

Interleukin 4 –590C/T (rs2243250) Polymorphism Is Associated With Increased Risk of Atopic Dermatitis: Meta-Analysis of Case-Control Studies

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Background: Interleukin 4 (IL-4) –590C/T polymorphism has been reported to influence atopic dermatitis (AD) susceptibility, but the results are controversial.

Objective: This meta-analysis was performed to study the association between IL-4 –590C/T polymorphism and AD susceptibility.

Methods: The PubMed, Embase, and China National Knowledge Infrastructure databases were searched. Odds ratios (ORs) with 95% confidence intervals (CIs) were performed to estimate the strength of the association.

Results: Ten studies comprising 923 cases and 1215 controls were included. The overall population revealed significant associations between IL-4 –590C/T polymorphism and AD susceptibility under the allele (OR, 1.19; 95% CI, 1.03–1.38; $I^2 = 0.0\%$), recessive (OR, 1.27; 95% CI, 1.002–1.61; $I^2 = 0.0\%$), and dominant (OR, 1.33; 95% CI, 1.003–1.76; $I^2 = 0.0\%$) models; similar results were found under the allele (OR, 1.19; 95% CI, 1.01–1.39; $I^2 = 0.0\%$) and recessive (OR, 1.27; 95% CI, 1.001–1.62; $I^2 = 0.0\%$) models after excluding not-in-Hardy-Weinberg equilibrium studies. However, subgroup analyses by ethnicity showed no significant association in Asians or whites. Subgroup analyses by age indicated a significant association in children under the allele (OR, 1.30; 95% CI, 1.06–1.60; $I^2 = 0.0\%$) and dominant (OR, 1.42; 95% CI, 1.02–1.97; $I^2 = 0.0\%$) models, children in articles with Hardy-Weinberg equilibrium under the allele model (OR, 1.33; 95% CI, 1.05–1.69; $I^2 = 0.0\%$), and Asian children under the allele model (OR, 1.41; 95% CI, 1.02–1.95; $I^2 = 0.0\%$) but not in white children.

Conclusions: The IL-4 –590C/T polymorphism may contribute to AD susceptibility in the overall population and children, especially for Asian children, but large well-designed studies are warranted to confirm this conclusion.

Atopic dermatitis (AD) is a chronic multifactorial inflammatory skin disease with a prevalence of up to 30% in children and 10% in adults worldwide¹ characterized by relapsing, pruritic,

and eczematous lesions. Although the pathogenesis underlying AD is complex and not completely understood, it is widely thought that genetic, immunologic, and environmental factors interacting to cause skin barrier disturbance and immunologic dysregulation may mainly contribute to the disease development.^{2,3} Recent studies showed a strong genetic association with AD, for example, skin barrier function, immune deviation versus a T helper 2 (Th2) dominance, and increased immunoglobulin (Ig) E production are in large part influenced by genetic alterations.⁴ A positive family history is a very strong risk factor for AD.⁵ The concordance rate of 72% to 86% in monozygotic twins is significantly higher compared with 21% to 23% in dizygotic twins, suggesting that genetic factors may play a key role in the predisposition to AD.^{6,7} Genome-wide association and single-nucleotide polymorphism studies have identified many susceptibility loci and potential gene polymorphisms related to barrier and immune functions that were found to be associated with AD, such as filaggrin, interleukin 4 (IL-4), IL-4R α , IL-13, and signal transducer and activator of transcription 6 (STAT-6).^{4,8}

Interleukin 4 is central to the development of the Th2 phenotypes involved in humoral- and cell-mediated autoimmune/

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inflammatory processes, which is produced primarily by activated T cells, basophils, and mast cells.⁹ Clinical studies demonstrated that the levels of IL-4 are significantly increased both in serum and skin lesions of patients with AD.¹⁰ Interleukin 4 is overexpressed in skin of transgenic mice with AD-like lesions,⁸ and IL-4 knockout mice showed no eosinophil mobilization to the inflammation site.¹¹ Interleukin 4 is a glycoprotein encoded by the IL-4 gene, which is located in chromosomal 5q31-33 and approximately 9.01 kb in length.¹² It has been reported that genetic mutations in the promoter region of the IL-4 gene may alter its transcriptional activity and affect an individual's susceptibility to various diseases.^{13,14} Several promoter polymorphisms of IL-4 have been identified, of which the IL-4 –590C/T polymorphism (rs2243250) is the most widely studied.¹⁴ A number of case-control studies have assessed the association between IL-4 –590C/T polymorphism and the risk of AD,^{11,13,15–21} but the results are inconclusive and inconsistent because of the small sample sizes and low statistical power in these studies. Thus, we performed a systematic review and meta-analysis of all available data to provide a precise estimation of the relationship between IL-4 –590C/T polymorphism and AD.

METHODS

Literature Search Strategy

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines.²² Studies examining the association between IL-4 –590C/T polymorphism and AD were systematically searched using the following key words: (*interleukin-4* or *interleukin 4* or *IL-4*

or *IL4* or rs2243250) and (*polymorphism[s]* or *SNP[s]* or *variation* or *genotype[s]*) and (*atopic dermatitis* or *atopic eczema* or *eczema*) in the PubMed, Embase, and China National Knowledge Infrastructure up to August 8, 2016, by 2 independent investigators. Other potentially relevant studies were also obtained by reviewing the references on this topic listed in retrieved original and review articles. No language or publication date restriction was applied in this meta-analysis.

Selection Criteria

Eligible studies were selected using the following inclusion criteria: (1) they evaluated the association between IL-4 –590C/T polymorphism and AD; (2) they were case-control studies; and (3) they provided sufficient data concerning genotypes or/and allele frequencies in both cases and controls to estimate odds ratios (ORs) with 95% confidence intervals (CIs).

Data Extraction

Two reviewers independently extracted the relevant information from all included studies, and disagreements were discussed and resolved with consensus. The following information was collected from each study: the first author, year of publication, country in which the study was performed, ethnicity (Asian or white), age (children, adult, or mix), total numbers of cases and controls, genotypes, allele frequencies, and the genotyping methods.

Statistical Analysis

Deviation from Hardy-Weinberg equilibrium (HWE) for each control group of the included studies was examined by χ^2 tests.

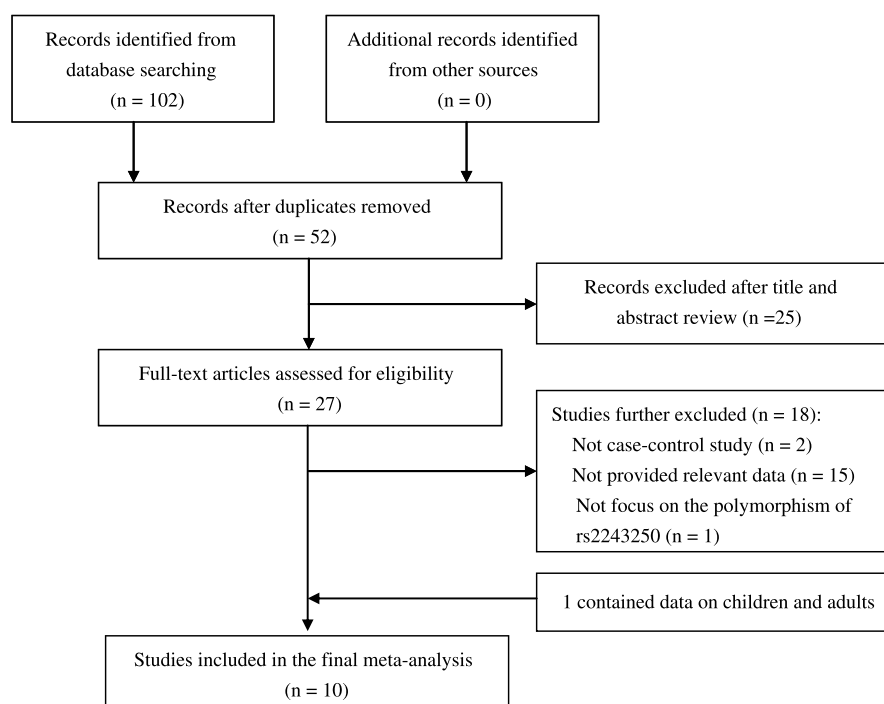


Figure 1. Flow chart of the study selection process.

Odds ratios with 95% CIs were used to assess the strength of association between IL-4 -590C/T polymorphism and AD susceptibility. The significance for pooled ORs was determined using the Z test with P less than 0.05 considered statistically significant. The ORs of the allele (T vs C), recessive (TT vs TC + CC), dominant (TT + TC vs CC), additive (TT vs CC), and heterozygote (TC vs CC) models were calculated by the fixed-effects or random-effects models according to the outcome of between-study heterogeneity detected by the χ^2 based on the Q test. The fixed-effects model with the Mantel-Haenszel method was performed for estimation of the pooled ORs when heterogeneity was indicated to be nonsignificant ($P > 0.10$ or $I^2 < 50\%$)²³; otherwise, the random-effects model based on the DerSimonian and Laird method was more appropriate.²⁴ Sensitivity analysis was performed by sequentially excluding individual studies to assess the stability and reliability of the results. A funnel plot and Egger tests were applied to evaluate publication bias across studies ($P < 0.05$ was considered statistically significant). Data were analyzed mainly using STATA version 12.0 (StataCorp LP, College Station, Tex).

RESULTS

Characteristics of Studies

A total of 102 published studies that matched our predefined search strategy were identified. After removing duplicate publications and screening titles and abstracts, 27 potential studies were obtained. By reviewing full texts of these studies, 18 more were excluded, and 1 study¹⁹ that involved children and adults was considered as 2 separate studies (referred to as Chang et al. 2006a and Chang et al. 2006b) for subgroup analysis by age. Finally, 10 case-control studies published in the English language were included in the meta-analysis (Fig. 1), involving 923 patients with AD and 1215 controls. Six studies were based on Asians—3 with children^{13,15,19} as the study subjects, 1 with adults,¹⁹ and the other 2 with both children and adults.^{20,21} Four studies involved white populations—all used children as the study subjects.^{11,16–18} The genotype distributions of control from 2 studies were not in agreement with HWE.^{17,18} The polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) was the most commonly used genotyping method in these studies. The characteristics of the included studies were shown in the Table 1.

Association of IL-4 -590C/T Polymorphism With AD Susceptibility

The overall results showed significant associations between IL-4 -590C/T polymorphism and AD under the allele (OR, 1.19; 95% CI, 1.03–1.38; $I^2 = 0.0\%$), recessive (OR, 1.27; 95% CI, 1.002–1.61; $I^2 = 0.0\%$), and dominant (OR, 1.33; 95% CI, 1.003–1.76; $I^2 = 0.0\%$) models in the overall population including Asian children and adults and white children (Table 2; Figs. 2A–4A). Similarly, after excluding not-in-HWE studies in control, significant associations were found between IL-4 -590C/T polymorphism and AD susceptibility under the allele (OR, 1.19; 95% CI, 1.01–1.39; $I^2 = 0.0\%$)

TABLE 1. Details of the Individual Studies Included in the Meta-Analysis

Author, Year	Country (Ethnicity)	Age	Numbers		CC	CT	TT	T Allele (%)		Association of Allele		Genotyping Method	
			Case/Control	Case/Control				Case/Control	Case/Control	OR (95% CI)	P	HWE	Method
Shang et al ¹⁵ (2016)	China (Asian)	Children	82/100	17/33	3/6	17/33	62/61	86.0/77.5	1.78 (1.03–3.09)	0.041	Yes	Yes	PCR-RFLP
Hussein et al ¹³ (2016)	Saudi Arabia (Asian)	Children	50/50	32/38	16/10	16/10	2/2	20.0/14.0	1.54 (0.73–3.24)	0.261	Yes	Yes	PCR-RFLP
Lesiak et al ¹¹ (2014)	Poland (white)	Children	76/60	31/26	2/3	31/26	43/31	77.0/73.3	1.22 (0.70–2.11)	0.489	Yes	Yes	PCR-RFLP
Hussein et al ¹⁶ (2014)	Egypt (white)	Children	106/100	66/68	32/26	32/26	8/6	22.6/19.0	1.25 (0.77–2.01)	0.364	Yes	Yes	PCR-RFLP
Kayserova et al ¹⁷ (2012)	Czech Republic (white)	Children	88/102	54/77	30/20	30/20	4/5	21.6/14.7	1.60 (0.94–2.71)	0.082	No	No	PCR-SSP
Stavric et al ¹⁸ (2012)	Republic of Macedonia (white)	Children	27/286	11/95	15/187	15/187	1/4	31.5/34.1	0.89 (0.49–1.62)	0.699	No	No	PCR-SSP
Chang et al ¹⁹ (2006)a	Taiwan (Asian)	Children	77/186	NR	NR	NR	NR	80.5/78.2	1.15 (0.72–1.84)	0.558	Yes*	Yes*	Sequencing
Chang et al ¹⁹ (2006)b	Taiwan (Asian)	Adult	17/186	NR	NR	NR	NR	70.6/78.2	0.69 (0.31–1.45)	0.309	Yes*	Yes*	Sequencing
Tanaka et al ²¹ (2001)	Japan (Asian)	Mix	190/116	15/10	92/55	92/55	83/51	67.9/67.7	1.01 (0.71–1.43)	0.954	Yes	Yes	5' nuclease
Kawashima et al ²⁰ (1998)	Japan (Asian)	Mix	210/215	15/17	82/97	82/97	113/101	73.3/69.5	1.21 (0.89–0.62)	0.221	Yes	Yes	PCR-RFLP
Total			923/1215										

*Mentioned in the publication.

NR indicates no report; PCR-SSP, polymerase chain reaction–sequence-specific primer.

TABLE 2. Association Between the IL-4 –590C/T Polymorphism and AD

Comparison	Population	No. Studies	Test of Association		Test of Heterogeneity		
			OR (95% CI)	P	Model	P	I ² (%)
T vs C (allele)	Overall	10	1.19 (1.03–1.38)	0.021*	F	0.572	0.0
	Overall in HWE	8	1.19 (1.01–1.39)	0.038*	F	0.597	0.0
	Asian	6	1.17 (0.98–1.41)	0.080	F	0.364	8.2
	White	4	1.23 (0.95–1.61)	0.121	F	0.557	0.0
	Children	7	1.30 (1.06–1.60)	0.011*	F	0.688	0.0
TT vs TC + CC (recessive)	Children in HWE	5	1.33 (1.05–1.69)	0.020*	F	0.781	0.0
	Children (Asian)	3	1.41 (1.02–1.95)	0.037*	F	0.482	0.0
	Children (white)	4	1.23 (0.95–1.61)	0.121	F	0.557	0.0
	Overall	8	1.27 (1.002–1.61)	0.048*	F	0.813	0.0
	Overall in HWE	6	1.27 (1.001–1.62)	0.049*	F	0.693	0.0
	Asian	4	1.28 (0.98–1.67)	0.067	F	0.387	0.9
	White	4	1.22 (0.73–2.05)	0.452	F	0.882	0.0
	Children	6	1.46 (0.98–2.16)	0.060	F	0.840	0.0
	Children in HWE	2	1.86 (1.01–3.43)	0.047*	F	0.523	0.0
	Children (Asian)	2	1.86 (1.01–3.43)	0.047*	F	0.523	0.0
TT + TC vs CC (dominant)	Children (white)	4	1.22 (0.73–2.05)	0.452	F	0.882	0.0
	Overall	8	1.33 (1.003–1.76)	0.047*	F	0.691	0.0
	Overall in HWE	6	1.32 (0.94–1.86)	0.112	F	0.951	0.0
	Asian	4	1.31 (0.84–2.02)	0.230	F	0.812	0.0
	White	4	1.34 (0.93–1.94)	0.114	F	0.286	20.6
	Children	6	1.42 (1.02–1.97)	0.037*	F	0.522	0.0
	Children in HWE	4	1.47 (0.95–2.29)	0.084	F	0.915	0.0
	Children (Asian)	2	1.75 (0.84–3.68)	0.138	F	0.945	0.0
	Children (white)	4	1.34 (0.93–1.94)	0.114	F	0.286	20.6
	Overall	8	1.32 (0.88–2.02)	0.183	F	0.994	0.0
TT vs CC (additive)	Overall in HWE	6	1.33 (0.85–2.08)	0.211	F	0.977	0.0
	Asian	4	1.28 (0.77–2.12)	0.345	F	0.909	0.0
	White	4	1.45 (0.69–3.03)	0.328	F	0.942	0.0
	Children	6	1.52 (0.82–2.83)	0.187	F	0.987	0.0
	Children in HWE	4	1.60 (0.77–3.34)	0.208	F	0.952	0.0
	Children (Asian)	2	1.71 (0.54–5.43)	0.364	F	0.670	0.0
	Children (white)	4	1.45 (0.69–3.03)	0.328	F	0.942	0.0
	Overall	8	1.28 (0.97–1.73)	0.097	F	0.534	0.0
	Overall in HWE	6	1.24 (0.87–1.78)	0.242	F	0.908	0.0
	Asian	4	1.20 (0.76–1.90)	0.439	F	0.713	0.0
TC vs CC (heterozygote)	White	4	1.35 (0.92–1.98)	0.129	F	0.209	33.9
	Children	6	1.40 (0.99–1.97)	0.059	F	0.396	3.2
	Children in HWE	4	1.41 (0.88–2.26)	0.149	F	0.862	0.0
	Children (Asian)	2	1.61 (0.73–3.53)	0.236	F	0.496	0.0
	Children (white)	4	1.35 (0.92–1.98)	0.129	F	0.209	33.9
	Overall	4					

*Statistically significant result.

F indicates fixed-effects model.

and recessive (OR, 1.27; 95% CI, 1.001–1.62; $I^2 = 0.0\%$) models in the overall population (Table 2; Figs. 2B, 3B). However, subgroup analysis based on ethnicity revealed no significant associations in Asians or whites under all 5 genetic models (Table 2). Subgroup analysis by age showed significant associations in the overall population of children under the allele (OR, 1.30; 95% CI, 1.06–1.60; $I^2 = 0.0\%$) and dominant (OR, 1.42; 95% CI, 1.02–1.97; $I^2 = 0.0\%$) models (Table 2; Figs. 2C, 4B), children in articles with HWE under the allele model (OR, 1.33; 95% CI, 1.05–1.69; $I^2 = 0.0\%$) (Table 2, Fig. 2D), and Asian children under the allele model (OR, 1.41; 95% CI, 1.02–1.95; $I^2 = 0.0\%$) (Table 2) but not in white children.

Heterogeneity, Sensitivity Analysis, and Publication Bias

As shown in Table 2, there was no between-study heterogeneity under all 5 genetic models ($I^2 = 0.0\%$ –33.9%). Sensitivity analysis showed no evidence of any individual study having significant influence on corresponding pooled ORs, which confirmed the

reliability and stability of this meta-analysis (data not shown). Publication bias was examined by funnel plots and Egger test under all genetic models. After combining the included studies, the results of Begg funnel plot and Egger test showed no apparent evidence of publication bias in all comparison models (Fig. 5).

DISCUSSION

Interleukin 4 is a critical mediator of the Th1/Th2 balance that may play an important role in the development of various allergic disorders including AD.⁸ In serum and skin lesions of patients with AD, IL-4 levels were profoundly increased compared with those of the controls, and this elevation was associated with a shift in the Th1/Th2 balance toward Th2 dominance and the increased severity of AD.^{10,15} Interleukin 4 is able to induce B cells to produce IgE, recruit various immune cells into skin,⁹ and suppress anti-infectious immune responses via impairing Th1 immunity and

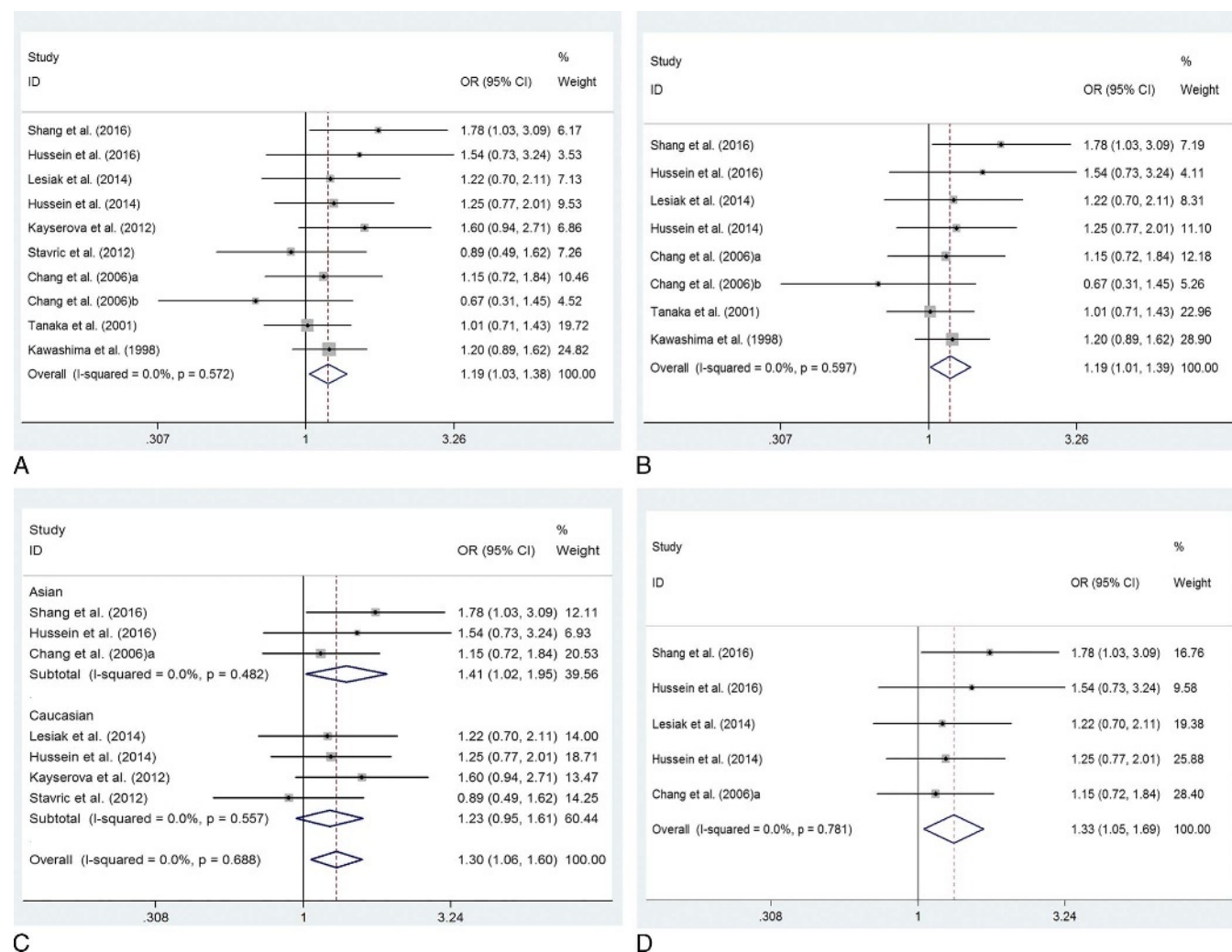


Figure 2. Forest plot of the IL-4 -590C/T polymorphism associated with increased AD susceptibility in the overall population (A), the overall population in studies with HWE (B), children (C), and children in studies with HWE under allele model (T vs C) (D). Pooled ORs and 95% CIs were derived from the fixed-effects model.

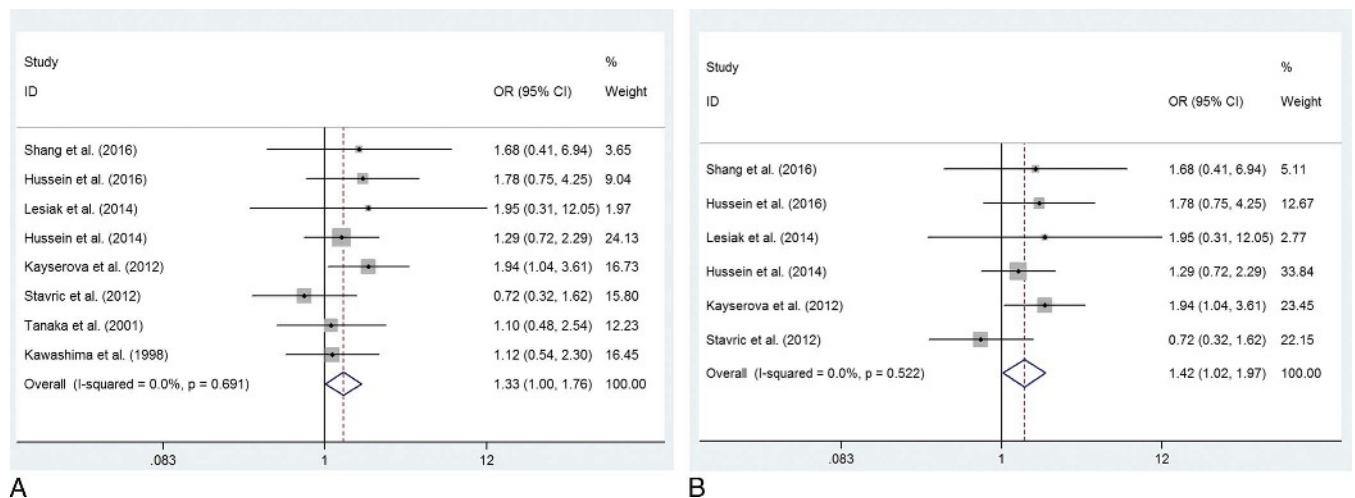


Figure 3. Forest plot of the IL-4 -590C/T polymorphism associated with increased AD susceptibility in the overall population (A), and the overall population in studies with HWE under recessive model (TT vs TC + CC) (B). Pooled ORs and 95% CIs were derived from the fixed-effects model.

downregulating the expression of antimicrobial peptides such as human β -defensin 2 and human β -defensin 3.²⁵ In addition, IL-4 also enhances expression of eotaxin-1 (CCL11)²⁶ as well as eotaxin-3 (CCL26)²⁷ which is essential to recruitment and function of eosinophils into AD lesions. Like immune dysregulation, epidermal barrier disruption was shown to be linked to the pathogenesis and severity of AD.²⁸ Interleukin 4 can significantly inhibit terminal differentiation of keratinocytes via STAT3, decrease production of epidermal lipids and the function of tight junctions, and reduce expression of skin barrier proteins such as filaggrin, loricrin, and involucrin.^{29,30} Interleukin 4 stimulates keratinocytes to express thymic stromal lymphopoietin that plays a crucial link between barrier defects and Th2 polarization⁸ and stimulates cutaneous sensory neurons to promote itch.³¹ Several polymorphisms in the promoter region of the *IL-4* gene were found to influence IL-4 transcription and AD

predisposition.^{13,14} Among them, the common IL-4 -590C/T polymorphism has been extensively studied in various diseases. The IL-4 -590T allele showed higher binding to nuclear transcription factors and 3-fold transcriptional activity compared with that of the -590C allele,^{32,33} and IL-4 -590C/T genotypes may differently influence the polarization of the immune response.³² The IL-4 -590T allele increases IL-4 expression and is associated with elevation of total serum IgE levels³⁴ and the severity of AD.³⁵ On the other hand, other studies found contradictory results: IL-4 -590C/T polymorphism did not affect IgE levels in allergic disease including AD³⁶ and was associated with the increased IgE levels but not associated with AD.^{13,16} Similarly, many previous studies have suggested that IL-4 -590C/T polymorphism is associated with increased AD risk,^{15,17,20} whereas other studies found no significant relation.^{11,13,16,18,19,21} Therefore, we performed a meta-analysis to

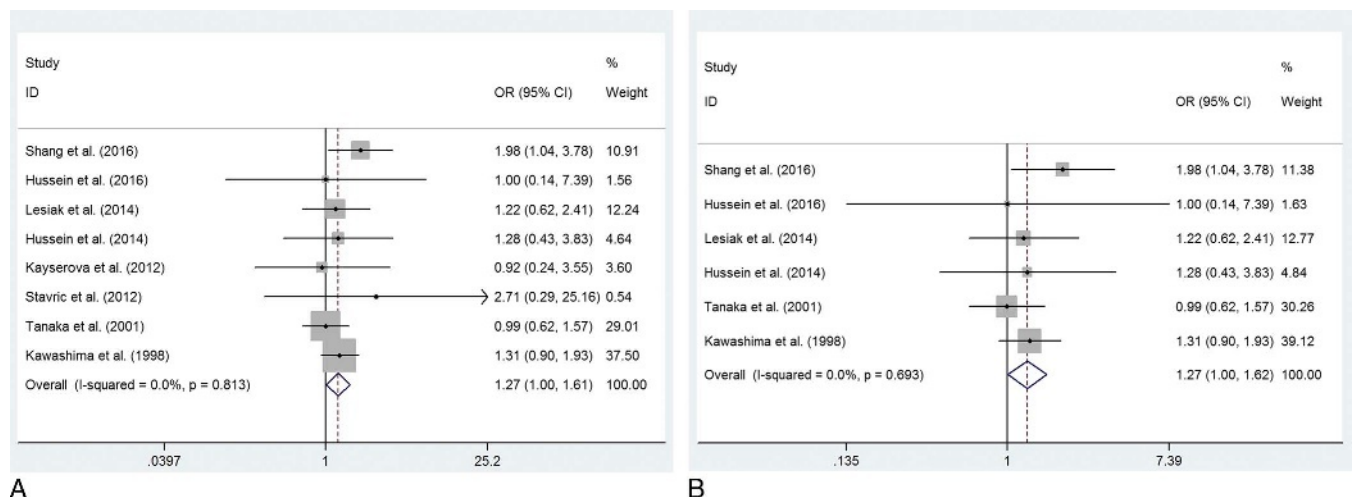


Figure 4. Forest plot of the IL-4 -590C/T polymorphism associated with increased AD susceptibility in the overall population (A), and children under dominant model (TT + TC vs CC) (B). Pooled ORs and 95% CIs were derived from the fixed-effects model.

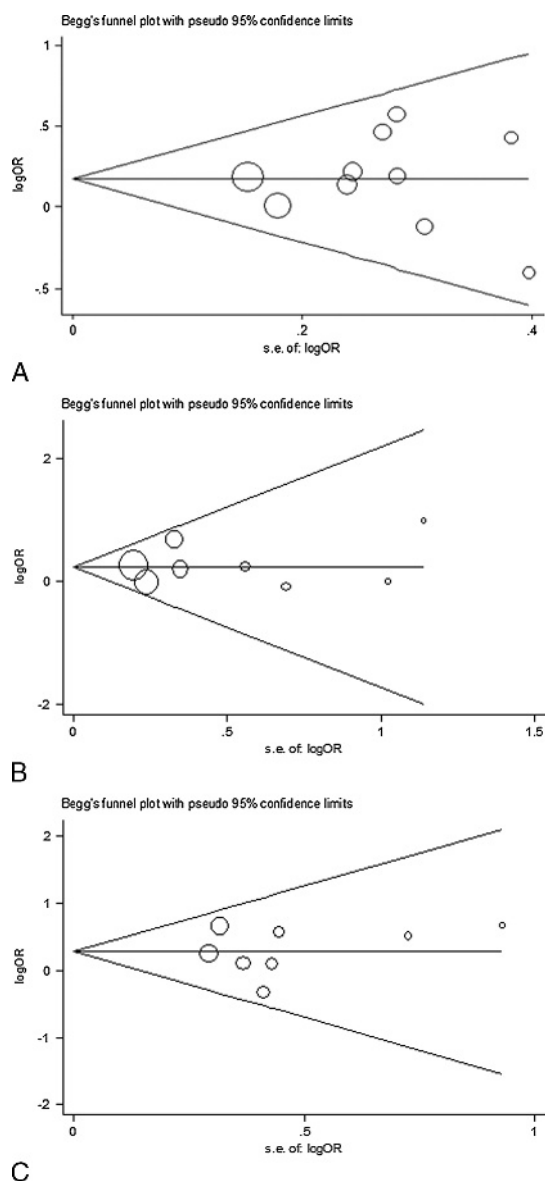


Figure 5. Analysis of funnel plot asymmetry and publication bias for the associations between the IL-4 -590C/T polymorphism and AD in the overall population under allele (T vs C; $P = 0.928$) (A), recessive (TT vs TC + CC; $P = 0.756$) (B), and dominant (TT + TC vs CC; $P = 0.855$) (C) models.

provide a more comprehensive and conclusive evidence for this polymorphism.

The present meta-analysis based on 10 case-control studies including 923 cases and 1215 controls systematically evaluated the association between IL-4 -590C/T polymorphism and AD susceptibility. The results showed that IL-4 -590C/T polymorphism was significantly associated with AD in the overall population. These results were robust in subgroup analyses stratified by studies with HWE and heterogeneity and sensitivity analyses, suggesting that the T allele may be an increased risk factor for the development of AD. However, in agreement with those findings from several

previous case-control studies,^{11,13,16,18,19,21} similar associations were not observed in Asians or whites when stratified by ethnicity, which may have insufficient statistical power to detect a potential effect because of the small sample size. Further subgroup analysis stratified by age and ethnicity revealed significant associations between IL-4 -590C/T polymorphism and increased risk in children, which was mainly in Asian children but not in white children. It is possible that different genetic backgrounds and environments may account for this discrepancy. Indeed, the frequency of the IL-4 -590T allele in controls in Japan (0.70), Kuwait (0.75), and China (0.78) was much higher than that reported in Australia (0.26), the United Kingdom (0.27), and the United States (0.23),^{15,37} indicating that there are underlying ethnic differences among these populations. Because the T allele is known to obviously enhance IL-4 gene promoter activity compared with the C allele, the IL-4 -590C/T polymorphism may increase the predisposition of development of AD in Asian children.

To the best of our knowledge, this is the first time a meta-analysis was performed to investigate the association between IL-4 -590C/T polymorphism and AD. Similar to other meta-analyses, several limitations should be addressed. First, our potential studies were searched from English and Chinese databases only; many potential studies were excluded because of insufficient data on genotype distribution, and all 4 included studies on white populations used only children as the study subjects,^{11,16–18} which may have caused publication bias even though it is not observed in the present study. Second, there were small sample sizes and relatively few eligible studies, particularly for the subgroup analysis based on ethnicities and age. Although a significant association with AD was detected in the Asian children population under allele and recessive models, which included only 3 and 2 studies in our statistical analysis, the results should be interpreted with caution and warrant further study. Third, we did not conduct a more precise meta-analysis adjusted by other factors such as age, sex, serum IgE levels, and environmental factors, and address gene-gene and gene-environment interactions because the included studies lacked the relevant data.

In summary, this meta-analysis supported evidence that IL-4 -590C/T polymorphism may confer susceptibility to AD in the overall population and children, especially for Asian children. Well-designed and larger studies in populations with the same ethnic background are required to confirm or refute these findings.

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