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Association of IL-10-1082G>A, -819C>T and -592C>A Polymorphisms with susceptibility to asthma in children: a Systematic Review and Meta-Analysis

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KEY WORDS

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Summary

Studies evaluating the association of Interleukin 10 (IL-10) polymorphisms with risk of pediatric asthma found inconsistent data. Here, we performed a meta-analysis to get a precise estimation of the associations. Relevant studies identified in the PubMed, Scopus, CNKI databases were used to perform a meta-analysis. A total of 23 case-control studies including nine studies with 1298 cases and 1079 controls on IL-10-1082G>A, four studies with 622 cases and 603 controls on -819C>T and ten studies with 1480 case and 1462 controls on -592C>A were selected. Overall, there was no significant association between IL-10 polymorphisms with pediatric asthma risk in global population. When stratified by ethnicity, there was a significant association of IL-10-1082G>A with pediatric asthma in Asians and Chinese. This meta-analysis result revealed that IL-10-1082G>A, -819C>T and -592C>A polymorphisms were not associated with pediatric asthma risk in the global population.

IMPACT STATEMENT

The IL-10-1082G>A, -819C>T and -592C>A polymorphisms are not associated with pediatric asthma risk.

Introduction

Pediatric asthma is a highly heterogeneous disorder with multiple clinical phenotypes and can have very serious consequences for children's health, their families, and the health care system (1-3). It is one of the most common chronic diseases among children and a leading cause of medical expenses (4-9). It is estimated that more than 13% of children had been diagnosed with asthma in Canada and the average direct cost from asthma exacerbations in 2013 was estimated to be around \$ 883.48 per patient per year (10-12). Interleukin 10 (IL-10) is a candi-

date gene in the mechanism of asthma since it has been shown to regulate both cellular and humoral immunity (13). IL-10 regulates IgE production and reduces IgE switching indirectly as a control point for modulation the effects of inflammatory cytokines (14).

IL-10 is important pleiotropic immunoregulatory cytokine with an anti-inflammatory properties that plays a central role in limiting host immune response to pathogens, thereby preventing damage to the host and maintaining normal tissue homeostasis (15). Human IL-10 has a broad-spectrum anti-inflammatory activity which is expressed by activated monocytes/

macrophages, natural killer (NK) cells, dendritic cells (DCs), mast cells, B cells, and regulatory T cell subsets (16). Moreover, IL-10 is known to have macrophage-deactivating properties and undermines the Th1-driven pro-inflammatory response by down-regulating the production of several cytokines (17, 18). Human IL-10 gene maps to chromosome 1q31-32, contains four introns and five exons, and spans about 4.7 kb (19).

The IL-10 promoter is highly polymorphic (17-20), and three single nucleotide polymorphisms (SNPs) at positions -1082G>A, -819C>T and -592C>A polymorphisms within the promoter region have been shown to correlate with IL-10 production (21-25). To date, several genetic epidemiology studies have assessed the association between IL-10-1082G>A, -819C>T and -592C>A polymorphisms and pediatric asthma in different populations (26, 27). But the results from these studies were often inconsistent and inconclusive. The reason for this inconsistency may derive from a number of issues, including sample size, lack of power, genotyping methods, false-positive errors, and minor impacts of IL-10 gene polymorphisms on risk of pediatric asthma. Thus, we conducted a systematic review and meta-analysis to combine and analyze the available studies in order to get a precise estimation of the association of IL-10-1082G>A, -819C>T and -592C>A polymorphisms with susceptibility to pediatric asthma.

Materials and methods

Literature search

The ethical approval was not necessary since the current meta-analysis was not a clinical trial study and was based on previously published studies. A comprehensive literature search was performed on major electronic literature databases, including the PubMed, Web of Sciences, Scopus, Google Scholar, EMBASE, SciELO, Islamic World Science Citation Center (ISC), Scientific Information Database (SID), Wanfang, and VIP, Wanfang and China National Knowledge Infrastructure (CNKI) databases to find all studies evaluated the association between IL-10-1082G>A, -819C>T and -592C>A polymorphisms and risk of pediatric asthma published up to May 15th, 2020. The following keywords and terms were used: ("Asthma" OR "Asthmatic" OR "Pediatric" OR "Childhood" OR "Children") AND ("Interleukin 10" OR "IL-10" OR "Cytokine Synthesis Inhibitory Factor" OR "CSIF") AND ("1082A>G" OR "rs1800896" OR "g.3943A>G" OR "c.-1117A>G") AND ("-819C>T" OR "rs1800871" OR "g.4206T>C" OR "c.-854T>C") AND ("-592C>A" OR "rs1800872" OR "g.4433A>C" OR "c.-627A>C") AND ("Gene" OR "Polymorphism" OR "Single-Nucleotide Polymorphism" OR "SNPs" OR "Mutation" OR "Mutant" OR "Variant" OR "Variation" OR "Allele" OR "Genotype"). The search was limited to human studies without language restriction. Moreover, no restrictions were placed on the year of publication, and sample size. Moreover, we have also

manually reviewed the reference lists of all retrieved articles, reviews and meta-analyses to find missed articles.

Inclusion and exclusion criteria

To select eligible studies in the current meta-analysis, the following criteria for inclusion were defined:

- full-text publications with case-control or cohort design;
- studies evaluated the association of IL-10-1082G>A, -819C>T and -592C>A polymorphisms with risk of pediatric asthma;
- provide sufficient data about IL-10 genotypes distributions to estimate the odds ratio (OR) with 95% confidence intervals (95% CI).

The exclusion criteria were as follows:

- case only studies (lack of control population);
- lack of eligible genotype frequencies;
- family based studies and linkage studies;
- studies on other polymorphisms of IL-10 gene;
- case reports, posters, abstracts, meeting reports, lectures, editorials, correspondence letters, reviews, previous meta-analyses;
- overlapped data or duplicated publications.

If there were multiple published articles from the same authors, the most recent study or study with larger sample size was included in this meta-analysis. Moreover, different case-control groups or cohorts in one publication were considered as independent studies.

Data extraction

Data of eligible studies were collected by two authors independently and carefully according to the inclusion and exclusion criteria and the third author adjudicated the conflicting data until consensus was reached. The following characteristics were collected from each eligible study: the name of first author, year of publication, country of origin, ethnicity (categorized as Caucasians, Asians, African, or Mixed), genotyping methods, sample size of cases and controls, allele and genotype frequency of IL-10-1082G>A, -819C>T and -592C>A polymorphisms in cases and healthy controls, minor allele frequencies (MAFs) and Hardy-Weinberg Equilibrium (HWE) in healthy controls.

Statistical analysis

The strength of the association between the IL-10-1082G>A, -819C>T and -592C>A polymorphisms and risk of pediatric asthma was measured by odds ratio (OR) with its 95% confidence interval (CI). The significance of pooled ORs was tested by Z-test, in which $P < 0.05$ was considered significant. The association of IL-10-1082G>A, -819C>T and -592C>A polymorphism was estimated under five genetic models, *i.e.*, allele (B *vs* A), homozygote (BB *vs* AA), heterozygote (BA *vs* AA), dominant (BB + BA *vs* AA), and the recessive (BB *vs* BA + AA). The between-heterogeneity was examined using chi-square. Moreover, I^2

test to quantify the heterogeneity, which ranges from 0 to 100% and represents the proportion of between-study variability attributable to heterogeneity rather than chance ($I^2 < 25\%$, no heterogeneity; I^2 25-50%, moderate heterogeneity; $I^2 > 50\%$, large or extreme heterogeneity). If the P-value for heterogeneity tests was > 0.01 or $I^2 < 50\%$, a fixed effect model (Mantel-Haenszel method) was used to calculate the pooled OR. Otherwise, a random effect model (DerSimonian-Laird method) was employed to analyze data. The goodness-of-fit Chi-square test for Hardy-Weinberg equilibrium (HWE) was performed in control group and a P-value < 0.05 was considered as significant disequilibrium. Sensitivity analysis was performed by removing one study at a time to the stability of the pooled data and the effect of each single study on the conclusions. Moreover, sensitivity analysis was performed by excluding HWE-violating studies. The publication bias among the selected studies was tested by Begg's test, in which an asymmetric plot suggests a possible publication bias. Moreover, Egger's linear regression test was performed to determine the significance of the asymmetry, in which $P < 0.05$ indicated that publication bias was significant. Additionally, if publication bias was seen, the "trim and fill" method which conservatively imputes hypothetical negative unpublished studies to mirror the positive studies that cause funnel plot asymmetry was used to further analyses the possible effect of publication bias. All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) Software version 2.0 (Biostat, Englewood, USA). All tests were two-sided, and the $P < 0.05$ was considered statistically significant.

Results

Characteristics of eligible studies

The study screening process was shown in **figure 1**. Initially, a total number of 259 studies were identified from the online databases and by manual search. In accordance with the eligibility criteria, 143 records were left after removing repeated studies and 82 studies were subsequently excluded for title and abstract review. Then, 48 studies were excluded because did not relevant to the IL-10 polymorphisms association with risk of pediatric asthma. In the end, the whole of the rest of the articles were checked based on the inclusion and exclusion criteria. Finally, a total of 23 case-control studies with 3400 pediatrics with asthma and 3144 healthy controls were included in the meta-analysis (28, 29, 30-37, 38-42.). Of these studies, nine studies with 1298 cases and 1079 controls were on -1082G>A, four studies with 622 cases and 603 controls on -819C>T and ten studies with 1480 case and 1462 controls were on -592C>A polymorphism. The characteristics of the main studies are shown in **table I**. The studies were published between 2002 and 2017 and sample sizes varied from 30 to 333 in cases with asthma. Of these studies, 18 were conducted on Asians, three studies on African and two studies on Caucasian populations. In the

selected studies, seven genotyping methods including PCR-SSP, ARMS-PCR, PCR-RFLP, MALDI-TOF-MS, MassARRAY, RealTime-PCR, and TaqMan were used to genotyping the IL-10 polymorphisms. The HWE was performed on all of the included studies, and the genotype distributions in the controls for all studies were consistent with the HWE, except for three studies for -1082G>A and one study for -592C>A (**table II**).

Quantitative data synthesis

IL-10-1082G>A

The summary results for the association between IL-10-1082G>A polymorphism and risk of pediatric asthma are shown in **table II**. Overall, pooled data revealed that IL-10-1082G>A polymorphism was not significantly associated with an increased risk of pediatric asthma in the global population (**figure 2 A**). Moreover, we performed subgroup analysis based on ethnicity and country of origin. The stratified analysis showed that IL-10-1082G>A polymorphism was associated with an increased risk of pediatric asthma in Asian (GG *vs* AA: OR = 0.784, 95% CI 0.128-0.554, $p \leq 0.001$, **figure 2 B**; GG *vs* GA + AA: OR = 0.409, 95% CI 0.229-0.729, $p = 0.002$, **figure 2 C**) and Chinese (GA *vs* AA: OR = 0.098, 95% CI 0.011-0.898, $p = 0.040$). There was no significant association in the African populations (**table II**).

IL-10-819C>T

The summary results for the association between IL-10-819C>T polymorphism and risk of pediatric asthma are shown in **table II**. Pooled data showed that IL-10-819C>T polymorphism was not significantly associated with an increased risk of pediatric asthma in the global population (**figure 3 A**).

IL-10-592C>A

The summary results for the association between IL-10-592C>A polymorphism and risk of pediatric asthma are shown in **table III**. Pooled data showed that IL-10-592C>A polymorphism was not significantly associated with an increased risk of pediatric asthma in the global population (**figure 3 B**). Moreover, we performed subgroup analysis based on ethnicity and country of origin. The subgroup analysis revealed that the IL-10-592C>A polymorphism was not associated with increased to susceptibility of pediatric asthma in Asians, Caucasians and Chinese (**table III**).

Between-study heterogeneity

There was considerable between-study heterogeneity for three IL-10-1082G>A, -819C>T and -592C>A polymorphisms in this meta-analysis. Thus, we have conducted subgroup analyses by ethnicity and country of origin to describe the potential source of heterogeneity. As shown in **tables II** and **III**, when stratified analyses were conducted, the heterogeneity did not disappear considerably, which indicating that ethnicity and country of origin were not the major sources of heterogeneity in the current meta-analysis.

Table 1 - Main characteristics of studies included in this meta-analysis.

First Author/ year	Country (Ethnicity)	Genotyping Method	Atopic Status	Case/Control	Cases				Controls				MAFs	HWE									
					Genotype		Allele		Genotype		Allele												
					GG	GA	AA	G	A	GG	GA	AA			G	A							
IL-10 -1082G>A	Li 2007	China (Asian)	PCR-SSP	NA	30/26	20	8	2	48	12	16	7	3	39	13	0.250	0.150						
	Movahedi 2008	Iran (Asian)	PCR-SSP	NA	59/140	0	59	0	59	59	53	75	12	181	99	0.354	0.041						
	Zedan 2008	Egypt (African)	PCR-SSP	Atopic	69/98	11	39	19	61	77	8	85	5	101	95	0.485	≤0.001						
	Hussein 2011	Egypt (African)	ARMS-PCR	Mixed	220/110	82	90	48	254	186	23	54	33	100	120	0.545	0.916						
	Kim 2011	Korea (Asian)	PCR-RFLP	Mixed	333/248	291	40	2	622	44	215	30	3	460	36	0.073	0.110						
	Tan 2013	China (Asian)	MALDI-TOF-MS	NA	157/198	134	23	0	291	23	182	16	0	380	16	0.040	0.553						
	Hussein 2014	KSA (Asian)	ARMS-PCR	Atopic	200/50	75	86	39	236	164	8	25	17	41	59	0.590	0.812						
	Xu 2014	China (Asian)	MassARRAY	NA	200/189	161	39	0	361	39	73	108	8	254	124	0.328	≤ 0.001						
	Shahin 2017	Egypt (African)	qRT-PCR	NA	30/20	4	9	17	17	43	18	2	0	38	2	0.050	0.813						
	IL-10 -819C>T														C	CT	TT	C	T	C	T		
Li 2007	China (Asian)	PCR-SSP	NA	30/26	7	17	6	31	29	10	9	7	29	23	0.442	0.128							
Movahedi 2008	Iran (Asian)	PCR-SSP	NA	59/140	2	57	0	61	57	71	57	12	199	81	0.289	0.907							
Kim 2011	Korea (Asian)	PCR-RFLP	Mixed	333/248	155	138	40	448	218	113	108	27	334	162	0.327	0.875							
Xu 2014	China (Asian)	MassARRAY	NA	200/189	93	87	20	273	127	94	77	18	265	113	0.299	0.700							
IL-10 -592C>A														C	CA	AA	C	A	CC	CA	AA	C	A
Li 2002	China (Asian)	PCR-RFLP	NA	50/36	20	24	6	64	36	16	17	3	49	23	0.319	0.605							
Schubert 2006	Germany (Caucasian)	PCR-RFLP	NA	231/273	131	86	14	348	114	145	109	19	399	147	0.269	0.808							
Li 2007	China (Asian)	PCR-SSP	NA	30/26	7	17	6	31	29	10	9	7	29	23	0.442	0.128							
Movahedi 2008	Iran (Asian)	PCR-SSP	NA	59/140	1	58	0	60	58	71	57	12	199	81	0.289	0.907							
Undarmaa 2010	Japan (Asian)	TaqMan	Atopic	325/336	154	141	30	449	201	146	151	39	443	229	0.341	0.996							
Kim 2011	Korea (Asian)	PCR-RFLP	Mixed	333/248	146	143	44	435	231	111	106	31	328	168	0.339	0.470							
Wei 2011	China (Asian)	PCR-RFLP	NA	186/198	75	89	22	239	133	83	99	16	265	131	0.331	0.068							
Xie 2012	China (Asian)	PCR-RFLP	NA	110/63	23	78	9	124	96	23	38	2	84	42	0.333	0.004							
Ji 2013	China (Asian)	PCR-RFLP	NA	92/92	52	32	8	136	48	32	44	16	108	76	0.413	0.895							
Smolnikova 2013	Russia (Caucasian)	PCR-RFLP	Atopic	64/50	40	19	5	99	29	37	13	0	87	13	0.130	0.290							

IL-10: interleukin 10; KSA: kingdom of Saudi Arabia; PCR: polymerase chain reaction; SSP: sequence-specific primers; ARMS: amplification-refractory mutation system; RFLP: restriction fragment length polymorphism; qRT-PCR: RealTime-PCR; NA: not applicable; MAFs: minor allele frequencies; HWE: hardy-Weinberg equilibrium.

Figure 1 - Flowchart of literature search and selection process. **Sensitivity analysis**

Sensitivity analysis was conducted to check the influence of individual studies on the stability of the pooled data by excluding one study at a time. The exclusion of any single study did not significantly affect the pooled ORs or 95% CIs for three IL-10-1082G>A, -819C>T and -592C>A polymorphisms. Then, sensitivity analysis was performed by excluding those four HWE-violating studies for IL-10-1082G>A and -592C>A polymorphisms.

The results showed that none of the pooled data for IL-10-1082G>A and -592C>A polymorphisms under all five genetic models were significantly changed by excluding the HWE-violating studies. Hence, results of the sensitivity analysis indicated that our pooled data for IL-10-1082G>A, -819C>T and -592C>A polymorphisms were statistically stable and reliable.

Figure 2 - Forest plot for association of IL-10-1082G>A polymorphism with risk of pediatric asthma. (A) global population (allele model: G vs A); (B) Asians (homozygote model: GG vs AA); (C) Asians (recessive model: GG vs GA + AA).

Table II - Summary risk estimates for association of IL-10-1082G>A and -819C>T polymorphisms with risk of pediatric asthma.

Subgroup	Genetic Model	Type of Model	Heterogeneity			Odds Ratio			Publication Bias	
			I ² (%)	P _H	OR	95% CI	Z _{test}	P _{OR}	P _{Beggs}	P _{Eggers}
-1082G>A										
Overall	G <i>vs</i> A	Random	92.12	≤ 0.001	1.076	0.596-1.944	0.243	0.808	0.251	0.107
	GG <i>vs</i> AA	Random	77.49	≤ 0.001	0.699	0.224-2.180	- 0.617	0.537	0.548	0.448
	GA <i>vs</i> AA	Random	97.94	≤ 0.001	0.763	0.129-4.502	- 0.299	0.765	0.602	0.357
	GG + GA <i>vs</i> AA	Random	90.99	≤ 0.001	1.054	0.451-2.465	0.122	0.903	0.117	0.064
	GG <i>vs</i> GA + AA	Random	79.39	≤ 0.001	0.845	0.308-2.319	- 0.327	0.744	1.000	0.848
Ethnicity										
Asians	G <i>vs</i> A	Random	92.18	≤ 0.001	0.784	0.376-1.634	- 0.650	0.516	0.707	0.473
	GG <i>vs</i> AA	Fixed	13.31	0.326	0.267	0.128-0.554	- 3.547	≤ 0.001	1.000	0.748
	GA <i>vs</i> AA	Random	97.43	≤ 0.001	0.356	0.054-2.355	- 1.071	0.284	0.707	0.433
	GG + GA <i>vs</i> AA	Random	91.94	≤ 0.001	0.873	0.302-2.529	- 0.250	0.803	0.452	0.276
	GG <i>vs</i> GA + AA	Fixed	0.00	0.494	0.409	0.229-0.729	- 3.032	0.002	0.086	0.186
Africans	G <i>vs</i> A	Random	94.23	≤ 0.001	2.464	0.666-0.122	1.351	0.177	0.296	0.149
	GG <i>vs</i> AA	Random	89.42	≤ 0.001	3.573	0.296-43.147	1.002	0.316	0.296	0.028
	GA <i>vs</i> AA	Random	93.43	≤ 0.001	3.257	0.324-32.706	1.003	0.316	1.000	0.967
	GG + GA <i>vs</i> AA	Random	92.39	≤ 0.001	1.875	0.236-14.904	0.594	0.553	0.296	0.344
	GG <i>vs</i> GA + AA	Random	91.30	≤ 0.001	4.509	0.478-42.497	1.316	0.188	1.000	0.295
Chinese	G <i>vs</i> A	Random	93.70	≤ 0.001	0.665	0.158-2.797	- 0.557	0.578	1.000	0.431
	GG <i>vs</i> AA	Random	65.55	0.088	0.213	0.044-1.042	- 1.910	0.055	NA	NA
	GA <i>vs</i> AA	Random	96.54	≤ 0.001	0.098	0.011-0.898	- 2.055	0.040	1.000	0.744
	GG + GA <i>vs</i> AA	Random	94.96	≤ 0.001	0.608	0.101-3.647	- 0.544	0.586	1.000	0.532
	GG <i>vs</i> GA + AA	Fixed	44.02	0.181	0.272	0.057-1.303	- 1.629	0.103	NA	NA
HWE*										
	G <i>vs</i> A	Random	88.04	≤ 0.001	1.216	0.623-2.374	0.574	0.566	0.132	0.057
	GG <i>vs</i> AA	Random	75.00	0.003	0.718	0.217-2.380	- 0.542	0.588	0.086	0.219
	GA <i>vs</i> AA	Random	98.04	≤ 0.001	0.220	0.024-2.047	- 1.331	0.183	0.707	0.698
	GG + GA <i>vs</i> AA	Random	87.01	≤ 0.001	1.171	0.500-2.742	0.364	0.716	0.452	0.276
	GG <i>vs</i> GA + AA	Random	59.32	0.043	0.736	0.330-1.643	- 0.748	0.454	0.462	0.357
-819C>T										
Overall	T <i>vs</i> C	Random	71.51	0.015	1.284	0.895-1.841	1.358	0.174	0.308	0.463
	TT <i>vs</i> CC	Fixed	0.00	0.999	1.107	0.735-1.665	0.486	0.627	0.734	0.318
	TC <i>vs</i> CC	Random	87.77	≤ 0.001	2.369	0.943-5.948	1.836	0.066	0.089	0.103
	TT + TC <i>vs</i> CC	Random	85.91	≤ 0.001	2.071	0.914-4.694	1.744	0.081	0.089	0.121
	TT <i>vs</i> TC + CC	Fixed	12.35	0.331	0.997	0.678-1.467	- 0.015	0.988	0.089	0.024

NA: not applicable; *by excluding HWE violating studies.

Publication bias

The Begg's and Egger's linear regression tests were applied to test the potential publication bias for association of IL-10-1082G>A, -819C>T and -592C>A polymorphisms with risk

of pediatric asthma in the global population. **Table II** lists the publication bias assessment method with its respective P-value for three IL-10 polymorphisms. The shapes of the funnel plots did not show any evidence of publication bias in the global pop-

Figure 3 - Forest plot for association of IL-10-819C>T and -592C>A polymorphism with risk of pediatric asthma in the global population. (A) -819C>T (homozygote model: TT vs CC); and (B) -592C>A (dominant model: AA + AC vs CC).

ulation for IL-10-1082G>A polymorphism. However, there was evidence of publication bias under the recessive model (AC vs CC: $P_{\text{Beggs}} = 0.089$; $P_{\text{Eggers}} = 0.024$) for IL-10-819C>T and under the heterozygote model (AC vs CC: $P_{\text{Beggs}} = 0.031$; $P_{\text{Eggers}} = 0.044$) for IL-10-592C>A polymorphisms. Thus, we applied the Duval and Tweedie nonparametric “trim and fill” method to adjust the pooled risk for association of IL-10-819C>T and -592C>A polymorphisms and pediatric asthma under the recessive model and heterozygote model, respectively (figure 4). However, the “trim and fill” method did not significantly change results, indicating that our pooled data were statistically robust and reliable.

Discussion

The results of the current meta-analysis may improve our understanding of the role of IL-10-1082G>A, -819C>T and -592C>A polymorphisms in susceptibility to pediatric asthma. Our pooled data revealed that three -1082G>A, -819C>T and -592C>A polymorphisms at promoter region of IL-10 gene were not significantly associated with risk of pediatric asthma in the global population. However, the stratified analyses by ethnicity and country of origin found a significant association between IL-10-1082G>A polymorphism and an increased risk of pediatric asthma in Asians and Chinese children.

Table III - Summary risk estimates for association of IL-10-592C>A polymorphisms with risk of pediatric asthma.

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio			Publication Bias		
			I ² (%)	P _H	OR	95% CI	Z _{test}	P _{OR}	P _{Beggs}	P _{Eggers}
Overall	A vs C	Random	73.45	≤ 0.001	1.117	0.882-1.414	0.917	0.359	0.283	0.255
	AA vs CC	Fixed	40.32	0.089	0.963	0.735-1.261	- 0.277	0.782	0.283	0.192
	AC vs CC	Random	71.69	≤ 0.001	1.155	0.819-1.629	0.823	0.410	0.031	0.044
	AA + AC vs CC	Random	74.02	≤ 0.001	1.164	0.827-1.638	0.869	0.385	0.031	0.051
	AA vs AC + CC	Fixed	30.01	0.169	0.955	0.678-1.346	- 0.263	0.793	0.591	0.823
Ethnicity										
Asians	A vs C	Random	76.44	≤ 0.001	1.109	0.841-1.462	0.733	0.464	0.536	0.490
	AA vs CC	Fixed	43.50	0.088	0.966	0.721-1.294	- 0.235	0.814	0.536	0.445
	AC vs CC	Random	77.24	≤ 0.001	1.246	0.799-1.942	0.971	0.332	0.063	0.090
	AA + AC vs CC	Random	78.34	≤ 0.001	1.216	0.788-1.876	0.885	0.376	0.035	0.120
	AA vs AC + CC	Random	78.34	≤ 0.001	1.216	0.788-1.876	0.885	0.376	0.035	0.120
Caucasians	A vs C	Random	75.37	0.044	1.230	0.574-2.636	0.532	0.595	NA	NA
	AA vs CC	Random	62.79	0.101	0.945	0.466-1.919	- 0.156	0.876	NA	NA
	AC vs CC	Fixed	0.00	0.348	0.938	0.669-1.314	- 0.374	0.709	NA	NA
	AA + AC vs CC	Random	56.16	0.131	0.964	0.698-1.331	- 0.224	0.823	NA	NA
	AA vs AC + CC	Random	58.55	0.120	0.986	0.493-1.973	- 0.038	0.969	NA	NA
Chinese	A vs C	Random	71.38	0.007	1.028	0.688-1.538	0.136	0.892	0.806	0.968
	AA vs CC	Random	62.62	0.030	1.191	0.502-2.824	0.396	0.692	0.462	0.663
	AC vs CC	Random	68.57	0.013	1.121	0.634-1.983	0.394	0.694	0.462	0.520
	AA + AC vs CC	Random	73.74	0.004	1.117	0.616-2.025	0.364	0.716	0.462	0.622
	AA vs AC + CC	Fixed	39.60	0.157	1.062	0.677-1.667	0.263	0.792	0.806	0.908
HWE*										
	A vs C	Random	73.96	≤ 0.001	1.078	0.842-1.380	0.595	0.552	0.251	0.358
	AA vs CC	Random	30.90	0.171	0.922	0.701-1.213	- 0.582	0.561	0.465	0.374
	AC vs CC	Random	70.78	0.001	1.076	0.757-1.528	0.409	0.683	0.047	0.079
	AA + AC vs CC	Random	72.76	≤ 0.001	1.077	0.762-1.521	0.419	0.675	0.076	0.093
	AA vs AC + CC	Fixed	27.78	0.197	0.923	0.712-1.197	- 0.607	0.544	0.754	0.872

NA: not applicable; *by excluding HWE violating studies.

In 2016, Huang *et al.*, in meta-analysis of 16 case-control studies including 2494 cases and 2160 controls evaluated the association of IL-10 promoter polymorphisms with the risk of pediatric asthma. Their pooled data showed that IL-10 promoter polymorphisms were not significantly associated with a risk of pediatric asthma in any of the genetic models in the global population. Moreover, their stratified analyses based on ethnicity revealed that IL -1082G>A polymorphism was associated with the risk of pediatric asthma in Asians under the dominant model (OR = 3.607, 95% CI = 1.141-11.407, P = 0.029) and

non-Asian populations under the recessive model (OR = 2.429, 95% CI = 1.620-3.642, P < 0.001) (26). However, our subgroup analysis showed that IL -1082G>A polymorphism was not significantly associated with risk of pediatric asthma in non-Asian populations (**table II**). In 2014, Zheng *et al.*, in a meta-analysis based on A total of 4,716 asthmatic patients and 5,093 controls revealed that -1082G>A and -592C>A polymorphisms and their haplotypes at IL-10 gene were correlated with asthma risk in the overall population, but not -819C>T polymorphism. However, their subgroup analysis based on eleven

Figure 4 - The funnel plots of publication bias for association of the IL-10-819C>T polymorphism with risk of pediatric asthma in the global population under the homozygote model (AC vs CC), before (hollow circles) and after (solid circles) "Trim-and-Fill" method.

studies showed that IL-10-1082G>A and -592C>A polymorphisms were not associated with risk of asthma in children (27). Between-study heterogeneity is to be expected in a meta-analysis, which may have affected result when interpreting of the pooled data (43-45). It is described that several factors such as study design, ethnicity, sample size, source of controls, genotyping method, and HWE may be among the major causes of the heterogeneity (45, 46). In this meta-analysis, there was a significant heterogeneity under most genetic models for three -1082G>A, -819C>T and -592C>A polymorphisms at promoter region of IL-10 gene. When subgroup analyses by ethnicity and country of origin were performed the heterogeneity still existed with a slight reduction. Thus, ethnicity and country of origin could not be considered as the source of the heterogeneity, suggesting the existence of other unknown factors influencing the heterogeneity among included studies.

Similar to other meta-analysis, there were several limitations in the current study. First, no restrictions were placed on the language. However, we have found only studies published in English or Chinese language, which might introduce potential selection bias. Second, the majority of the included studies in the current meta-analysis were conducted in Asian and Africans populations, which may introduce ethnicity bias, and further studies should conduct on Caucasian and mixed populations. Third, in view of the limited

number of studies for IL-10-819C>T polymorphism, the power used to detect the association of this polymorphism with risk of pediatric asthma may not be strong enough. Thus, our pooled data revealed that IL-10-819C>T polymorphism might be associated with an increased risk of pediatric asthma in the global population and by ethnicity. Fourth, there was significant between-study heterogeneity under most genetic models for IL-10-1082G>A, -819C>T and -592C>A polymorphisms in the global population, which could be owing to the fact that the analysis included few studies in the analysis or due to insufficient data that limited further subgroup analysis. Therefore, more relevant case-control studies are required to be performed and then included in the meta-analysis so as to get a more reliable and scientific data. Finally, this meta-analysis exclusively concentrated on the association of IL-10-1082G>A, -819C>T and -592C>A polymorphisms with risk of pediatric asthma without considering gene-gene or gene-environment interactions. Hence, in order to comprehensively demonstrate the etiology of pediatric asthma, it is extremely required to study the combined interaction of the related genes.

Conclusions

Our pooled data revealed that the IL-10-1082G>A, -819C>T and -592C>A polymorphisms were not significantly associated with risk of pediatric asthma in the global population. Howev-

er, the stratified analyses by ethnicity and country of origin revealed a significant association between IL-10-1082G>A polymorphism and risk of pediatric asthma in Asians and Chinese children. Due to limitations mentioned above in the meta-analysis, it is critical that larger and well-designed studies in different ethnicities are needed to confirm our data.

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Conflict of interests

The authors declare that they have no conflict of interests.

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