Evaluation of association of maternal IL-10 polymorphisms with risk of preeclampsia by A meta-analysis

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Abstract

Emerging evidence shows that interleukin (IL)-10 gene polymorphisms can regulate its expression level and thus influence person's susceptibility to preeclampsia. However, various published results were inconsistent. To explore the association between maternal IL-10 gene polymorphisms and preeclampsia, we performed a meta-analysis based upon 11 individual studies here. Our meta-analysis results indicated that IL-10 -819C/T (C *versus* T, OR = 1.28, 95% CI = 1.08–1.50, P = 0.003) and -592C/A (C *versus* A, OR = 1.28, 95% CI = 1.03–1.59, P = 0.03) polymorphisms were associated with preeclampsia. Although there was no overall association between -1082A/G polymorphism and preeclampsia (G *versus* A, OR = 0.93, 95% CI = 0.77–1.13, P = 0.49), such association existed among Asian (G *versus* A, OR = 1.29, 95% CI = 1.04–1.60, P = 0.02) and South American (G *versus* A, OR = 0.72, 95% CI = 0.54–0.94, P = 0.02) populations in the subgroup analysis stratified by continents.

Keywords: IL-10 • polymorphism • preeclampsia • meta-analysis

Introduction

Preeclampsia is a common pregnancy-specific disorder characterized by new-onset hypertension in combination with proteinuria after 20 weeks of gestation [1]. It occurs in about 2–8% pregnancies and has become one of the three leading causes of maternal and neonatal morbidity and mortality [2, 3]. Although the precise aetiology of preeclampsia is unknown because of its heterogeneous origins, the immune system has been found to play a significant role in the development of preeclampsia [4].

Normal pregnancy entails the shift of Th1/Th2 ratio towards Th2type reactions [5, 6]. Th1-type cytokines are responsible for several cell-mediated cytotoxic and inflammatory reactions and can produce a proinflammatory milieu. Excessive Th1-type cytokines like interleukin (IL)-2, tumour necrosis factor-alpha (TNF- α) and interferongamma (IFN- γ) have been reported to be detrimental to foetus and associated with preeclampsia [6–9]. Th2 cells are involved in the regulation of Th1 cell development and the maintenance of an antiinflammatory environment besides the common antibody responses

Management Department, Shanghai Medical Instrumentation College, Shanghai 200093, China. Tel.: 86 21-65485551-3324 Fax: +86 21-65485551-3324 E-mail: chaosyw@126.com Interleukin-10, originally described as a crucial Th2-type cytokine because of its anti-inflammatory actions, plays a pivotal role in pregnancy maintenance and development [12, 13]. It can help to establish the Th2 immune environment and inhibit the secretion of Th1-type cytokines like IL-6, TNF- α and IFN-gamma [14–16]. Also, IL-10 has been reported to contribute to trophoblast invasion, corpus luteum maturation and placental angiogenesis during pregnancy [12, 15, 17–20]. Evidence showed that the expression levels of placental and decidual IL-10 were altered in preeclampsia patients [21–23]. Reduced production of IL-10 has been suggested to cause a proinflammatory cytokine response and thus lead to the pathogenesis of preeclampsia [24, 25].

As polymorphisms in regulatory regions of cytokine genes can influence their expression levels, they may be related to person's predisposition to certain diseases [26]. Given the recognized importance of IL-10 in pregnancy, several polymorphic sites in its regulatory regions including -1082A/G (rs1800896), -819C/T (rs1800871) and -592C/A (rs1800872) have been widely investigated for their potential correlation with preeclampsia because of their reported capability of altering the gene expression level of IL-10[27–30]. However, the results are still inconclusive or controversial. Although three meta-analyses have suggested that the -1082A/G polymorphism of the

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^{[5, 10, 11].} As foetus is like a semi-allograft, the ability of Th2 cells to protect against allograft rejection plays a vital role during pregnancy [5, 10].

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IL-10 gene was not associated with preeclampsia [31–33], the latest study still supported such association [15]. Although Daher *et al.* have pointed out that such association could be subject to ethnicity, no related meta-analysis based upon a specific ethnicity has been reported so far [34]. Besides, there is still a lack of meta-analysis of other IL-10 polymorphic sites' association with preeclampsia. To address these issues, we performed a systemic review and a meta-analysis of all genetic association studies of maternal IL-10 polymorphisms related to preeclampsia to investigate the association between maternal IL-10 polymorphisms and preeclampsia. This systemic review may help to enhance our understanding of the role of IL-10 in the aetiology of preeclampsia and early identification of persons predisposed to preeclampsia.

Materials and methods

Literature search

A systematic literature search of PubMed, Web of Science and Scopus databases was conducted by two researchers independently for all relevant articles published before March 2014. The research key words included 'pregnancy induced hypertension', 'gestational hypertension', 'preeclampsia', 'genotype', 'SNP', 'mutation', 'polymorphism' 'IL-10' and 'interleukin 10'.

Inclusion and exclusion criteria

Studies included for this meta-analysis should meet the following criteria: (*i*) case-control studies or cohort studies focusing on the association between IL-10 polymorphism and preeclampsia; (*ii*) patients have been clinically diagnosed with preeclampsia and preeclampsia was defined as hypertension (\geq 140/90 mm Hg on two occasions \geq 6 hrs apart) with proteinuria (>300 mg/24 hrs or \geq 1+ dipstick in urine sample) after 20 weeks of gestation; (*iii*) the numbers of patients and normotensive pregnant women with various genotypes were available. The exclusion criteria of the meta-analysis were: (*i*) animal studies; (*ii*) meta-analyses, reviews, meeting abstracts or editorial comments; (*iii*) studies with duplicate data or incomplete data for odds ratio (OR) calculation; (*iv*) IL-10 polymorphic sites reported only once.

Data extraction

Information was extracted from all eligible studies by two authors independently and checked by a third author with disparities resolved by consensus. The collected data included the first author's name, publication date, region/ethnicity, genotyping method and the total number of cases and controls.

Statistical analysis

We used Review Manager 5.2 (Cochrane Collaboration, Oxford, UK) and Stata (Version 12.0; Stata Corporation, College Station TX, USA) for all

the statistical analysis. The association was evaluated with the use of the allelic model (mutation [M] allele *versus* wild [W] allele), the dominant model (WM+MM *versus* WW), the recessive model (MM *versus* WM+WW) and the co-dominant model (WM *versus* WW+MM) respectively. We calculated the OR and 95% CI for each study as well as the combined OR and corresponding 95% CI for all the included studies. The heterogeneity between individual studies was assessed using chi-squared-based Q-tests with the significance level set at P < 0.1. If the heterogeneity existed among the included studies, we calculated the pooled OR using the random-effect model (the DerSimonian and Laird method). Otherwise, we adopted the fixed-effect model (the Mantel–Haenszel method). The significance of the pooled OR was assessed by *Z*-test with P < 0.1 considered significant.

For each study, the Hardy–Weinberg equilibrium (HWE) was assessed by Fisher's exact test with P < 0.05 considered significant. In every pooled analysis, studies with controls not in HWE were still considered but the corresponding sensitivity analysis without these studies was also performed. The potential publication bias was checked by Begg's funnel plot and the funnel plot asymmetry was assessed by Egger's linear regression test with the significance level set at P < 0.05.

Results

Literature selection

We found a total of 375 articles after an initial search from the Pub-Med, Web of Science and Scopus databases. By reviewing the titles and abstracts, 355 of them were excluded because of no relevance to the association of IL-10 polymorphisms with preeclampsia. After excluding reviews, meta-analyses, studies without sufficient data or replication study, 12 eligible studies were finally included in this meta-analysis [6, 7, 15, 24, 34–41]. A total of 1861 preeclampsia patients and 3632 normotensive pregnant women were included in this study.

Table 1 summarized the characteristics of 12 included studies. There were 10 case-control studies [6, 7, 15, 24, 34–39] and 1 cohort study [40] involving IL-10 -1082A/G polymorphism, 5 casecontrol studies involving IL-10 -819C/T polymorphism [6, 7, 37, 38, 41] and 3 case-control studies involving IL-10 -592C/A polymorphism [6, 7, 38]. Only one study investigated the association of IL-10 -2849G/A polymorphism with preeclampsia [42].

Association between IL-10 -1082A/G polymorphism and preeclampsia

A total of 1368 cases and 3410 controls from 10 case–control studies and 1 cohort study were included for the evaluation. Significant heterogeneity existed and therefore the random-effect model was adopted to pool the results ($P_{heterogeneity} = 0.002$, $l^2 = 63\%$). The meta-analysis result showed that IL-10 -1082A/G polymorphism was not associated with the risk of preeclampsia under the allelic model (G allele *versus* A allele, OR = 0.93, 95% CI = 0.77–1.13, P = 0.49; Fig. 1A). As there were two studies with controls not in HWE [6, 39], we con-

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First author	Year	Country/Continent	Ethnicity	Sample size (preeclampsia/control)	SNP studied	Method
Stonek [35]	2008a	Austria/Europe	Caucasian	107/107	-1082A/G	Microarray
Valencia Villalvazo [36]	2012	Mexico/the Americas	Mexican-Mestizo, Maya-Mestizo	411/613	-1082A/G	TaqMan technology
Haggerty [37]	2005	USA/the Americas	Black, White	150/661	-1082A/G, -819C/T	TaqMan technology
Mirahmadian [6]	2008	Iran/Asia	Asian	160/100	-1082A/G, -819C/T, -592C/A	PCR-SSP
Kamali-Sarvestani [7]	2006	Iran/Asia	Asian	134/164	-1082A/G, -819C/T, -592C/A	PCR-SSP (-1082A/G), PCR-RFLP (-819 C/T, -592C/A)
de Lima [38]	2009	Brazil/the Americas	Mulatto	165/101	-1082A/G, -819C/T, -592C/A	PCR-SSP
Daher [34]	2006	Brazil/the Americas	Black, White, Mulatto	151/189	-1082A/G	PCR-SSP
Sowmya [39]	2013	India/Asia	Asian	88/100	-1082A/G	PCR-SSP
Stonek [40]	2008b	Austria/Europe	Caucasian	254/1362	-1082A/G	Microarray
Elhawary [15]	2013	Egypt/Africa	African	20/20	-1082A/G	PCR-RFLP
Sowmya [41]	2014	India/Asia	Asian	120/120	-819C/T	PCR-SSP
Vural [24]	2010	Turkey/Europe-Asia	European-Asian	101/95	-1082A/G	PCR-SSP

Table 1 Characteristics of the 12 eligible studies included for the investigation of IL-10 polymorphisms' association with preeclampsia

ducted a sensitivity analysis with these two studies excluded and the result still indicated that there was a lack of association between IL-10 -1082A/G polymorphism and the risk of preeclampsia (G allele *versus* A allele, OR = 0.89, 95% Cl = 0.71–1.10, P = 0.28; Fig. 1B).

In the subgroup analysis stratified by continents, we found that the heterogeneity was significantly lower in the Asia ($P_{heterogeneity} = 0.35$, $l^2 = 6\%$), Europe ($P_{heterogeneity} = 0.58$, $l^2 = 0\%$), South America ($P_{heterogeneity} = 0.91$, $l^2 = 0\%$) and North America groups ($P_{heterogeneity} = 0.37$, $l^2 = 0\%$) than in the whole population ($P_{heterogeneity} = 0.002$, $l^2 = 63\%$; Fig. 2). Therefore, the regions where the individual studies were performed could explain the source of heterogeneity. This result was somewhat reminiscent of Daher *et al*'s previous report that the association between IL-10 -1082A/G polymorphism and preeclampsia were only observed in white women instead of non-white women [34]. However, our meta-analysis results based upon four previously published relevant studies did not support the association between IL-10 -1082A/G polymorphism and the risk of preeclampsia among white women under the allelic model (G allele *versus* A allele, OR = 0.83, 95% CI = 0.56– 1.21, P = 0.32; Fig. 3).

Besides, we observed a significant association between IL-10 -1082A/G polymorphism and the risk of preeclampsia in the Asia (G allele *versus* A allele, OR = 1.29, 95% CI = 1.04–1.60, P = 0.02) and the South America (G allele *versus* A allele, OR = 0.72, 95% CI = 0.54-0.94, P = 0.02) subgroups under the allelic model. However, under the allelic model (G allele versus A allele), there was no such association in the Europe (OR = 1.13, 95% CI = 0.80-1.59, P = 0.49) or the North America group (OR = 0.97, 95% CI = 0.82-1.15, P = 0.75; Fig. 2). To further explore the potential way the G allele affected the risk of preeclampsia among Asian and South American populations, we then evaluated the association under other three genetic models. For Asian population, as there was no obvious heterogeneity under the dominant (GG+GA versus AA, $P_{\text{heterogeneity}} = 0.11$, $l^2 = 55\%$) or co-dominant model (GA versus GG+AA, $P_{heterogeneity} =$ 0.54, $l^2 = 0\%$), the fixed-effect model was used for these two genetic models. The random-effect model was used for the recessive model (GG versus GA+AA) because of the existence of significant heterogeneity ($P_{\text{heterogeneity}} = 0.08$, $l^2 = 60\%$). Under the dominant model, the pooled data indicated that the GG and GA phenotypes were linked to the increased risk of preeclampsia among Asian population (OR = 1.62, 95% CI = 1.14-2.30, P = 0.007; Fig. 4A). There was no evidence for similar association under the recessive (OR = 1.31, 95% CI = 0.63–2.73. P = 0.47: Fig. 4B) or co-dominant model (OR = 1.35, 95% CI = 0.97-1.89, P = 0.08; Fig. 4C). As for South American population, the fixed-effect model was used for the dominant ($P_{\text{heterogeneity}} = 0.96$, $l^2 = 0\%$), recessive ($P_{\text{heterogeneity}} = 0.79$, $l^2 = 0\%$) and co-dominant ($P_{\text{heterogeneity}} = 0.79$, $l^2 = 0\%$) models

J. Cell. Mol. Med. Vol 18, No 12, 2014

Α	Preeclam	npsia	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Daher 2006	76	284	122	358	10.6%	0.71 [0.50, 0.99]	
de Lima 2009	46	176	62	190	8.5%	0.73 [0.46, 1.15]	
Elhawary 2013	16	40	23	30	2.8%	0.20 [0.07, 0.58] 🕈	
Haggerty 2005	106	264	505	1170	12.1%	0.88 [0.67, 1.16]	
Kamali-Sarvestani 2006	95	244	97	318	10.4%	1.45 [1.02, 2.06]	
Mirahmadian 2008	172	320	92	200	10.3%	1.36 [0.96, 1.94]	
Sowmya 2013	56	146	78	200	8.7%	0.97 [0.63, 1.51]	
Stonek 2008a	95	214	91	214	9.8%	1.08 [0.74, 1.58]	
Stonek 2008b	12	24	1143	2724	4.2%	1.38 [0.62, 3.09]	
Valencia Villalvazo 2012	177	822	257	1226	13.2%	1.03 [0.83, 1.28]	
Vural 2010	71	202	86	190	9.3%	0.66 [0.44, 0.98]	
Total (95% CI)		2736		6820	100.0%	0.93 [0.77, 1.13]	•
Total events	922		2556				
Heterogeneity: Tau ² = 0.0	6; Chi² = 27	.29, df =	= 10 (P = 0	0.002);	l² = 63%	H	
Test for overall effect: Z =	0.68 (P = 0	.49)				0.1	0.2 0.5 1 2 5 10
							Favours case Favours control

В	Preeclam	npsia	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Daher 2006	76	284	122	358	13.1%	0.71 [0.50, 0.99]	
de Lima 2009	46	176	62	190	10.6%	0.73 [0.46, 1.15]	
Elhawary 2013	16	40	23	30	3.5%	0.20 [0.07, 0.58]	←
Haggerty 2005	106	264	505	1170	14.8%	0.88 [0.67, 1.16]	
Kamali-Sarvestani 2006	95	244	97	318	12.8%	1.45 [1.02, 2.06]	
Stonek 2008a	95	214	91	214	12.1%	1.08 [0.74, 1.58]	
Stonek 2008b	12	24	1143	2724	5.4%	1.38 [0.62, 3.09]	
Valencia Villalvazo 2012	177	822	257	1226	16.1%	1.03 [0.83, 1.28]	- + -
Vural 2010	71	202	86	190	11.6%	0.66 [0.44, 0.98]	
Total (95% CI)		2270		6420	100.0%	0.89 [0.71, 1.10]	•
Total events	694		2386				
Heterogeneity: Tau ² = 0.0	7; Chi² = 23	.19, df =	8 (P = 0.	.003); l ²	² = 66%		
Test for overall effect: Z =	1.09 (P = 0	.28)	`			C	0.1 0.2 0.5 1 2 5 10
	(,					Favours case Favours control

Fig. 1 Forest plot of preeclampsia associated with IL-10 -1082A/G polymorphism under the allelic model (G allele versus A allele) (A) and the corresponding sensitivity analysis with the exclusion of studies not in HWE (B).

because of lack of between-study heterogeneity. Under the dominant model, the pooled data indicated that the GG and GA phenotypes were linked to the decreased risk of preeclampsia among South American population (OR = 0.67, 95% CI = 0.47–0.95, P = 0.03; Fig. 5A). There was no evidence for similar association under the recessive (OR = 0.57, 95% CI = 0.29–1.12, P = 0.10; Fig. 5B) or co-dominant model (OR = 0.79, 95% CI = 0.55–1.12, P = 0.18; Fig. 5C).

Association between IL-10 -819C/T polymorphism and preeclampsia

A total of 631 cases and 1059 controls from 5 case–control studies were included for data synthesis. Under the allelic model, there was no evidence of between-study heterogeneity and therefore the fixed-effect model was adopted to pool the results (C allele *versus* T allele, $P_{\text{heterogeneity}} = 0.15$, $l^2 = 41\%$). The meta-analysis

results showed that the C allele was associated to the risk of preeclampsia under the allelic model (C allele *versus* T allele, OR = 1.28, 95% Cl = 1.08–1.50, P = 0.003; Fig. 6A).

As significant between-study heterogeneity was absent under the dominant model (CC+CT *versus* TT, $P_{heterogeneity} = 0.23$, P = 29%) and existed under the recessive (CC *versus* CT+TT, $P_{heterogeneity} = 0.02$, P = 29%) and co-dominant (CT *versus* CT+TT, $P_{heterogeneity} = 0.01$, P = 29%) models, the fixed-effect model was used for the dominant model and the random-effect model was used for the other two genetic models. Under the dominant model, the CC and CT genotypes were not significantly associated with the risk of preeclampsia (CC+CT *versus* TT, OR = 0.98, 95% CI = 0.67–1.39, P = 0.83; Fig. 6B). The CC genotype was linked to the risk of preeclampsia under the recessive model (CC *versus* CT+TT, OR = 1.62, 95% CI = 1.10–2.38, P = 0.01; Fig. 6C) and the CT genotype did not contribute to the risk of preeclampsia under the co-dominant model (CT *versus* CC+TT, OR = 0.59, 95% CI = 0.40–0.88, P = 0.01; Fig. 6D).

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Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI M-H, Fixed, 95% CI 1.1.1 Africa Image: Comparison of the state o		Preeclam	psia	Contr	rol		Odds Ratio	Odds Ratio
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Elhawary 2013 16 40 23 30 2.3% 0.20 [0.07, 0.58] Total events 16 23 Heterogeneity: Not applicable Test for overall effect: $Z = 2.96$ (P = 0.003) 1.12 Asia Kamali-Sarvestani 2006 95 244 97 318 7.6% 1.45 [1.02, 2.06] Mirahmadian 2008 172 320 92 200 7.8% 1.36 [0.66, 1.34] Sownya 2013 56 146 78 200 6.0% 0.97 [0.63, 1.51] Subtotal (95% CI) 710 718 21.4% 1.29 [1.04, 1.60] Total events 323 267 Heterogeneity: Chi ^p = 2.12, df = 2 (P = 0.35); P = 6% Test for overall effect: $Z = 2.28$ (P = 0.35); P = 6% Test for overall effect: $Z = 2.28$ (P = 0.35); P = 6% Test for overall effect: $Z = 0.59$ (P = 0.49) 1.1.3 Europe Stomk 2008b 95 214 91 214 7.5% 1.08 [0.74, 1.58] Subtotal (95% CI) 238 2938 9.0% 1.13 [0.80, 1.59] Otal events 107 1234 Heterogeneity: Chi ^p = 0.30, df = 1 (P = 0.58); P = 0% Test for overall effect: $Z = 0.69$ (P = 0.49) 1.1.4 Europe-Asia Vural 2010 71 202 86 190 8.5% 0.66 [0.44, 0.98] Otal events 71 86 Heterogeneity: Not applicable Test for overall effect: $Z = 2.04$ (P = 0.58); P = 0% Test for overall effect: $Z = 2.04$ (P = 0.04) 1.1.5 bouth Amorica Daher 2006 76 284 122 358 11.7% 0.71 [0.50, 0.99] de Lima 2009 46 176 62 190 6.5% 0.73 [0.44, 0.38] Total events 122 184 Heterogeneity: Chi ^p = 0.0.3 (1 = 1 (P = 0.37); P = 0% Test for overall effect: $Z = 2.41$ (P = 0.02) 1.1.6 North America Daher 2006 76 284 122 358 11.7% 0.71 [0.50, 0.99] de Lima 2009 46 176 62 190 6.5% 0.37 [0.45, 1.16] Total events 122 184 Heterogeneity: Chi ^p = 0.0.3 (1 = 1 (P = 0.37); P = 0% Test for overall effect: $Z = 2.41$ (P = 0.37); P = 0% Test for overall effect: $Z = 2.41$ (P = 0.37); P = 0% Test for overall effect: $Z = 2.41$ (P = 0.37); P = 0% Test for overall effect: $Z = 2.41$ (P = 0.37); P = 0% Test for overall effect: $Z = 0.32$ (P = 0.75) Total events 28 772 Heterogeneity: Chi ^p = 2.0.32, (P = 0.75) Total events 28 772 Heterogeneity: Chi ^p = 2.0.32, (P = 0.02); P = 63% Test for overall effect: $Z = 0.32$ (P = 0.00); P = 63% Test for overall effect: $Z = 0.32$ (P = 0.	1.1.1 Africa							
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Sowmya 2013 56 146 76 200 6.0% 0.97 [0.63, 1.51] Subtotal (95% CI) 710 718 21.4% 1.29 [1.04, 1.60] Total events 323 267 Heterogeneity: Ch ² = 2.12, df = 2 (P = 0.35); P = 6% Test for overall effect: Z = 2.28 (P = 0.02) 1.1.3 Europe Stonek 2008b 95 214 91 214 7.5% 1.08 [0.74, 1.58] Stonek 2008b 12 24 1143 2724 1.5% 1.38 [0.62, 3.09] Total events 107 1234 Heterogeneity: Ch ² = 0.30, df = 1 (P = 0.58); P = 0% Test for overall effect: Z = 0.69 (P = 0.49) 1.1.4 Europe-Asia Vural 2010 71 202 190 8.5% 0.66 [0.44, 0.98] Subtotal (95% CI) 202 190 8.5% 0.66 [0.44, 0.98] Subtotal (95% CI) 202 190 8.5% 0.66 [0.44, 0.98] Total events 71 86 Heterogeneity: Not applicable Test for overall effect: Z = 2.04 (P = 0.04) 1.1.5 South America Daher 2006 76 284 122 358 11.7% 0.71 [0.50, 0.99] de Lima 2009 46 176 62 190 6.5% 0.73 [0.46, 1.15] Subtotal (95% CI) 460 548 18.3% 0.72 [0.54, 0.94] Total events 122 184 Heterogeneity: Ch ² = 0.01, df = 1 (P = 0.91); P = 0% Test for overall effect: Z = 2.41 (P = 0.02) 1.1.6 North America Haggerty 2005 106 264 505 1170 16.5% 0.88 [0.67, 1.16] Valencia Villalvazo 2012 177 822 257 1226 24.0% 1.03 [0.83, 1.28] Subtotal (95% CI) 1086 2396 40.5% 0.97 [0.82, 1.15] Total events 922 556 Heterogeneity: Ch ² = 0.80, df = 1 (P = 0.37); P = 0% Test for overall effect: Z = 0.32 (P = 0.75) Total events 922 2556 Heterogeneity: Ch ² = 27.29, df = 10 (P = 0.002); P = 79.2% Favours case Favours case Favours case Favours case Favours case Favours case Favours case	Mirahmadian 2008	172	320	92	200	7.8%	1.36 [0.96, 1.94]	
Subtotal (95% CI) 710 718 21.4% 1.29 [1.04, 1.60] Total events 323 267 Heterogeneity: $Ch^2 = 2.12$, $df = 2$ ($P = 0.35$); $P = 6\%$ Test for overall effect: $Z = 2.28$ ($P = 0.02$) 1.1.3 Europe Stonek 2008b 12 2.4 1143 2724 1.5% 1.38 [0.62, 3.09] Subtotal (95% CI) 238 2938 9.0% 1.13 [0.62, 3.09] Subtotal (95% CI) 238 2938 9.0% 1.13 [0.62, 3.09] Total events 107 1234 Heterogeneity: $Ch^2 = 0.30$, $df = 1$ ($P = 0.58$); $P = 0\%$ Test for overall effect: $Z = 0.69$ ($P = 0.49$) 1.1.4 Europe-Asia Vural 2010 71 202 190 8.5% 0.66 [0.44, 0.98] Subtotal (95% CI) 71 202 190 8.5% 0.66 [0.44, 0.98] Subtotal (95% CI) 71 86 Heterogeneity: Not applicable Test for overall effect: $Z = 2.04$ ($P = 0.04$) 1.1.5 South America Daher 2006 76 284 122 358 11.7% 0.71 [0.50, 0.99] de Lima 2006 46 176 62 190 6.5% 0.73 [0.46, 1.15] Subtotal (95% CI) 122 184 Heterogeneity: $Ch^2 = 0.01$, $df = 1$ ($P = 0.02$) 1.1.6 North America Haggety 2005 106 264 505 1170 16.5% 0.88 [0.67, 1.16] Valencia Villalvazo 2012 177 822 257 1226 24.0% 1.03 [0.83, 1.28] Subtotal (95% CI) 1086 2396 40.5% 0.97 [0.82, 1.15] Total events 283 762 Heterogeneity: $Ch^2 = 0.80$, $df = 1$ ($P = 0.002$); $P = 0\%$ Test for overall effect: $Z = 0.32$ ($P = 0.002$); $P = 70\%$ Test for overall effect: $Z = 0.32$ ($P = 0.002$); $P = 70\%$ Test for overall effect: $Z = 0.71$ ($P = 0.07$); $P = 0\%$ Test for overall effect: $Z = 0.71$ ($P = 0.02$); $P = 70\%$ Test for overall effect: $Z = 0.71$ ($P = 0.02$); $P = 70\%$ Test for overall effect: $Z = 0.71$ ($P = 0.02$); $P = 70\%$ Test for overall effect: $Z = 0.71$ ($P = 0.02$); $P = 70\%$ Test for overall effect: $Z = 0.71$ ($P = 0.02$); $P = 70\%$ Test for overall effect: $Z = 0.71$ ($P = 0.405$); $P = 70\%$ Test for overall effect: $Z = 0.71$ ($P = 0.405$); $P = 70\%$ Test for overall effect: $Z = 0.71$ ($P = 0.405$); $P = 70\%$ Test for overall effect: $Z = 0.71$ ($P = 0.405$); $P = 70\%$ Test for overall effect: $Z = 0.71$ ($P = 0.405$); $P = 70\%$	Sowmya 2013	56	146	78	200	6.0%	0.97 [0.63, 1.51]	
Total events 323 267 Heterogeneity: $Ch^{\mu} = 2.12$, $df = 2 (P = 0.35)$; $P = 6\%$ Test for overall effect: $Z = 2.28 (P = 0.02)$ 1.13 Europe Stonek 2008a 95 214 91 214 7.5% 1.08 [0.74, 1.58] Stonek 2008b 12 24 1143 2724 1.5% 1.38 [0.52, 3.09] Subtotal (95% Cl) 238 2293 9.0% 1.13 [0.80, 1.59] Total events 107 1234 Heterogeneity: $Ch^{\mu} = 0.30$, $df = 1 (P = 0.58)$; $P = 0\%$ Test for overall effect: $Z = 0.69 (P = 0.49)$ 1.14 Europe-Asia Vural 2010 71 202 86 190 8.5% 0.66 [0.44, 0.98] Subtotal (95% Cl) 202 190 8.5% 0.66 [0.44, 0.98] Otal events 71 86 Heterogeneity: Not applicable Test for overall effect: $Z = 2.04 (P = 0.04)$ 1.1.5 South America Daher 2006 76 284 122 358 11.7% 0.71 [0.50, 0.99] de Lima 2009 46 176 62 190 6.5% 0.73 [0.46, 1.15] Subtotal (95% Cl) 460 548 18.3% 0.72 [0.54, 0.54] Total events 122 184 Heterogeneity: $Ch^{\mu} = 0.01$, $df = 1 (P = 0.91)$; $P = 0\%$ Test for overall effect: $Z = 2.41 (P = 0.02)$ 1.1.6 North America Haggerty 2005 106 264 505 1170 16.5% 0.88 [0.67, 1.16] Valencia Villalvazo 2012 177 822 257 1226 24.0% 1.03 [0.83, 1.28] Subtotal (95% Cl) 1088 2396 40.5% 0.97 [0.82, 1.15] Total events 283 762 Heterogeneity: $Ch^{\mu} = 0.80$, $df = 1 (P = 0.37)$; $P = 0\%$ Test for overall effect: $Z = 0.32 (P = 0.75)$ Total events 922 2556 Heterogeneity: $Ch^{\mu} = 27.29$, $df = 10 (P = 0.002)$; $P = 63\%$ Test for overall effect: $Z = 0.71 (P = 0.48)$ Pavours control Favours control	Subtotal (95% CI)		710		718	21.4%	1.29 [1.04, 1.60]	\blacksquare
Heterogeneity: $Ch^2 = 2.12$, $df = 2$ ($P = 0.35$); $P = 6\%$ Test for overall effect: $Z = 2.28$ ($P = 0.02$) 1.1.3 Europe Stonek 2008a 95 214 91 214 7.5% 1.08 [0.74, 1.58] Stonek 2008b 12 24 1143 2724 1.5% 1.38 [0.62, 3.09] Subtotal (95% C) 238 2938 9.0% 1.13 [0.80, 1.59] Total events 107 1234 Heterogeneity: $Ch^2 = 0.30$, $df = 1$ ($P = 0.58$); $P = 0\%$ Test for overall effect: $Z = 0.69$ ($P = 0.49$) 1.1.4 Europe-Asia Vural 2010 71 202 86 190 8.5% 0.66 [0.44, 0.98] Subtotal (95% C) 202 190 8.5% 0.66 [0.44, 0.98] Subtotal (95% C) 202 190 8.5% 0.66 [0.44, 0.98] Total events 71 86 Heterogeneity: Not applicable Test for overall effect: $Z = 2.04$ ($P = 0.04$) 1.1.5 South America Daher 2006 76 284 122 358 11.7% 0.71 [0.50, 0.99] de Lima 2009 46 176 62 190 6.5% 0.73 [0.46, 1.15] Subtotal (95% C) 460 548 18.3% 0.72 [0.54, 0.94] Total events 122 184 Heterogeneity: $Ch^2 = 0.01$, $df = 1$ ($P = 0.91$); $P = 0\%$ Test for overall effect: $Z = 2.41$ ($P = 0.02$) 1.1.6 North America Haggerty 2005 106 264 505 1170 16.5% 0.88 [0.67, 1.16] Valencia Villalvazo 2012 177 822 257 1226 24.0% 1.03 [0.83, 1.28] Subtotal (95% C) 1086 2396 40.5\% 0.97 [0.82, 1.15] Total events 283 762 Heterogeneity: $Ch^2 = 0.30$, $df = 1$ ($P = 0.37$); $P = 0\%$ Test for overall effect: $Z = 0.32$ ($P = 0.75$) Total events 222 256 Heterogeneity: $Ch^2 = 27.29$, $df = 10$ ($P = 0.002$); $P = 79.2\%$ Total events 922 2566 Favours control Favours control	Total events	323		267				
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Subtotal (95% CI) 238 2938 9.0% 1.13 [0.80, 1.59] Total events 107 1234 Heterogeneity: Ch ² = 0.30, df = 1 ($P = 0.58$); $P = 0\%$ Test for overall effect: $Z = 0.69$ ($P = 0.49$) 1.1.4 Europe-Asia Vural 2010 71 202 86 190 8.5% 0.66 [0.44, 0.98] Subtotal (95% CI) 202 190 8.5% 0.66 [0.44, 0.98] Total events 71 86 Heterogeneity: Not applicable Test for overall effect: $Z = 2.04$ ($P = 0.04$) 1.1.5 South America Daher 2006 76 284 122 358 11.7% 0.71 [0.50, 0.99] de Lima 2009 46 176 62 190 6.5% 0.73 [0.46, 1.15] Subtotal (95% CI) 2460 548 18.3% 0.72 [0.54, 0.94] Total events 122 184 Heterogeneity: Ch ² = 0.01, df = 1 ($P = 0.91$); $P = 0\%$ Test for overall effect: $Z = 2.41$ ($P = 0.02$) 1.1.6 North America Haggerty 2005 106 264 505 1170 16.5% 0.88 [0.67, 1.16] Valencia Villalvazo 2012 177 822 257 1226 24.0% 1.03 [0.83, 1.28] Subtotal (95% CI) 1086 2396 40.5% 0.97 [0.82, 1.15] Total events 283 762 Heterogeneity: Ch ² = 0.30, df = 1 ($P = 0.37$); $P = 0\%$ Test for overall effect: $Z = 0.32$ ($P = 0.75$) Total events 922 2556 Heterogeneity: Ch ² = 27.29, df = 10 ($P = 0.002$); $P = 63\%$ Test for overall effect: $Z = 0.71$ ($P = 0.48$) Test for overall effect: $Z = 0.71$ ($P = 0.48$) Test for overall effect: $Z = 0.72$ ($P = 0.48$) Test for overall effect: $Z = 0.72$ ($P = 0.48$) Test for overall effect: $Z = 0.72$ ($P = 0.48$) Test for overall effect: $Z = 0.72$ ($P = 0.48$) Test for overall effect: $Z = 0.72$ ($P = 0.48$) Test for overall effect: $Z = 0.72$ ($P = 0.48$) Test for overall effect: $Z = 0.72$ ($P = 0.48$) Test for overall effect: $Z = 0.72$ ($P = 0.48$) Favours case Favours control	Stonek 2008b	12	24	1143	2724	1.5%	1.38 [0.62, 3.09]	
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Taggerly 2005 106 264 305 1170 10.3% 0.88 [0.07, 1.16] Valencia Villalvazo 2012 177 822 257 1226 24.0% 1.03 [0.83, 1.28] Subtotal (95% CI) 1086 2396 40.5% 0.97 [0.82, 1.15] Total events 283 762 Heterogeneity: Chi ² = 0.80, df = 1 (P = 0.37); l ² = 0% Test for overall effect: Z = 0.32 (P = 0.75) Total events 922 2556 Heterogeneity: Chi ² = 27.29, df = 10 (P = 0.002); l ² = 63% Test for overall effect: Z = 0.71 (P = 0.48) Test for subproup differences: Chi ² = 24 05. df = 5 (P = 0.0002); l ² = 79 2%	Hoggorty 2005	106	264	505	1170	16 E0/		_ _
Valencia villavazo zonz 177 622 237 1226 24.0% 1.03 [0.63, 1.26] Subtotal (95% Cl) 1086 2396 40.5% 0.97 [0.82, 1.15] Total events 283 762 Heterogeneity: Chi ² = 0.80, df = 1 (P = 0.37); l ² = 0% 100.0% 0.96 [0.86, 1.07] Test for overall effect: Z = 0.32 (P = 0.75) 736 6820 100.0% 0.96 [0.86, 1.07] Total events 922 2556 100.0% 0.96 [0.86, 1.07] 0.1 0.2 0.5 1 2 5 10 Test for overall effect: Z = 0.71 (P = 0.48) 10 (P = 0.002); l ² = 63% 10.1 0.2 0.5 1 2 5 10 Test for suboroup differences: Chi ² = 24.05, df = 5 (P = 0.0002) l ² = 79.2% Favours case Favours control	Haggerty 2005	100	204	202	100	24.00/		
Constructor (557, 61) 1000 2350 40.5% 0.57 [0.02, 1.15] Total events 283 762 Heterogeneity: Chi ² = 0.80, df = 1 (P = 0.37); l ² = 0% Test for overall effect: Z = 0.32 (P = 0.75) Total (95% Cl) 2736 6820 100.0% 0.96 [0.86, 1.07] Total events 922 2556 Heterogeneity: Chi ² = 27.29, df = 10 (P = 0.002); l ² = 63% 1 1 2 5 Test for overall effect: Z = 0.71 (P = 0.48) 0.1 0.2 0.5 1 2 5 10 Test for subproup differences: Chi ² = 24 05. df = 5 (P = 0.0002), l ² = 79 2% Favours case Favours control	valencia villalvazo 2012 Subtotal (95% CI)	177	1096	257	1220	24.U% /0 5%	1.03 [0.03, 1.28] 0.97 [0.82, 4.45]	↓
Total events 203 702 Heterogeneity: Chi ² = 0.80, df = 1 (P = 0.37); l ² = 0% Test for overall effect: Z = 0.32 (P = 0.75) Total (95% Cl) 2736 6820 100.0% 0.96 [0.86, 1.07] Total events 922 2556 Heterogeneity: Chi ² = 27.29, df = 10 (P = 0.002); l ² = 63% 0.1 0.2 0.5 1 2 5 10 Test for overall effect: Z = 0.71 (P = 0.48) Favours cose Favours control	Total overta	000	1000	760	2030	40.0%	0.97 [0.02, 1.13]	Ţ
Test for overall effect: $Z = 0.32$ (P = 0.75) Total (95% Cl) 2736 6820 100.0% 0.96 [0.86, 1.07] Total events 922 2556 Heterogeneity: Chi ² = 27.29, df = 10 (P = 0.002); l ² = 63% 1 2 5 10 Test for overall effect: Z = 0.71 (P = 0.48) East for subgroup differences: Chi ² = 24 05. df = 5 (P = 0.0002), l ² = 79 2% Favours case Favours control	Hotorogonoity: Chi2 = 0.90	∠ö3) df = 1 /⊡ -	- 0 271.	/02 /0 – 21				
Total (95% Cl) 2736 6820 100.0% 0.96 [0.86, 1.07] Total events 922 2556 Heterogeneity: Chi ² = 27.29, df = 10 (P = 0.002); l ² = 63% 0.1 0.2 0.5 1 2 5 10 Test for overall effect: Z = 0.71 (P = 0.48) Favours case Favours control Test for subgroup differences: Chi ² = 24 05. df = 5 (P = 0.0002), l ² = 79 2% Favours case Favours control	Test for overall effect: 7 -	, ui − T (P = 0 32 (P = 0	- 0.37); 75)	i – U%				
Total (95% Cl) 2736 6820 100.0% 0.96 [0.86, 1.07] Total events 922 2556 Heterogeneity: Chi ² = 27.29, df = 10 (P = 0.002); l ² = 63% 10.02 0.5 1 2 5 10 Test for overall effect: Z = 0.71 (P = 0.48) 10.02 0.5 1 2 5 10 Test for subgroup differences: Chi ² = 24 0.5 $d = 5$ $P = 0.0002$) $l2 = 79$ P^{26} Favours case Favours control		0.02 (F = U	., 5)					
Total events 922 2556 Heterogeneity: Chi ² = 27.29, df = 10 (P = 0.002); l ² = 63% 0.1 0.2 0.5 1 2 5 10 Test for overall effect: Z = 0.71 (P = 0.48) Favours case Favours case Favours control	Total (95% CI)		2736		6820	100.0%	0.96 [0.86. 1.07]	4
Heterogeneity: $Chi^2 = 27.29$, df = 10 (P = 0.002); l ² = 63% Test for overall effect: Z = 0.71 (P = 0.48) Test for subgroup differences: $Chi^2 = 24.05$, df = 5 (P = 0.0002), l ² = 79.2% Favours case Favours control	Total events	922		2556				
Test for overall effect: $Z = 0.71$ (P = 0.48) Test for subgroup differences: Chi ² = 24 05. df = 5 (P = 0.0002), l ² = 79.2% Test for subgroup differences: Chi ² = 24.05. df = 5 (P = 0.0002), l ² = 79.2%	Heterogeneity: Chi ² = 27 2	9. df = 10.0	⊃ = 0 ∩r)2): l ² = 6	3%		⊢	-++ -+++
Test for subgroup differences: $Chi^2 = 24.05$, df = 5 (P = 0.0002), $l^2 = 79.2\%$ Favours case Favours control	Test for overall effect: 7 =	0.71 (P = 0	.48)	,, . 0.	~ /0		0.1	0.2 0.5 1 2 5 10
	Test for subaroup differen	ces: Chi ² = 3	24.05. d	f = 5 (P =	: 0.000	2), $ ^2 = 79^{\circ}$	2%	Favours case Favours control

Fig. 2 Forest plot of preeclampsia associated with IL-10 -1082A/G polymorphism stratified by continents under the allelic model (G allele versus A allele). The Europe-Asia subgroup included countries spanning Europe and Asia.

J. Cell. Mol. Med. Vol 18, No 12, 2014

	Preeclampsia Control				Odds Ratio		Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	N M	H, Rando	om, 95% Cl	
Daher 2006	24	108	64	166	22.4%	0.46 [0.26, 0.79]				
Haggerty 2005	92	224	387	816	33.4%	0.77 [0.57, 1.04]		-==+		
Stonek 2008a	95	214	91	214	29.5%	1.08 [0.74, 1.58]		-	F	
Stonek 2008b	12	24	1143	2724	14.7%	1.38 [0.62, 3.09]		+		
Total (95% CI)		570		3920	100.0%	0.83 [0.56, 1.21]		•		
Total events	223		1685							
Heterogeneity: Tau ² =	= 0.09; Chi² =	= 8.14, c	df = 3 (P =	= 0.04);	l² = 63%					
Test for overall effect:	Z = 0.99 (P	= 0.32		,			0.01 0.	1 1	10	100
	- 0.00 (i	0.0Z)					Favou	's case	Favours co	ntrol

Fig. 3 Forest plot of the risk of preeclampsia among white women associated with IL-10 -1082A/G polymorphism under the allelic model (G allele *versus* A allele).

Α	Preeclam	ipsia	Contr	ol		Odds Ratio			Od	ds F	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95%	CI		M-H, F	ixec	l, 95% (CI	
Kamali-Sarvestani 2006	72	122	78	159	56.1%	1.50 [0.93, 2.41]			+	-		
Mirahmadian 2008	155	160	87	100	6.8%	4.63 [1.60, 13.43]					-	→
Sowmya 2013	43	73	53	100	37.1%	1.27 [0.69, 2.34]		-	+			
Total (95% CI)		355		359	100.0%	1.62 [1.14, 2.30]]				•		
Total events	270		218										
Heterogeneity: Chi ² = 4.46	6, df = 2 (P	= 0.11);	l² = 55%				H	-+		+	<u> </u>	<u>+</u>	
Test for overall effect: Z =	2.72 (P = 0)	.007)					0.1	0.2	0.5	1	2	5	10
	(,						Favou	rs case		Favour	s cont	rol

В	Preeclam	npsia	Conti	rol	Odds Ratio				Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C		N	I-H, Ra	ndo	m, 95%	CI	
Kamali-Sarvestani 2006	23	122	19	159	38.4%	1.71 [0.88, 3.31]				+	_	-	
Mirahmadian 2008	17	160	5	100	26.5%	2.26 [0.81, 6.33]				+			
Sowmya 2013	13	73	25	100	35.1%	0.65 [0.31, 1.38]					_		
Total (95% CI)		355		359	100.0%	1.31 [0.63, 2.73]			-				
Total events	53		49										
Heterogeneity: Tau ² = 0.2	5; Chi² = 5.	04, df =	2 (P = 0.	08); I² =	= 60%					-+			
Test for overall effect: Z =	0.72 (P = 0).47)					0.1	Favou	irs case	, ,	Favour	s conti	rol

С	Preeclam	npsia	Contr	ol		Odds Ratio	Odds I	Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed	l, 95% Cl
Kamali-Sarvestani 2006	49	122	59	159	52.4%	1.14 [0.70, 1.85]		
Mirahmadian 2008	138	160	82	100	23.7%	1.38 [0.70, 2.72]		
Sowmya 2013	30	73	28	100	23.8%	1.79 [0.95, 3.40]	t	
Total (95% CI)		355		359	100.0%	1.35 [0.97, 1.89]	-	•
Total events	217		169					
Heterogeneity: Chi ² = 1.24	4, df = 2 (P	= 0.54);	l² = 0%			ŀ		
Test for overall effect: Z =	1.76 (P = 0)).08)				0.	1 0.2 0.5 1	2 5 10
		,					Favours case	Favours control

Fig. 4 Forest plot of the risk of preeclampsia among Asian population associated with IL-10 -1082A/G polymorphism under the dominant (GG+GA versus AA) (A), recessive (GG versus GA+AA) (B) and co-dominant (GA versus GG+AA) (C) model.

Α	Preeclampsia		Contr	ol		Odds Ratio	Ode			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	I M-H, F	i xed, 95%	CI	
Daher 2006	67	142	102	179	63.2%	0.67 [0.43, 1.05]	—	F -{		
de Lima 2009	41	88	54	95	36.8%	0.66 [0.37, 1.19]		+		
Total (95% CI)		230		274	100.0%	0.67 [0.47, 0.95]	-			
Total events	108		156							
Heterogeneity: Chi ² = (0.00, df = 1	(P = 0.9	96); l² = 0	%		c.		-		
Test for overall effect:	Z = 2.23 (P	= 0.03)				l	0.1 0.2 0.5	1 2	5	10
	,	,					Favours case	Favou	rs cont	rol





Fig. 5 Forest plot of the risk of preeclampsia among South American population associated with IL-10 -1082A/G polymorphism under the dominant (GG+GA versus AA) (A), recessive (GG versus GA+AA) (B) and co-dominant (GA versus GG+AA) (C) model.

Association between IL-10 -592C/A polymorphism and preeclampsia

A total of 376 cases and 445 controls from 3 case–control studies were included for data synthesis. Under the allelic model, there was no evidence of between-study heterogeneity and therefore the fixed-effect model was adopted to pool the results (C allele *versus* A allele, $P_{heterogeneity}$ = 0.48, P = 0%). The pooled data demonstrated that the C allele was associated to the risk of preeclampsia under the allelic model (C allele *versus* A allele, OR = 1.28, 95% CI = 1.03–1.59, P = 0.03; Fig. 7A).

As significant between-study heterogeneity was absent under the dominant model (CC+CA *versus* AA, $P_{heterogeneity} = 0.13$, $l^2 = 50\%$) and existed under the recessive (CC *versus* CA+AA, $P_{heterogeneity} = 0.01$, $l^2 = 77\%$) and co-dominant (CA *versus* CC+AA, $P_{heterogeneity} < 0.00001$, $l^2 = 91\%$) models, the fixed-effect model was used for the dominant model and the random-effect model was used for the other two genetic models. There was no evidence for any significant association under the dominant (CC+CA *versus* AA, OR = 1.38, 95% CI = 0.86–2.22, P = 0.18; Fig. 7B), recessive (CC *versus* CA+AA, OR = 1.34, 95% CI = 0.73–2.44, P = 0.34; Fig. 7C) or co-dominant

(CA versus CC+AA, OR = 0.88, 95% CI = 0.32–2.43, P = 0.80; Fig. 7D) model.

Publication bias

We used Begg's funnel plot and Egger's linear regression test to evaluate the potential publication bias of the included studies. We did not observe obvious asymmetry of the funnel plot under the allelic model (-1082A/G, P = 0.276; -819C/T, P = 1.000; Fig. 8). Egger's linear regression test did not show any significant statistical evidence of publication bias under the allelic model (-1082A/G, P = 0.307; -819C/T, P = 0.844), either. Therefore, no evident publication bias existed in this meta-analysis.

Discussion

Although the pathogenesis of preeclampsia remains poorly understood, the immunological system is thought to play a pivotal role

J. Cell. Mol. Med. Vol 18, No 12, 2014

Α	Preeclan	npsia	Conti	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
de Lima 2009	114	176	129	190	17.0%	0.87 [0.56, 1.34]	
Haggerty 2005	198	264	852	1190	30.0%	1.19 [0.88, 1.62]	
Kamali-Sarvestani 2006	190	262	220	318	21.2%	1.18 [0.82, 1.69]	-+=
Mirahmadian 2008	244	320	133	200	15.1%	1.62 [1.09, 2.39]	
Sowmya 2014	148	240	108	220	16.8%	1.67 [1.15, 2.42]	
Total (95% CI)		1262		2118	100.0%	1.28 [1.08, 1.50]	◆
Total events	894		1442				
Heterogeneity: Chi ² = 6.8	2, df = 4 (P	= 0.15);	l² = 41%			H	
Test for overall effect: Z =	: 2.94 (P = 0	0.003)				0.1	
							Favours case Favours control
В	Preeclam	npsia	Contr	ol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
de Lima 2009	75	88	89	95	21.7%	0.39 [0.14, 1.07]	
Haggerty 2005	126	132	548	595	15.5%	1.80 [0.75, 4.31]	
Kamali-Sarvestani 2006	117	131	143	159	23.7%	0.94 [0.44, 1.99]	
Mirahmadian 2008	158	160	100	100	3.3%	0.32 [0.01, 6.64] 🔸	
Sowmya 2014	91	120	83	110	35.9%	1.02 [0.56, 1.86]	
Total (95% CI)		631		1059	100.0%	0.96 [0.67, 1.39]	•
Total events	567		963				
Heterogeneity: Chi ² = 5.60), df = 4 (P	= 0.23);	l² = 29%			H	
Toot for averall offects 7 -		1 0 0 1 ^{//}				0.1	0.2 0.5 1 2 5 10

Test for overall effect: Z = 0.21 (P = 0.83)



D Preeclampsia		Conti	ol		Odds Ratio	C	Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95%	CI M-H, I	Random,	, 95 %	CI	
de Lima 2009	36	88	49	95	17.9%	0.65 [0.36, 1.17	′]				
Haggerty 2005	54	132	244	595	23.1%	1.00 [0.68, 1.46	6]				
Kamali-Sarvestani 2006	44	131	66	159	20.5%	0.71 [0.44, 1.15	5] —				
Mirahmadian 2008	72	160	67	100	19.5%	0.40 [0.24, 0.68	3]	-			
Sowmya 2014	34	120	58	110	18.9%	0.35 [0.21, 0.61]	-			
Total (95% CI)		631		1059	100.0%	0.59 [0.40, 0.88					
Total events	240		484								
Heterogeneity: Tau ² = 0.1	4; Chi² = 12	2.84, df :	= 4 (P = 0	0.01); l²	= 69%				+	<u> </u>	-
Test for overall effect: Z =	2.57 (P = 0)).01)	·				0.1 0.2 0.5	о 1	2	5	10
							Favours ca	se Fa	avours	contr	ol

Fig. 6 Forest plot of preeclampsia associated with IL-10 -819C/T polymorphism under the allelic (C allele *versus* T allele) (A), dominant (CC+CT *versus* TT) (B), recessive (CC *versus* CT+TT) (C) and co-dominant (CT *versus* CC+TT) (D) model.

Α	Preeclan	npsia	Conti	ol		Odds Ratio		Odd	s Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fix	ced, 95%	CI	
de Lima 2009	114	176	230	368	36.6%	1.10 [0.76, 1.60]		-	-		
Kamali-Sarvestani 2006	187	256	220	322	36.7%	1.26 [0.87, 1.81]			+		
Mirahmadian 2008	248	320	138	200	26.7%	1.55 [1.04, 2.30]					
Total (95% CI)		752		890	100.0%	1.28 [1.03, 1.59]			•		
Total events	549		588								
Heterogeneity: Chi ² = 1.4	9, df = 2 (P	= 0.48);	l² = 0%							— <u>+</u>	-+
Test for overall effect: Z =	= 2.20 (P = 0	0.03)				(J.1 U.Z	0.5	1 Z	5	10
	,	,					Favou	irs case	Favou	rs cont	rol

В	Preeclampsia		Control			Odds Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fix	ed, 95%	CI	
de Lima 2009	75	88	135	184	42.7%	2.09 [1.07, 4.11]					
Kamali-Sarvestani 2006	114	128	143	161	45.9%	1.02 [0.49, 2.15]					
Mirahmadian 2008	156	160	100	100	11.4%	0.17 [0.01, 3.25]	←			_	
Total (95% CI)		376		445	100.0%	1.38 [0.86, 2.22]					
Total events	345		378								
Heterogeneity: Chi ² = 4.02	2, df = 2 (P	= 0.13);	l² = 50%			0			+ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$ $+$		
Test for overall effect: Z =	1.35 (P = 0)).18)				0	.1 0.2	0.5	1 Z	5	10
		,					Favou	urs case	Favou	rs contr	rol

С	Preeclampsia		Control		Odds Ratio		Ode				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Rai	M-H, Random, 95% Cl			
de Lima 2009	39	88	95	184	32.9%	0.75 [0.45, 1.24]		■			
Kamali-Sarvestani 2006	73	128	77	161	34.2%	1.45 [0.91, 2.31]		+			
Mirahmadian 2008	92	160	38	100	32.9%	2.21 [1.32, 3.68]					
Total (95% CI)		376		445	100.0%	1.34 [0.73, 2.44]					
Total events	204		210								
Heterogeneity: Tau ² = 0.2	22; Chi² = 8.	84, df =	2 (P = 0.0	ŀ		+	<u>+</u>				
Test for overall effect: $7 = 0.95$ (P = 0.34)						0.	1 0.2 0.5	1 Z	5	10	
							Favours case	Favo	urs cont	trol	

D	Preeclampsia		Control			Odds Ratio	Odds				a Ratio			
Study or Subgroup	Events	Total	Events Tot		l Weight	M-H, Random, 95% C	I I	M	M-H, Random, 95% C					
de Lima 2009	36	88	40	184	33.0%	2.49 [1.44, 4.32]								
Kamali-Sarvestani 2006	41	128	66	161	33.7%	0.68 [0.42, 1.10]				+				
Mirahmadian 2008	64	160	62	100	33.4%	0.41 [0.24, 0.68]		_	-					
Total (95% CI)		376		445	100.0%	0.88 [0.32, 2.43]								
Total events	141		168											
Heterogeneity: Tau² = 0.74; Chi² = 23.31, df = 2 (P < 0.00001); l² = 91%										+				
Test for overall effect: $Z = 0.25$ (P = 0.80)							0.1	0.2	0.5	1	2	5	10	
		,						Favou	irs case	•	Favou	rs cont	trol	

Fig. 7 Forest plot of preeclampsia associated with IL-10 -592C/A polymorphism under the allelic (C allele versus A allele) (A), dominant (CC+CA versus AA) (B), recessive (CC versus CA+AA) (C) and co-dominant (CA versus CC+AA) (D) model.

[43]. It is well know that IL-10 can exert a regulatory effect on Th1/ Th2 balance and is a crucial cytokine for pregnancy and development [12, 13]. Given the great importance of IL-10 during pregnancy and the influence of its several polymorphic sites in the regulatory regions on its expression levels, several case-control studies have investigated the association between IL-10 gene polymorphisms and the risk of preeclampsia. In the present study, we investigated the association of three maternal IL-10 polymorphisms with preeclampsia.

Interleukin-10 -1082A/G polymorphism was most extensively investigated and there have been three relevant meta-analyses [31-33]. Consistent with these three previous reports, we found that IL-10 -1082A/G polymorphism was not associated with the risk of preeclampsia after including those new relevant studies published between 2011 and 2013. As there existed significant between-study heterogeneity, we performed the subgroup analysis to explore its source. When stratified by continents, the heterogeneity was greatly



Fig. 8 Begger's funnel plot of the meta-analysis of preeclampsia associated with IL-10 -1082A/G (A) and -819C/T (B) polymorphisms under the allelic model. Each point represents an individual study. Logor: natural logarithm of OR; horizontal line: mean magnitude of the effect; s.e.: standard error.

diminished. Therefore, geographical region was probably a critical factor in between-study heterogeneity and should be better matched between individual studies to further reduce heterogeneity. As Daher et al. have reported that the association between IL-10 -1082A/G polymorphism and preeclampsia could be influenced by ethnicity and was only observed in white women instead of non-white women in their study, we analysed such association among white women using four previously published relevant studies and the meta-analysis result did not support the existence of such association among white women. The lack of such association among white women might also be because of the fact that the included studies were from different geographical regions. Besides, we also observed that IL-10 -1082G allele was correlated with the risk of preeclampsia in the Asia and the South American subgroups and both related meta-analysis results favoured the dominant model. Similar association was not observed in the subgroups of Europe and North America. However, meta-analysis could not be performed with only one relevant study available in the subgroups of Africa and Europe-Asia. Therefore, more studies are still called upon to further evaluate the association between IL-10 -1082A/G polymorphism and preeclampsia among persons from different geographical regions.

Both the -819 C allele and the -592 C allele of IL-10 showed evident association with the risk of preeclampsia in our meta-analysis. As these two alleles were related to higher expression levels of IL-10 [30, 44] and IL-10 has been thought to facilitate successful pregnancy with IL-10 deficiency leading to preeclampsia [12, 24, 25], such correlations were somewhat counterintuitive. However, our findings were consistent with the latest meta-analysis result of the association between IL-10 expression level and preeclampsia, which also indicated the elevated IL-10 levels in women with preeclampsia [45]. Although higher IL-10 expression levels have been proposed to provide protection against preeclampsia, further experiments are badly needed to better elucidate the underlying mechanism [6, 46]. Besides, our meta-analysis results supported the recessive model for IL-10 -819C/T polymorphism. The association between IL-10 -592C/A polymorphism and preeclampsia was not observed in the dominant, recessive or co-dominant model and probably more studies are needed to investigate the way this polymorphism affects the predisposition to preeclampsia. de Groot et al. have reported that IL-10 -2849G/A polymorphism site was also associated with the risk of preeclampsia [42]. However, no other similar studies of such association have been reported. More relevant studies are needed to perform corresponding meta-analyses and confirm such association.

We must admit that there are several limitations in the present study. The total number of the included studies was still relatively small, especially for the meta-analysis of IL-10 -819C/T and -592C/A polymorphisms' association with preeclampsia. The same problem also existed in the subgroup analysis of IL-10 -1082A/G polymorphism's association with preeclampsia stratified by continents. More studies are needed to investigate the role of geographical regions in determining the association between IL-10 -1082A/G polymorphism and preeclampsia. Moreover, other clinical factors like age, gestational weeks and subtypes of preeclampsia (early-onset, late-onset or complicated by other diseases, *etc.*) may result in bias. Further investigation is called upon to determine if these factors affect the results of our meta-analysis.

In conclusion, our meta-analysis results suggested that IL-10 -819C/T and -592C/A polymorphisms were associated with the risk of preeclampsia. Although IL-10 -1082A/G polymorphism had no obvious association with preeclampsia in the overall meta-analysis, it showed association with preeclampsia among Asian and South American populations. However, further studies are essential to validate the association between IL-10 polymorphisms and the risk of preeclampsia.

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Conflicts of interest

The authors confirm that there are no conflicts of interest.

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