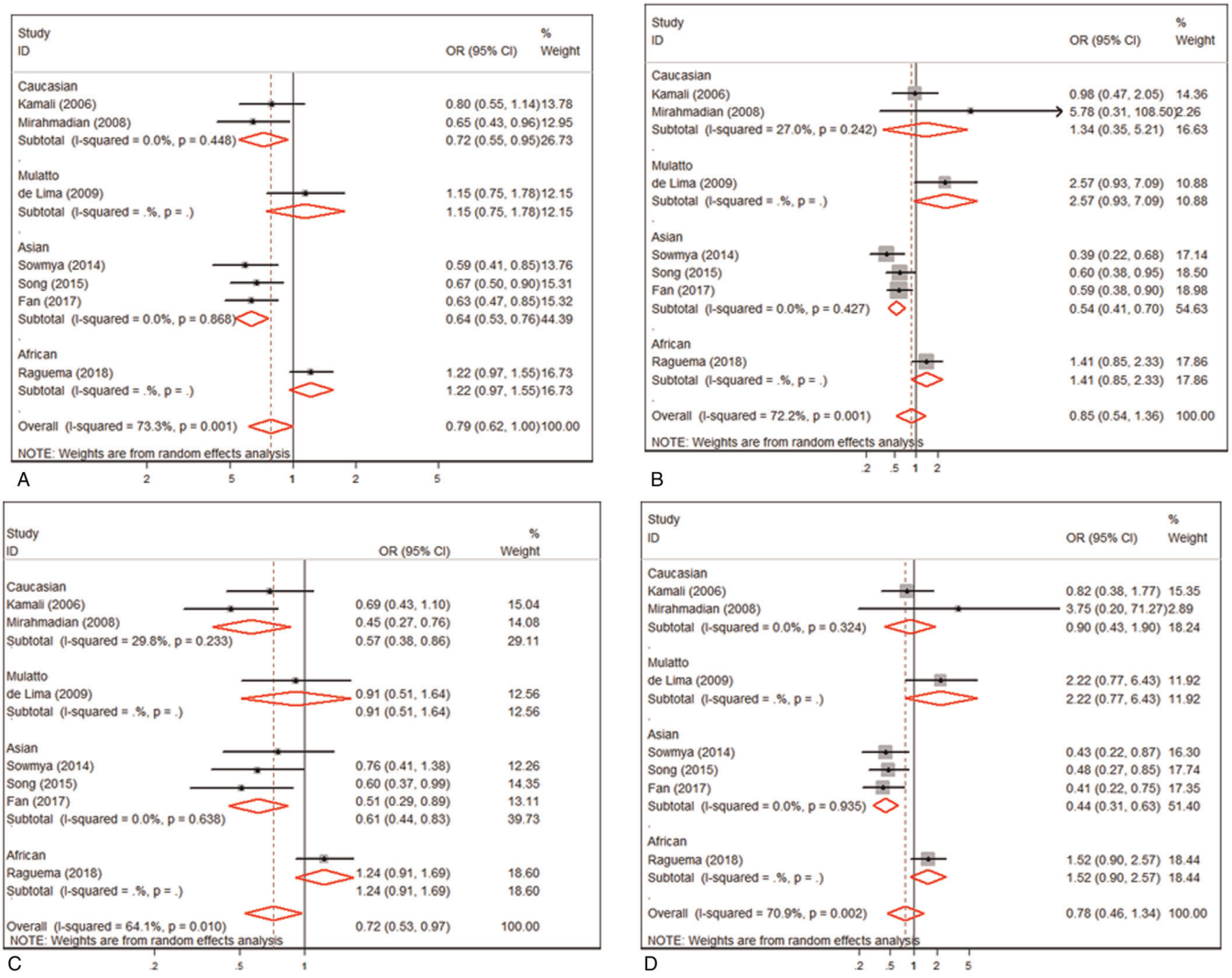

Figure 3. Meta-analysis of the association between the *IL10* -592 A/C polymorphism and PE. (A). allele control model; (B). recessive genotype model; (C). dominant genotype model; (D). homozygous genotype model.

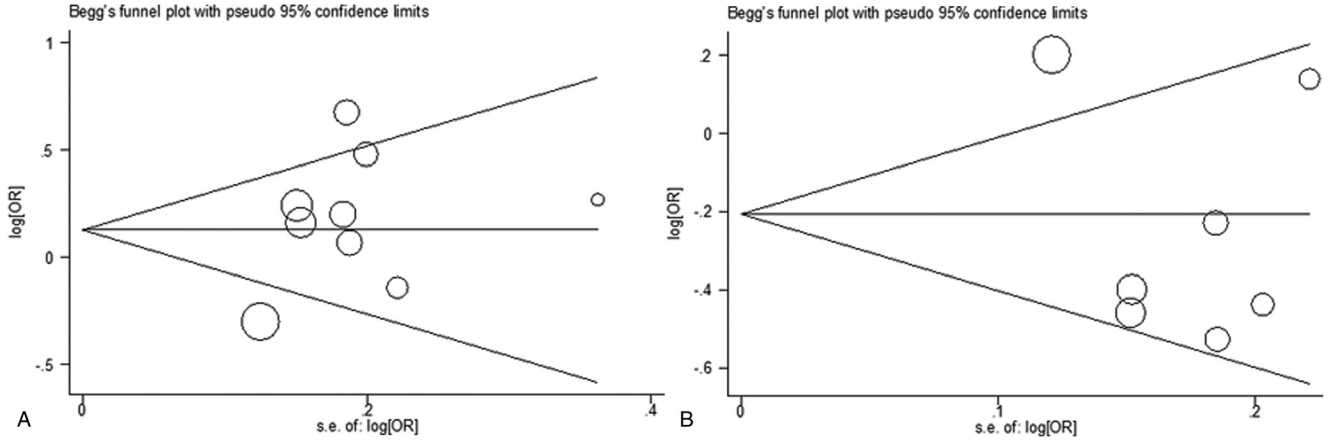

Figure 4. Begger funnel plot for publication bias among included studies. (A). *IL10* -819 C/T polymorphism; (B). *IL10* -592 A/C polymorphism.

IL-10 -819C/T and -592A/C polymorphisms and PE risk.[22] Due to the limitation of sample size and the genetic characteristics of different ethnicity, the conclusion is contradictory. In order to attenuate the analytical bias of the results depended on sample size and ethnicity, we conducted a meta-analysis.

In our meta-analysis, the *IL-10* -819C/T and -592A/C polymorphisms had no correlation with the risk of PE overall under an allele contrast, but had a significantly strong relation with the risk of PE in Asian under an allele contrast, dominant contrast model, recessive contrast model or homozygous contrast. Besides, *IL-10* -819 C allele and *IL-10* -592 C allele were related to PE susceptibility in Caucasian. The possible reason for this discrepancy was difference in study population. Ethnicity with different genetic backgrounds has a significant heterogeneity. Therefore, our results are not consistent with the meta-analysis results of Yang et al,[52] which showed that *IL-10* -819C/T and -592A/C polymorphisms were associated with PE risk under the allelic model. Due to the small number of literatures and people included for data analysis, the ethnic group analysis was not carried out in their meta-analysis. In our meta-analysis, a total of 1281cases and 1771 controls from 8 studies were included in *IL-10* -819 C/T polymorphism, 1133 cases, and 1238 controls from 7 studies were included in IL10 -592 A/C polymorphism. Nevertheless, only 5 case-control studies with 631 cases and 1059 controls for *IL-10* -819 C/T polymorphism and a total of 376 cases and 445 controls from 3 case-control studies were included in the 2014 meta-analysis. The inconsistent results may be that more studies containing a larger sample size and more populations, have been included in our meta-analysis, which attenuating statistical analysis results bias.

We must admit that there are some limitations in our meta-analysis. Although we updated the original meta-analysis and increased the number of included case-control studies, the number of subjects is still relatively small, which indicates that the final results may not be enough to study the real relationship statistically. It is necessary to follow up the research progress in order to update the results of system review and meta-analysis in time. Secondly, the source of control was inconsistent in each case-control study, which may lead to bias in the results. In the future investigation, the source of the control group should be unified as far as possible.

Finally, our meta-analysis results showed that there was no significant association between *IL-10* -819C/T, -592A/C polymorphisms and PE susceptibility overall, but the different genotypes and alleles of *IL-10* -819C/T, -592A/C polymorphisms had different effects on PE susceptibility in different ethnic groups. Therefore, according to the different genotypes and alleles, different regular follow-up are adopted for pregnant women of different ethnic groups. For example, an Asian pregnant woman with a CC genotype in the *IL-10* -819C/T polymorphism should pay more attention to the monitoring of blood pressure during pregnancy, whether she has symptoms related to gestational hypertension.

5. Conclusion

Our meta-analysis suggested that *IL-10* -819C/T and -592A/C polymorphisms had no correlation with the risk of PE overall, but had a significant association with PE susceptibility in Asian and Caucasian.

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