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Review Article

Association between IL-4, IL-6, IL-18 polymorphisms and *atopic dermatitis* risk: a meta-analysis

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Abstract: Background: Atopic dermatitis (AD) is one of common chronic and relapsing inflammatory diseases with a strong genetic predisposition. Abnormal cytokine production might have an effect on the biology of AD development. Objective: The aim of this study was to identify whether polymorphisms of interleukin (IL)-4, IL-6 and IL-18 were associated with AD susceptibility. Methods: Relevant investigations between 2000 and 2015 were searched from online databases. The value of odds ratio (OR) and its 95% confidence interval (CI) were calculated to assess these relationship. Results: A total of 14 papers were finally selected for this study, including 1550 controls and 1021 AD patients. There were seven studies for IL-18, five for IL-4, and four for IL-6 polymorphisms, respectively. Meta-analysis revealed an obvious relationship between IL-18 -137G/C polymorphism and AD under the homozygous model (CC vs. GG: OR=0.27, 95% CI=0.13-0.54, *P*=0.0002) and recessive model (CC vs. GC+GG: OR=0.31, 95% CI=0.16-0.61, *P*=0.0007) in a fixed-effect model. The GA genotype of IL-6 nt565G/A polymorphism in heterozygous model was correlated with increased the risk of AD (GA vs. GG: OR=0.68, 95% CI=0.48-0.96, *P*=0.03) as well. However, this significant association was not found in other genotypes (all *P*>0.05). Conclusions: These results indicated that CC genotype of IL-18 -137G/C polymorphism and GA genotype of IL-6 nt565G/A polymorphism were risk factors for AD. Future studies with large population were still needed to further explore these corrections.

Keywords: Atopic dermatitis, interleukin, polymorphism, meta-analysis

Introduction

Atopic dermatitis (AD), commonly called atopic eczema, were considered to be a one kind of chronic and relapsing inflammatory diseases of skin with high heterogeneity and heritability [1]. It is characterized by xerosis, recurrence, pruritus, and distributed eczematous skin lesions [2], posing a significant burden on healthcare resources [3]. AD typically begins during infancy or early childhood, and it can affect 15%-30% of children and up to 10% of adults, leading to significant morbidity [4]. More than 60% of children with AD are at risk to develop asthma and allergic rhinitis [5]. Prevalence continues to vary and has changed in different regions of the world [6]. Although the exact etiology of AD remains unknown, genetic predisposition like cytokines (interleukin) and environmental factors like microorganisms (*Staphylococcus aureus* and *Malassezia*) might be in parts attributed to a pathogenic role in AD [7]. Many AD patients have a favorable response to topical medications and anti-itch methods. however, a part subset require additional systemic therapies [8]. Therefore, exploration of novel biomarkers was urgent for early detection and targeted therapies for AD patients.

AD is regarded as mediated by type 2 T-helper (Th2)-type immunity. Genetic factors of specific immune and inflammatory mechanisms are involved in AD risk, and abnormal cytokine production has been implicated in its pathogenesis [9]. Several effector T cell subsets, such as pro-inflammatory cells, together with the anti-inflammatory, immune-modulating Treg cells, seem to play a role in this condition [10]. Interleukin (IL) genes are a group of cytokines that contribute to cell migration, growth, differentiation, and inflammatory and anti-inflammatory responses by the immune system [11]. They are also implicated in cancer and inflammatory disease [12, 13]. IL-4 gene, localized on human chromosomal region 5q31-33, encodes a glycoprotein [14]. High amounts of IL-4-producing T

cells at birth may enhance the risk of subsequent development of AD [15]. IL-6 gene is located on human chromosome 7p15 [16]. It is regarded as a prominent target for clinical intervention, and has context-dependent pro- and anti-inflammatory properties [17]. IL-18 gene is located on human chromosomal region 11q22.2-22.3 [18]. It can induce the production of immunoglobulin E (IgE) and Th2 cytokines by antigen-stimulated helper T cells [19]. Serum levels of IL-4, IL-6 and IL-18 were found significantly higher in children with AD, and importantly correlate with clinical severity of AD [20-22]. Studies have confirmed that IL-4, IL-6 and IL-18 might be candidate genes for atopic health outcomes [23], and cytokine-directed therapies for treatment of AD [24].

Functional polymorphisms of IL genes may affect constitutive and inducible pathways for cytokine production, contribute to the disease-associated cytokine imbalance, and thus influence susceptibility to AD. Many studies have identified the role of IL-4, IL-6 and IL-18 genes polymorphisms in AD, however, the results remain inconclusive. Furthermore, with small sample sizes, these studies lacked adequate statistical power to detect small to moderate effects. Therefore, we conducted this meta-analysis to systematically review all the published studies on this issue to obtain a relatively reliable results of IL-4, IL-6 and IL-18 polymorphisms in AD susceptibility.

Materials and methods

Study design

Systematic online document retrieval was carried out to search relevant literature published from January 2000 to 2015 in databases of PubMed, Web of science, CNKI (China National Knowledge Infrastructure), Medline and Embase. “Atopic dermatitis or atopic eczema or atopic diseases”, “the interleukin genes or IL genes or IL-4 or IL-6 or IL-18” and “polymorphism or variant or mutation” as well as their combination were employed as the searching words. The search was only limited on English and Chinese languages. In addition, for cases of similar articles reported by same authors, only the newest paper was included.

Selection criteria

Inclusion criteria of this study: 1) case-control study mainly researched on the effect of IL-4, IL-6, IL-18 polymorphisms on AD risk; 2) patients should meet the diagnostic criteria of AD described by Hanifin and Rajka [25], healthy controls must be matched with patients at age and sex; 3) the information of genotype and allele of AD patients and healthy controls were available to obtained; 4) all data of the results were represented by OR with 95% CI. And the exclusion criteria: 1) studies with duplicate data; 2) without control group; 3) review or conference papers; and 4) data could not be obtained.

Data extraction and analysis

According to the PRISMA guidelines, the data from all included articles were extracted and evaluated through two experienced investigators independently. The information of author, year of publication, ethnicity, mean age, country, genotype methods, number of sample, allele and genotype distributions in AD patients and healthy controls, and the Hardy-Weinberg equilibrium (HWE) in controls were extracted and recorded, respectively.

Statistical analysis

The correlation between IL-4, IL-6, IL-18 polymorphisms and AD risk was presented through ORs and its 95% CI under five genetic models: allele model (A vs. a), homozygous model and heterozygous model (AA vs. aa; Aa vs. aa), dominant model and recessive model (AA+Aa vs. aa; AA vs. Aa+aa). Z test was performed to assess the significance of ORs and $P<0.05$ considered statistical significant. I^2 test and the Q statistic test were carried out to measure the Between-study heterogeneity. When the effect was homologous ($I^2<50\%$ and P of the Q test>0.01), the fixed-effect model was applied; else, the analysis was performed by the random-effect model. All data were performed and analyzed through using Review manager 5.2.

Results

Characteristics of eligible articles

Through filtering using inclusion and exclusion criteria, 14 papers were finally be selected for next research, including 1021 AD and 1550 controls. **Figure 1** showed the selection process of this meta-analysis. Of the 14 studies, 2 papers were written in Chinese [26, 27] and 12 were written in English [28-39]. Three genes containing five polymorphic sites were concerned: IL-4 gene (-590C/T), IL-6 gene (-174G/

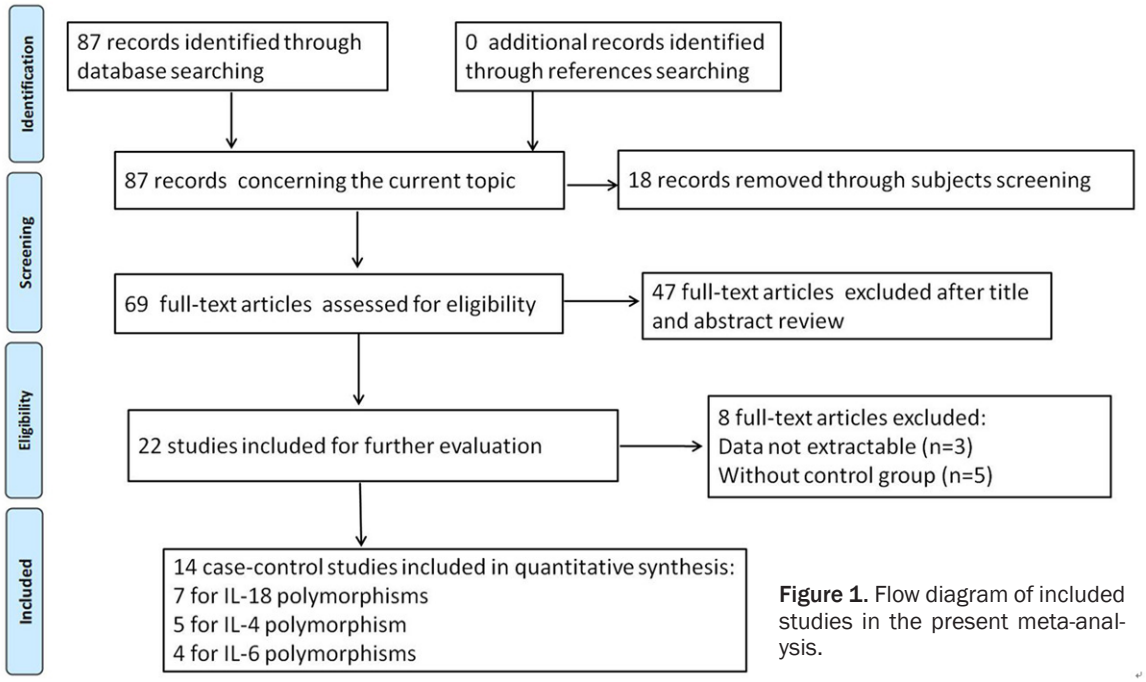

Figure 1. Flow diagram of included studies in the present meta-analysis.

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

First author	Year	Country	Ethnicity	Mean age		Sample size		Genotyping method	SNP
				Cases	Controls	Cases	Controls		
Ohnishi H	2003	Japan	Asian	4.9±4.6	4.8±4.4	18	20	PCR-SSP	IL-18 -137G/C
Reich K	2003	Germany	Caucasian	27.3±9.5	36.9±13.4	94	214	PCR-RFLP	IL-6 -174G/C
Chang YT	2006	Taiwan	Asian	26.9	-	94	186	Sequencing	IL-4 -590C/T
Osawa K	2007	Japan	Asian	31±6	23±3	21	100	PCR-SSP	IL-18 -137G/C, -607C/A
Luo XY	2008	China	Asian	4.82±2.91	8.43±3.76	82	100	PCR-SSP	IL-18 -137G/C, -607C/A
Kato T	2009	Japan	Asian	27.1	32.6	160	104	PCR-RFLP	IL-18 -137G/C
Qu SB	2010	China	Asian	28±9	26±8	28	52	PCR-SSP	IL-18 -137G/C, -607C/A
Trzeciak M	2010	Poland	Caucasian	-	-	67	46	ARMS-PCR	IL-18 -137G/C
Ibrahim GH	2012	Egypt	African	6.9±3.5	28.5±8.6	25	25	PCR-RFLP	IL-18 -137G/C
Kayserova J	2012	Czech Republic	Caucasian	-	-	94	103	PCR-SSP	IL-4 -590C/T; IL-6 -174G/C, nt565G/A
Stavric K	2012	Republic of Macedonia	Caucasian	0.5-5	-	67	301	PCR-SSP	IL-4 -590C/T; IL-6 -174G/C, nt565G/A
Gharagozlou M	2013	Iran	Asian	-	-	89	139	PCR-SSP	IL-6 -174G/C, nt565G/A
Hussein YM	2014	Egypt	African	8.1±4.3	8.9±3.4	106	100	PCR-RFLP	IL-4 -590C/T
Lesiak A	2014	Poland	Caucasian	11.4	11.4	76	60	PCR-RFLP	IL-4 -590C/T

-, not available; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; SSP, sequence-speciic primers.

C, nt565G/A) and IL-18 gene (-137G/C, -607C/A). The included articles contained nine countries and three ethnicities (Asian, African and Caucasian). The numbers of sample were from 38 to 368 in 1414 studies. The genotype distributions in the controls were in line with HWE except two studies for IL-4 and for IL-6, respectively [35, 37]. The main characteristics of 14 studies were recorded in **Table 1**. The allele and genotype information of cases and controls were presented in **Table 2**.

The correlation between IL-4 polymorphism (-590C/T) and AD risk

Summary ORs and test for heterogeneity were shown in **Table 3**. There were five studies containing 391 AD patients and 734 healthy con-

Table 2. Alleles and genotypes information of each gene in each single included study

Gene	Case					Control					HWE
IL-4											
-590C/T	CC	TC	TT	C	T	CC	TC	TT	C	T	
Chang YT*	1	38	55	40	148	4	73	109	81	291	0.12
Kayserova J	54	30	4	138	38	77	20	5	174	30	0.09
Stavric K	11	15	1	37	17	95	187	4	377	195	<0.001
Hussein YM	66	32	8	164	48	68	26	6	162	38	0.30
Lesiak A	2	31	43	35	117	3	26	31	32	88	0.70
IL-6											
-174G/C	GG	GC	CC	G	C	GG	GC	CC	G	C	
Reich K	27	48	19	102	86	66	104	44	236	192	0.97
Kayserova J	43	33	17	119	67	30	53	20	113	93	0.92
Stavric K	33	23	9	89	41	144	132	25	420	182	0.79
Gharagozlou M	63	22	4	148	30	42	93	4	177	101	<0.001
nt565G/A	GG	GA	AA	G	A	GG	GA	AA	G	A	
Kayserova J	44	32	17	120	66	33	54	16	120	86	0.73
Stavric K	33	23	9	89	41	153	123	25	429	173	0.99
Gharagozlou M	63	22	4	148	30	93	42	4	228	50	0.96
IL-18											
-137G/C	GG	GC	CC	G	C	GG	GC	CC	G	C	
Ohnishi H	15	3	0	33	3	13	7	0	33	7	0.64
Osawa K	18	3	0	39	3	74	25	1	173	27	0.78
Luo XY	43	38	1	124	40	71	27	2	169	31	0.95
Kato T	123	36	1	282	38	75	24	5	174	34	0.28
Qu SB	23	5	0	51	5	38	13	1	89	15	0.99
Trzeciak M	46	15	6	107	27	13	16	17	42	50	0.13
Ibrahim GH	11	9	5	31	19	11	8	6	30	20	0.25
-607C/A	CC	CA	AA	C	A	CC	CA	AA	C	A	
Osawa K	4	11	6	19	23	18	48	34	84	116	0.99
Luo XY	24	43	15	91	73	39	45	16	123	77	0.88
Qu SB	9	11	8	29	27	13	28	11	54	50	0.85

*, Genotype frequencies were estimated based on reported allele frequencies, assuming HWE among cases and controls; HWE, Hardy-Weinberg Equilibrium.

trols. There was no heterogeneity found between these studies. Thus, the fixed-effect model was applied to synthesize and analyze these data. The results illustrated that the frequency of T allele was higher in AD patients than that in healthy controls (47.1% vs. 43.7%). However, there was no significant difference between -590C/T polymorphism of IL-4 gene and AD risk through analyzing the following classification (T vs. C: OR=1.17, 95% CI=0.94-1.47, *P*=0.17; TT vs. CC: OR=1.50, 95% CI=0.75-3.02, *P*=0.25; TC vs. CC: OR=1.37, 95% CI=0.94-2.00, *P*=0.11; TT+TC vs. CC: OR=1.36, 95% CI=0.95-1.95, *P*=0.09; TT vs. TC+CC: OR=1.10, 95% CI=0.77-1.58, *P*=0.61) (**Figure 2**).

Relationship between IL-6 polymorphisms (-174G/C, nt565G/A) and AD risk

Duo to analyzing IL-6 -174G/C polymorphism, four articles were included (341 patients and 757 controls). No significant correction was found between -174G/C polymorphism of IL-6 gene and AD risk under each genetic classification (C vs. G: OR=0.73, 95% CI=0.46-1.17, *P*=0.19; CC vs. GG: OR=0.94, 95% CI=0.61-1.45, *P*=0.78; GC vs. GG: OR=0.49, 95% CI=0.21-1.15, *P*=0.10; CC+GC vs. GG: OR=0.54, 95% CI=0.25-1.20, *P*=0.13; CC vs. GC+GG: OR=1.13, 95% CI=0.77-1.66, *P*=0.54) (**Figure 3**). For nt565G/A polymorphism of IL-6 gene, three articles contained 247 patients and 543

Table 3. Meta-analysis of IL-4, IL-6, IL-18 polymorphisms with risk of allergic dermatitis

Gene SNPs	N	Test for association		Test for heterogeneity		
		OR (95% CI)	P	Ph	I^2	Model
IL-4 -590C/T						
T vs. C	5	1.17 (0.94, 1.47)	0.17	0.63	0%	F
TT vs. CC	5	1.50 (0.75, 3.02)	0.25	0.98	0%	F
TC vs. CC	5	1.37 (0.94, 2.00)	0.11	0.32	15%	F
TT+TC vs. CC	5	1.36 (0.95, 1.95)	0.09	0.42	0%	F
TT vs. TC+CC	5	1.10 (0.77, 1.58)	0.61	0.91	0%	F
IL-6 -174G/C						
C vs. G	4	0.73 (0.46, 1.17)	0.19	0.001	82%	R
CC vs. GG	4	0.94 (0.61, 1.45)	0.78	0.39	0%	F
GC vs. GG	4	0.49 (0.21, 1.15)	0.10	<0.0001	88%	R
CC+GC vs. GG	4	0.54 (0.25, 1.20)	0.13	<0.0001	88%	R
CC vs. GC+GG	4	1.13 (0.77, 1.66)	0.54	0.59	0%	F
IL-6 nt565G/A						
A vs. G	3	0.93 (0.72, 1.20)	0.58	0.40	0%	F
AA vs. GG	3	1.17 (0.67, 2.02)	0.58	0.44	0%	F
GA vs. GG	3	0.68 (0.48, 0.96)	0.03	0.27	23%	F
AA+GA vs. GG	3	0.77 (0.56, 1.07)	0.12	0.26	25%	F
AA vs. GA+GG	3	1.45 (0.86, 2.43)	0.16	0.79	0%	F
IL-18 -137G/C						
C vs. G	7	0.62 (0.33, 1.18)	0.15	<0.0001	79%	R
CC vs. GG	6	0.27 (0.13, 0.54)	0.0002	0.17	36%	F
GC vs. GG	7	0.75 (0.40, 1.41	0.38	0.006	67%	R
CC+GC vs. GG	7	0.65 (0.32, 1.31)	0.23	0.0003	76%	R
CC vs. GC+GG	6	0.31 (0.16 0.61)	0.0007	0.38	6%	F
IL-18 -607C/A						
A vs. C	3	1.12 (0.82, 1.52)	0.49	0.60	0%	F
AA vs. CC	3	1.21 (0.64, 2.28)	0.56	0.71	0%	F
CA vs. CC	3	1.16 (0.70, 1.94)	0.56	0.30	17%	F
AA+CA vs. CC	3	1.19 (0.73, 1.93)	0.48	0.39	0%	F
AA vs. CA+CC	3	1.11 (0.65, 1.89)	0.69	0.68	0%	F

N, number of included studies; OR, odds ratio; 95% CI, 95% confidence interval; Ph, *p*-value for the Q-test; F, the fixed-effect model; R, the random-effect model.

controls. Our result showed that only the GA genotype in heterozygous model was obviously correlated with increased the risk of AD (GA vs. GG: OR=0.68, 95% CI=0.48-0.96, *P*=0.03) in the fixed-effect model as shown in **Figure 4**. While no relationship was found bet-ween nt565G/A polymophism of IL-6 and the risk of AD in other genetic models (A vs. G: OR=0.93, 95% CI=0.72-1.20, *P*=0.58; AA vs. GG: OR=1.17, 95% CI=0.67-2.02, *P*=0.58; AA+GA vs. GG: OR=0.77, 95% CI=0.56-1.07, *P*=0.12; AA vs. GA+GG: OR=1.45, 95% CI=0.86-2.43, *P*=0.16).

Correlation between IL-18 (-137G/C, -607C/A) polymorphism and the risk of AD

Seven articles concerned the IL-18 -137G/C variant, including 401 AD patients and 447 controls. Meta-analysis revealed an obviously association between the -137G/C polmorphism of IL-18 gene and the risk of AD for the homozygous model (CC vs. GG: OR=0.27, 95% CI=0.13-0.54, *P*=0.0-002) and recessive model (CC vs. GC+GG: OR=0.31, 95% CI=0.16-0.61, *P*=0.0-0-07) in the fixed-effect model as shown in **Figure 5**. However, this significant correction was not found in other classification (C vs. G: OR=0.62, 95% CI=0.33-1.18, *P*=0.15; GC vs. GG: OR=0.75, 95% CI=0.40-1.41, *P*=0.38; CC+GC vs. GG: OR=0.65, 95% CI= 0.32-1.31, *P*=0.23) in the random-effect model. For -607C/A polymorphism of IL-18 gene, only three articles were included. We found that -607C/A polymorphism was not related with AD susceptibility in any classification (A vs. C: OR= 1.12, 95% CI=0.82, 1.52, *P*=0.49; AA vs. CC: OR= 1.21, 95% CI=0.64, 2.28, *P*=0.56; CA vs. CC: OR=1.16, 95% CI=0.70, 1.94, *P*=0.56; AA+CA vs. CC: OR=1.19, 95% CI=0.73, 1.93, *P*=0.48; AA vs. CA+CC: OR=1.11, 95% CI=0.65, 1.89, *P*=0.69).

Sensitivity analysis and publication bias

Each study in each comparison model was deleted every time to estimate whether the single article affects the overall ORs. In the present study, the results indicated that the pooled ORs were not remarkably changed. Publication

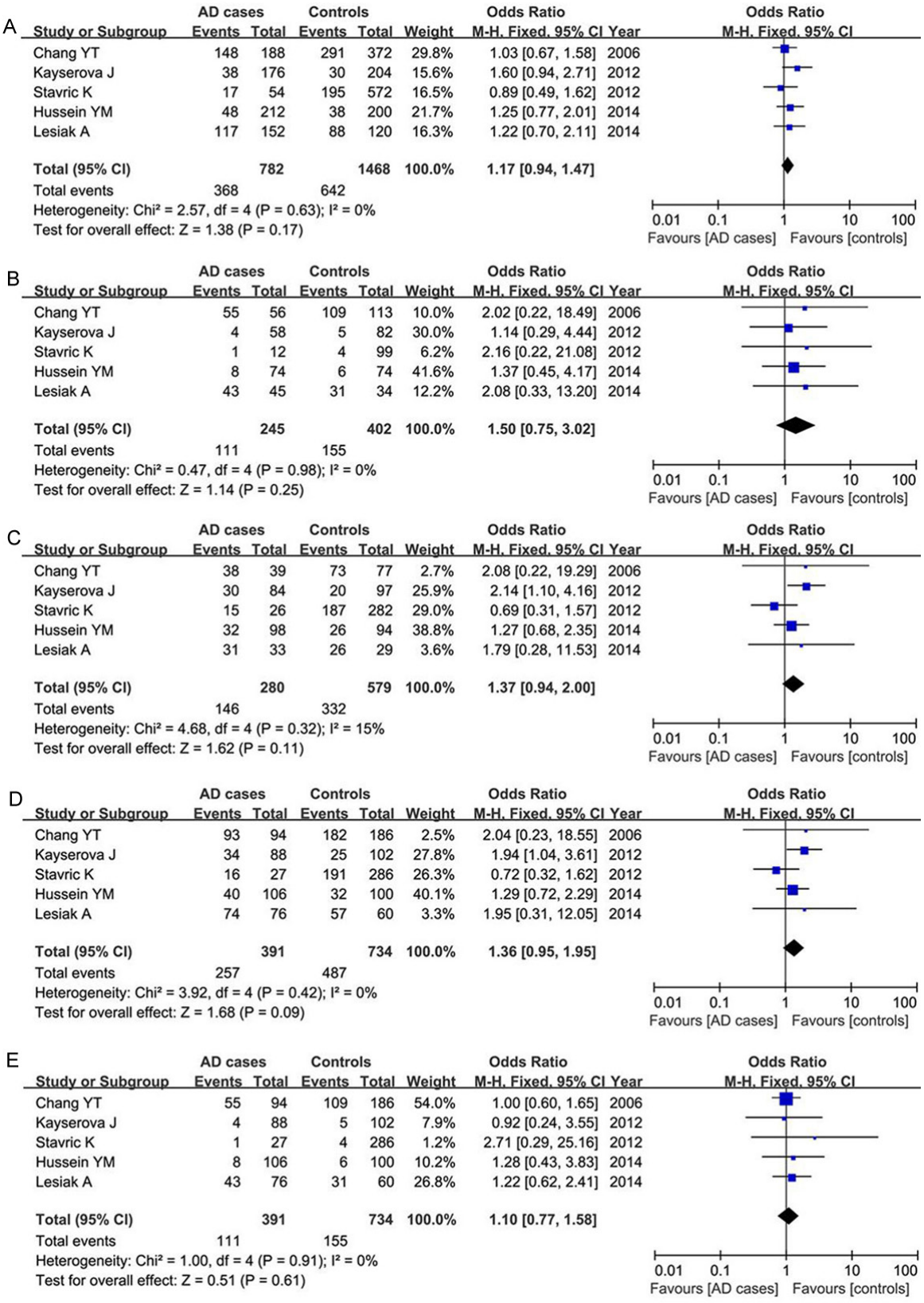

Figure 2. Forest plots for IL-4 -590C/T polymorphism and atopic dermatitis risk under allele model (A), homozygous model (B), heterozygous model (C), dominant model (D), and recessive model (E).

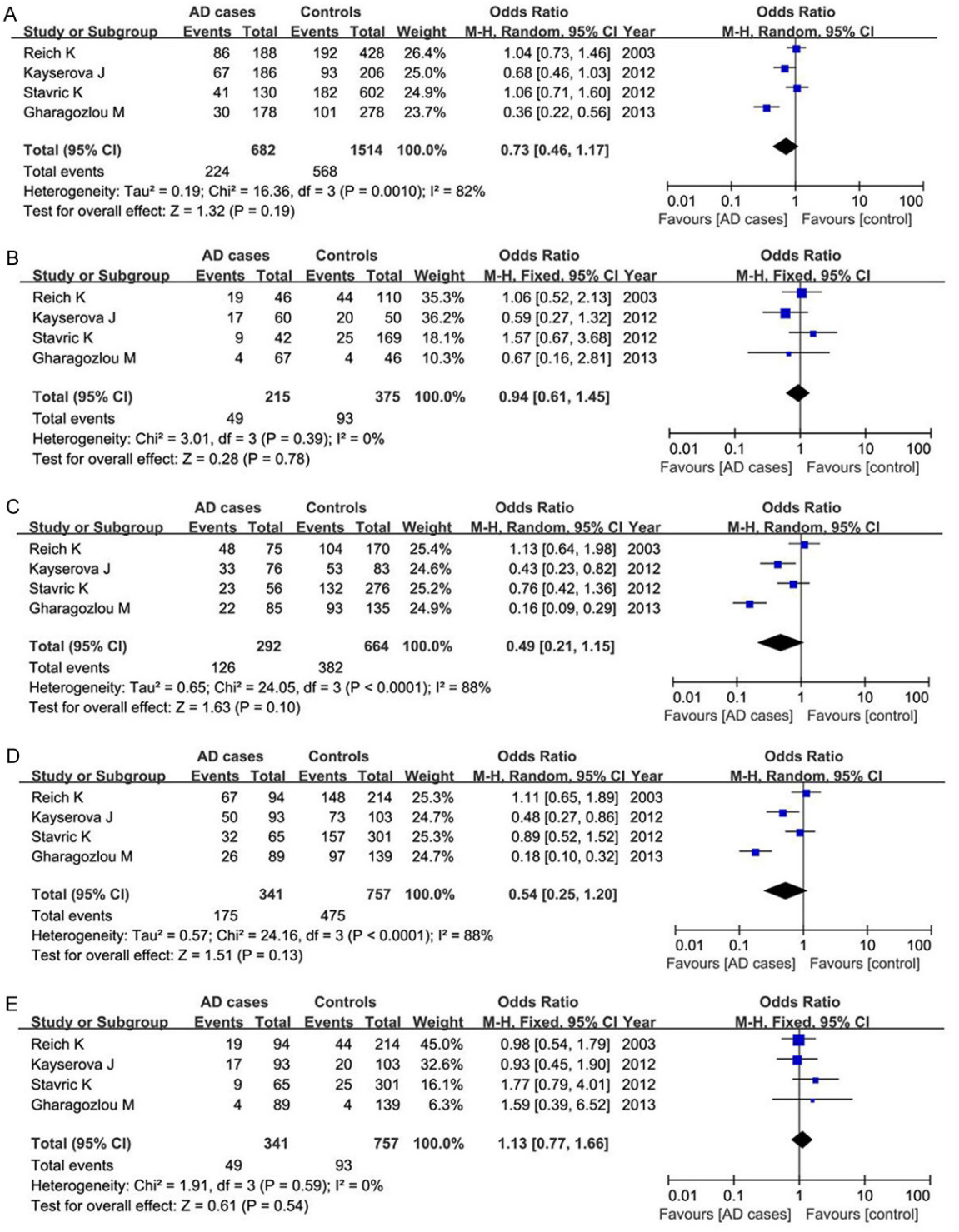

Figure 3. Forest plots for IL-6 -174G/C polymorphism and atopic dermatitis risk under allele model (A), homozygous model (B), heterozygous model (C), dominant model (D), and recessive model (E).

bias in our meta-analysis was assessed via the funnel plot. Each dot represents one included study. As shown in **Figure 6**, no publication bias was found in this meta-analysis.

Discussion

In the present meta-analysis, we screened out 14 relevant studies. The results demonstrated

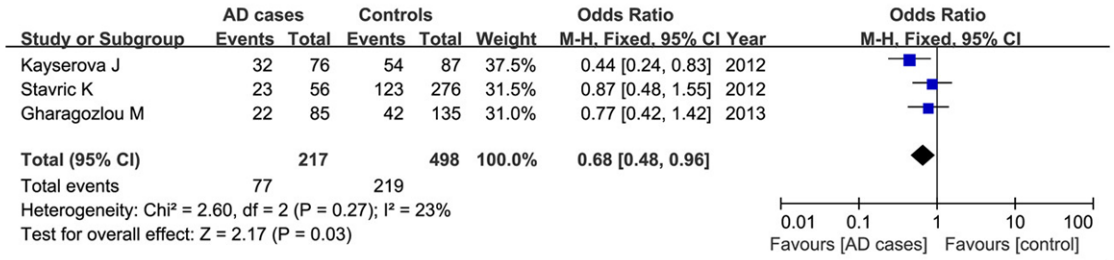

Figure 4. Meta-analysis for IL-6 nt565G/A polymorphism and atopic dermatitis risk under heterozygous model (GA versus GG).

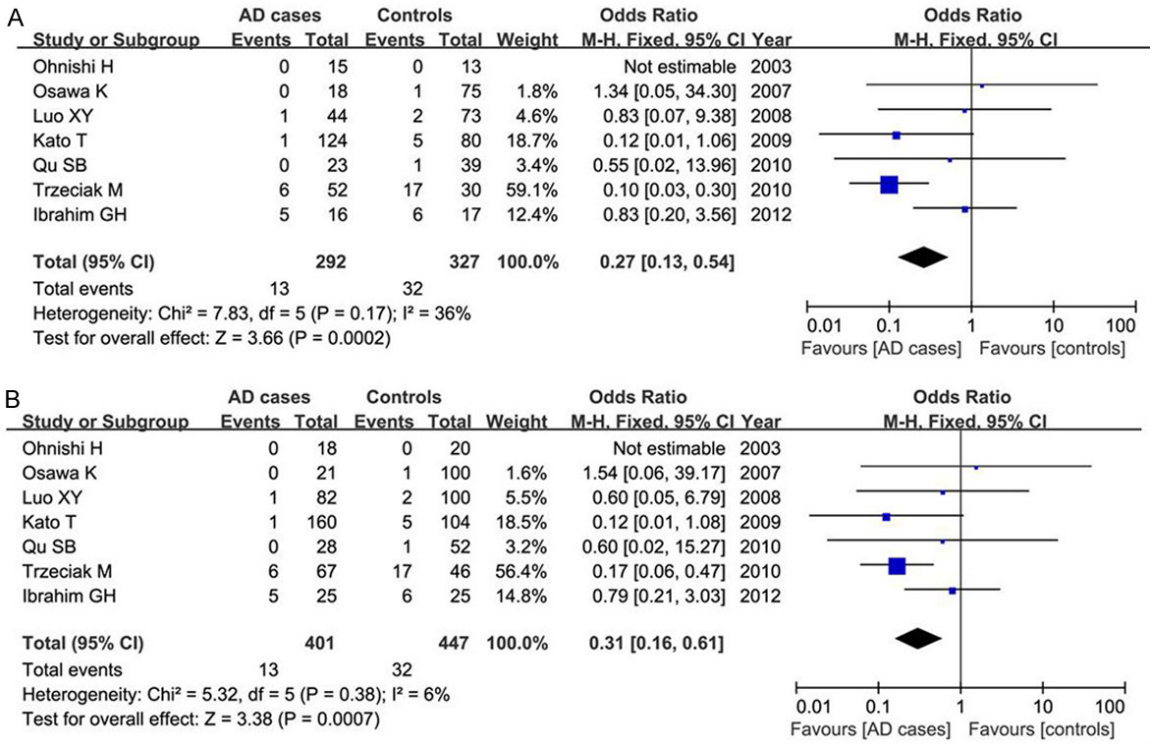

Figure 5. Meta-analysis for IL-18 -137G/C polymorphism and atopic dermatitis risk under homozygous model (A: CC versus GG) and recessive model (B: CC versus GC+GG).

that GA genotype of IL-6 nt565G/A polymorphism in heterozygous model, CC genotype of IL-18 -137G/C in homozygous model and recessive model, were significantly associated with increased the risk of AD. This significant relationship was not found neither in other genotypes of IL-6 nt565G/A and IL-18-137G/C polymorphisms, nor in all alleles and genotypes of IL-4 -590C/T, IL-6-174G/C and IL-18-607C/A polymorphisms. This is the first meta-analysis concerning these three gene polymorphisms in AD risk.

IL-4 is crucial for the growth and development of the Th2 cells, and can induce IgE production which is linked to the pathophysiology of anaphylaxis and other acute allergic reactions [40]. Elevated IgE may reflect increased responses of Th2 cytokines with a concomitant decrease in interferon-gamma production in patients with AD [41]. Higher serum IL-4 concentration was found in AD patients at the time of diagnosis and correlated with disease activity before and after treatment [41]. IL-4 also mediates other genes, which was considered to participate in the pathogenesis of AD [42, 43]. Recently, a new therapeutic strategy that targets blocking IL-4 signaling has been shown significant improvement in patients with moderate-to-severe AD [44]. The emerging evidence

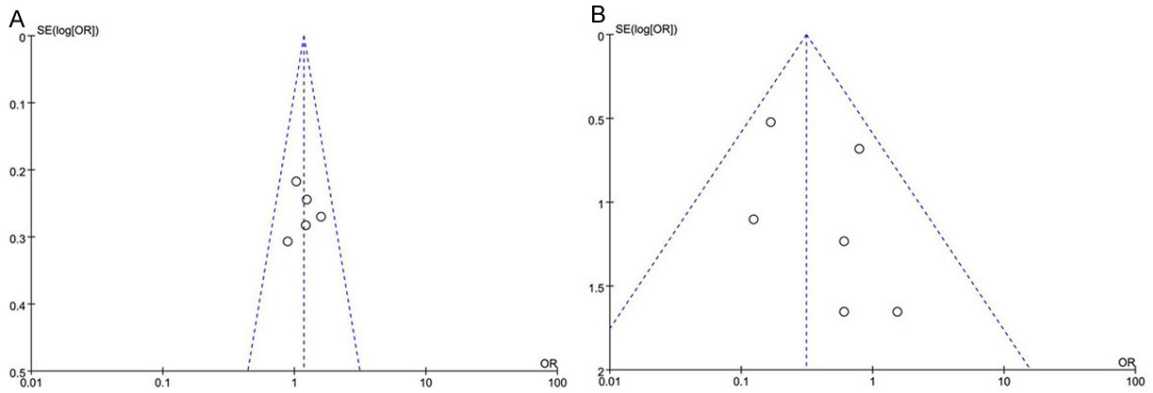

Figure 6. Funnel plot for the association between IL-4 polymorphism (A) and IL-18 polymorphism (B) and the risk of atopic dermatitis.

showed that IL-4 polymorphisms were significantly associated with AD risk. Kawashima et al. found that the frequency of the T allele of IL-4 -590 C/T polymorphism was higher especially in Japanese, which could promote IL-4 gene promoter transcriptional activity, thus influenced AD predisposition [45]. He et al. demonstrated that IL-4 -589C/T was associated with the development of AD in at-risk children at 24 months of age [46]. However, Elliott et al. showed that the IL-4 -590C/T polymorphism had a limited association with AD risk in childhood [47]. In our study, we did not find a significant association between IL-4 -590C/T variant and AD risk.

IL-6 is a key cytokine in the host defense mechanism and can function as both a pro-inflammatory cytokine and an anti-inflammatory cytokine. It regulates the T cell differentiation and activation [48], and plays a crucial role in the acute phase response [49] and in physiological and pathological conditions [50]. Family members of IL-6 can regulate cell invasion, metastasis, migration, proliferation, survival, angiogenesis and inflammation via gp130 [51]. Serum levels of IL-6 was found statistically significantly higher in AD patients than controls, and a statistically significant correlation between serum levels of IL-6 and Scoring Atopic Dermatitis in children with AD was found, indicating that serum levels of IL-6 might be useful in the assessment of disease severity and follow-up of children with AD [52]. Several studies concerned the IL-6 polymorphisms. However, the results were not consistent. Kayserova et al. showed an association between IL-6 -174C/G and nt565A/G polymorphisms and AD risk [36]. Gharagozlou et al. demonstrated that the G allele and GG genotype of IL-6 -174C/G polymorphism was associated with increased the risk of AD [37]. While Reich et al. and Stavric et al. found no association between IL-6 -174C/G and nt565A/G polymorphisms and AD risk [35, 39]. Our statistical analysis showed that only GA genotype of IL-6 nt565G/A polymorphism in heterozygous model was significantly associated with AD.

IL-18, a powerful activator of B-cells and an important regulator in both innate and acquired immune responses, is a novel cytokine [53]. It is also a proinflammatory cytokine, which plays an central role for Th1 and Th2 cytokine, and in inflammatory responses with emphasis on autoimmune diseases [54, 55]. L-18 can upregulate IgE production in AD patients [56]. In unstimulated monocytes, decreased IL-18 production and down-regulation of mRNA expression of IL-18 were significantly associated with AD [57]. Serum IL-18 has been found to be associated with AD severity. Evidences have shown that serum IL-18 concentration in young children or adults with AD was significantly higher than that of corresponding controls, especially in moderate to severe disease [58-60]. Previous studies have suggested that IL-18 gene polymorphisms might be involved in the development of AD by contributing to a functional dysregulation of the IL-18 production in vivo [61]. The haplotype T-T-C were strongly associated with the allergic type of AD [62]. In our study, we found that CC genotype of IL-18 -137G/C in homozygous model and recessive model, were significantly associated with increased the risk of AD.

There were several limitations in the present meta-analysis. Firstly, AD is a very heterogeneous disease; the severity of disease was not contained in most of included studies, which might restrict the accuracy of our results. Secondly, the number of included studies for some gene mutations was small, or the sample size of included studies was less. Thirdly, the age difference, unknown time of disease onset, and cases with various concomitant atopic diseases added to the between-study heterogeneity, which might influence our results. Fourthly, the contributions of haplotype and interaction effects such as gene-gene or gene-environment to AD require further study.

In conclusions, our results suggested that GA genotype of IL-6 nt565G/A polymorphism, CC genotype of -137G/C polymorphism of IL-18 gene, might be significantly associated with increased the AD risk. Our results might lay a foundation for the later research on the mechanism and treatment of AD. However, it is urgent to conduct more large-scale studies to confirm the relationship between IL gene polymorphisms and the risk of AD.

Disclosure of conflict of interest

None.

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