

Original Article

Interleukin-6 gene -174G/C polymorphism and bronchial asthma risk: a meta-analysis

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Abstract: The Interleukin-6 (IL-6) genetic polymorphism is associated with bronchial asthma, a number of studies have been conducted to investigate the association between IL-6 gene -174G/C polymorphism and bronchial asthma risk. However, the results are inconclusive. This meta-analysis aims to investigate whether -174G/C polymorphism is a potential risk factor for bronchial asthma. We searched Web of Science, PubMed, Google Scholar, China National Knowledge Infrastructure (CNKI) and Wanfang Database from inception through December 1st, 2014. Meta-analysis was performed using the STATA 12.0. Overall, a significantly reduced risk for asthma was found in IL-6 -174 CC genotype (CC vs. GG: OR = 0.51, 95% CI = 0.27-0.96, P = 0.038). Furthermore, analysis by ethnicity indicated that there was a markedly reduced risk for asthma in IL-6 -174 CC genotype in Caucasian (CC vs. GG: OR = 0.51, 95% CI = 0.27-0.96, P = 0.038). Analysis by age indicated that there was a significantly reduced risk for asthma in IL-6 -174 CC genotype in adults (CC vs. GG: OR = 0.47, 95% CI = 0.23-0.97, P = 0.042). In conclusion, the current meta-analysis indicates that IL-6 -174 CC genotype may be a protective factor against asthma in Caucasian and adults.

Keywords: IL-6, polymorphism, asthma, risk, meta-analysis

Introduction

Bronchial asthma is one of the most common chronic inflammatory respiratory diseases, characterized by airway hyper responsiveness, airway inflammation and reversible airway obstruction. The development of asthma appears to be determined by genetic and environmental factors [1, 2]. Numerous studies have reported that there is a significant correlation between the genetic polymorphism of cytokine genes and asthma [3-5]. Interleukin-6 (IL-6) functions as a pleiotropic pro-inflammatory and immunomodulatory cytokine, which regulates T cell differentiation and activation, induces Th2 cytokine production [6]. IL-6 is secreted by a variety of lymphoid and non-lymphoid cells including: T cells, B cells, monocytes, fibroblasts, hepatocytes, airway endothelial cells, alveolar macrophages, adipocytes, myocytes as well as other tissues and cells [7-9]. Accumulated evidences have shown that IL-6 is involved in the development of asthma [10-12].

A single-nucleotide polymorphism (SNP) at position -174 (also called rs1800795) in the

promoter region of the IL-6 gene, which was firstly described by Fishman et al., is located in chromosome 7p21 [13]. This SNP presents guanosine (G) or cytosine (C) at position -174 of IL-6 gene and this variability could be functional, because it modifies transcriptional regulation and cytokine levels, and regulates inflammatory phenotype [13]. Several studies have reported the correlation between IL-6 -174G/C polymorphism and bronchial asthma risk [14-19]. However, the results were contradictory and all above studies were performed in an individual medical center with less sample size. Therefore, it is important to clarify the relationship between IL-6 -174G/C polymorphism and bronchial asthma susceptibility based on all published studies, and the aim of present study is to address this issue using meta-analysis.

Materials and methods

Identification of eligible studies

To identify all eligible studies that investigated the association between IL-6 -174G/C polymorphism and bronchial asthma risk, a comprehen-

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Table 1. Main characteristics of all eligible studies

First author	Year	Country	Ethnicity	Age group	No. of case	No. of control	Case			Control			P for HWE
							GG	GC	CC	GG	GC	CC	
Kosugi	2013	Brazil	Caucasian	Adults	90	144	69	20	1	70	67	7	0.070
Daneshmandi	2012	Iran	Caucasian	Adults	81	124	60	15	6	83	32	9	0.027
Mahdavian	2009	Iran	Caucasian	Mixed	57	139	5	51	1	42	93	4	0.000
Settin	2008	Egypt	Caucasian	Children	69	98	11	52	6	5	87	6	0.000
Trajkov	2008	Macedonia	Caucasian	Adults	74	301	46	25	3	144	132	25	0.492
Liu	2008	China	Asian	Adults	108	88	72	36	0	71	17	0	0.316

HWE: Hardy-Weinberg equilibrium.

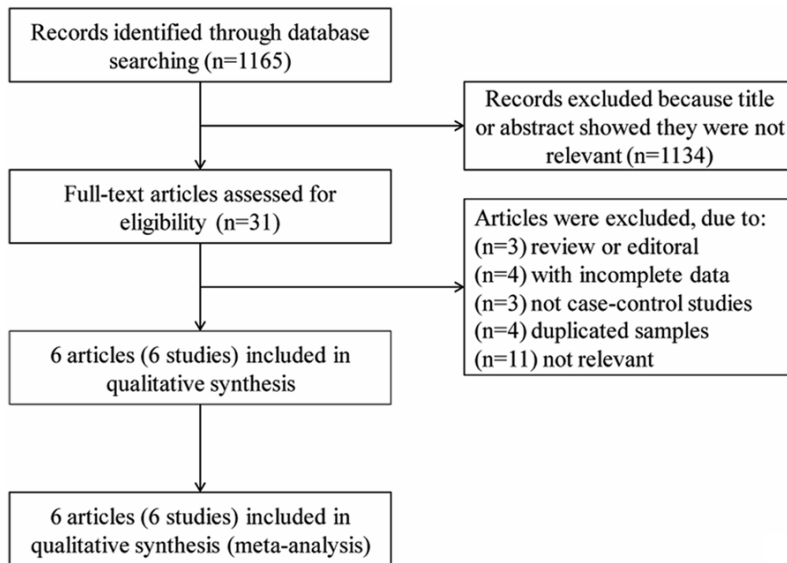


Figure 1. Flowchart shows study selection procedure.

sive electronic search of Web of Science, PubMed, Google Scholar, China National Knowledge Infrastructure (CNKI) and Wanfang Database was performed until December 1st, 2014. We applied various combinations of the following medical subject headings and key words: (interleukin-6 or IL-6 or cytokine) and (polymorphism or variant or variation or SNP) and (asthma or asthmatic). Furthermore, the reference lists of reviews and retrieved articles were manually screened for additional studies. No restrictions were placed on language, and only published studies with full-text articles were included.

Inclusion and exclusion criteria

The studies identified from the above mentioned databases were screened by two independent authors (Fangwei Li and Xinming Xie) according to the following predesigned inclu-

sion criteria: I) case-control design; II) evaluating the correlation of IL-6 -174G/C polymorphism with asthma risk; and III) providing sufficient data to calculate the odds ratio (OR) and its corresponding 95% confidence interval (CI). When several studies with overlapping data were eligible, those with smaller sample size or less reliability were excluded. In addition, studies without detailed information were excluded after the efforts to extract data from the original paper or contact the corresponding authors failed.

Data extraction

Data of eligible studies were extracted by two reviewers (Fangwei Li and Shaojun Li) independently and in duplicate according to the predesigned data-collection form. The following information was extracted: first author, publication year, country of origin, ethnicity, age, number of both cases and control subjects and phenotypic distribution in both groups. Different ethnic descents were categorized as Caucasian, Asian. Different age groups were categorized as adult, children. Discrepancies occurring during the process of study inclusion and data extraction were resolved by discussion with a third reviewer (Rui Ke), and consensus on each item was achieved eventually.

Data analysis

The statistical analysis was conducted using STATA12.0 software (Stata Corporation, College

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Table 2. The results of meta-analysis

	CC vs. GC + GG			CC vs. GG			C allele vs. G allele			CC + GC vs. GG		
	OR (95% CI)	P _(z)	I ² (%)	OR (95% CI)	P _(z)	I ² (%)	OR (95% CI)	P _(z)	I ² (%)	OR (95% CI)	P _(z)	I ² (%)
Overall	0.72 (0.40, 1.29)	0.270	0.0	0.51 (0.27, 0.96)	0.038	2.8	0.86 (0.54, 1.35)	0.504	81.0	0.81 (0.38, 1.74)	0.586	86.2
Caucasian	0.72 (0.40, 1.29)	0.270	0.0	0.51 (0.27, 0.96)	0.038	2.8	0.75 (0.47, 1.18)	0.209	79.1	0.61 (0.31, 1.21)	0.297	83.6
Adults	0.62 (0.29, 1.33)	0.221	0.0	0.47 (0.23, 0.97)	0.042	28.4	0.74 (0.40, 1.36)	0.334	82.4	0.69 (0.32, 1.48)	0.339	84.7

OR: odds ratio; CI: confidence interval; P_(z): P-value of pooled effect. Significant results (P < 0.05) for overall effect were marked in bold characters.

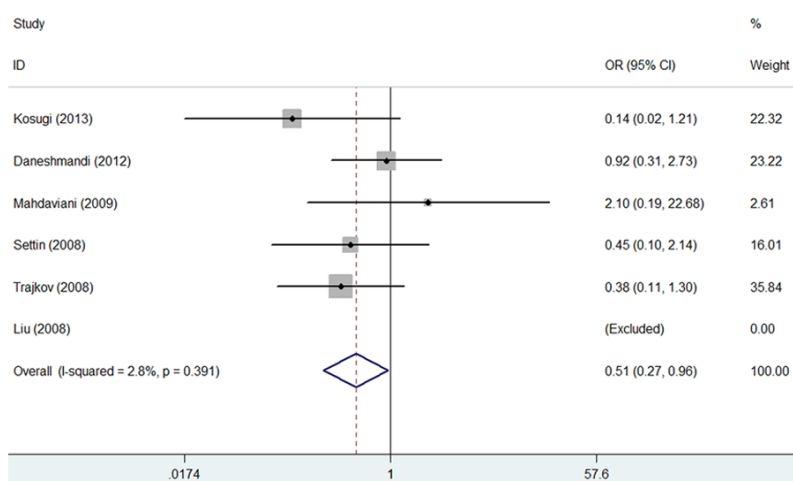


Figure 2. Forest plot for the association between IL-6-174G/C polymorphism and bronchial asthma risk in total analysis (CC vs. GG).

Station, Texas, USA). Hardy-Weinberg equilibrium (HWE) in controls was tested by the chi-square test, and it was considered statistically significant when P-value was less than 0.05. Heterogeneity among studies was examined with the X²-based Q testing and I² statistics [20]. If there was a significant heterogeneity (P < 0.10), a random-effects model (the DerSimonian and Laird method) was selected to pool the data [21]. Otherwise, a fixed-effects model (the Mantel-Haenszel method) was selected to pool the data [22]. The pooled odds ratio (OR) of asthma was performed for recessive model (CC vs. GC + GG), homozygote comparison (CC vs. GG), allele model (C allele vs. G allele) and dominant model (CC + GC vs. GG) respectively. The significance of the combined OR determined by a Z-test and two-sided P value < 0.05 was considered significant. To explore the source of the heterogeneity, Galbraith plot was used. Publication bias was examined with Begg's test and Egger's test [23, 24] and the P value < 0.10 indicated significant publication bias.

Results

Characteristics of eligible studies

A total of 1165 papers were obtained with the initial search of databases. After screening, six case-control studies with a total of 1373 participants (479 cases and 894 controls) fulfilled the inclusion criteria, from which genotype data of IL-6 -174G/C polymorphism were obtained. As for ethnicity, 5 studies were of Caucasian, 1 study was of Asian. As for age, 4 studies were of adults, 1 study was of children, and

1 study was of mixed (1.5-33 years, **Table 1**). The qualities of these studies were considered accessible for the meta-analysis. The flow chart of selection of studies and reasons for exclusion are presented in **Figure 1**.

Meta-analysis of IL-6 -174G/C polymorphism and bronchial asthma

A summary of association between IL-6 -174G/C polymorphism and bronchial asthma risk is shown in **Table 2**.

Overall, a significantly reduced risk was observed in CC genotype (CC vs. GG: OR = 0.51, 95% CI = 0.27-0.96, P = 0.038; **Figure 2**; **Table 2**) and no markedly increased or reduced risk for bronchial asthma under other genetic models was detected (CC vs. GC + GG: OR = 0.72, 95% CI = 0.40-1.29, P = 0.270; C allele vs. G allele: OR = 0.86, 95% CI = 0.54-1.35, P = 0.504; CC + GC vs. GG: OR = 0.81, 95% CI = 0.38-1.74, P = 0.586; **Table 2**).

In the subgroup analysis by ethnicity, results indicated a significantly reduced risk for asth-

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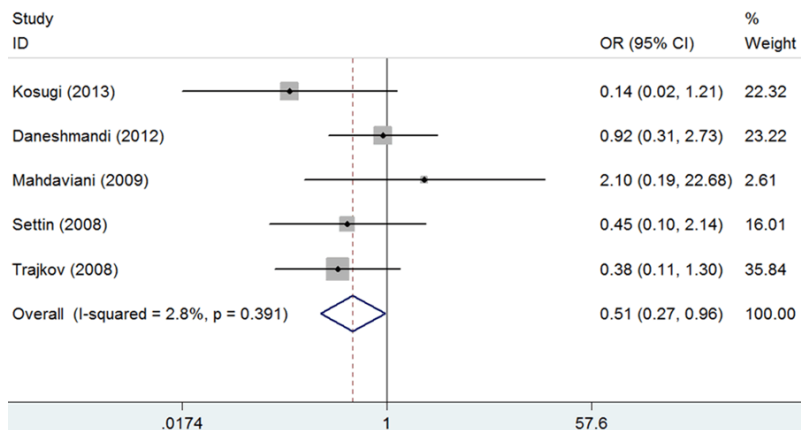


Figure 3. Forest plot for the association between IL-6 -174G/C polymorphism and bronchial asthma risk in Caucasian (CC vs. GG).

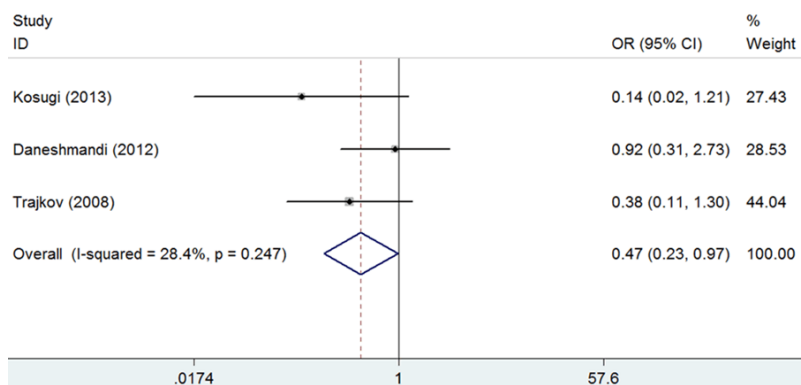


Figure 4. Forest plot for the association between IL-6 -174G/C polymorphism and bronchial asthma risk in adults (CC vs. GG).

ma in CC genotype in Caucasian (CC vs. GG: OR = 0.51, 95% CI = 0.27-0.96, P = 0.038; **Figure 3; Table 2**). There was only one study [19] in Asian, in which CC genotype was not found, so no subgroup analysis was performed. After subgroup analysis by age, results indicated a markedly reduced risk for asthma in CC genotype in adults (CC vs. GG: OR = 0.47, 95% CI = 0.23-0.97, P = 0.042; **Figure 4; Table 2**). There was only one study in children [17] or mixed (1.5-33 years) [16] respectively, so no subgroup analysis was performed.

Sensitivity analysis

Sensitivity analysis was also performed to explore the potential influence of each individual study on the overall results by deleting one single study each time from the pooled analysis. No substantial change was demonstrated

in the overall studies, indicating that no individual study could affect the pooled OR significantly (figure not shown).

Heterogeneity and publication bias

Among the four genetic models, significant heterogeneity was observed in allele model (C allele vs. G allele) and dominant model (CC + GC vs. GG) with P-value < 0.10. After stratifying for ethnicity and age respectively, significant heterogeneity was observed in Caucasian and adults (**Table 2**). So the Galbraith plot was used to find the source of the heterogeneity. As shown in **Figure 5**, three studies were the outliers [14, 16, 19]. For publication bias, results were observed with all P-value > 0.1 of Begg's test and Egger's test (**Table 3**).

Discussion

Human genetic study is an indispensable approach in understanding the molecular basis of diseases including bronchial asthma. Many candidate genes, including IL-6 [14-16], IL-4 [25], IL-13 [26, 27], tumor necrosis factor [27], beta 2-adrenoceptor [28, 29] and so on, have been reported to be involved in bronchial asthma susceptibility. IL-6 is a potential mediator of inflammation in asthma, which has been shown to be increased in serum and bronchoalveolar lavage fluid (BALF) during stable condition and exacerbation, predicting a faster decline in FEV₁ [9, 11]. IL-6 -174G > C has been shown to be associated with increased risk of cardiovascular events and factors such as C-reactive protein and hypertension [30-32]. The results of the relationship between IL-6 -174G > C polymorphism and bronchial asthma risk are inconsistent. Therefore, it is critical to systematically evaluate all studies from different groups and to quantify the overall association between IL-6 -174G > C polymorphism and bronchial asthma.

IL-6 gene polymorphism and asthma risk

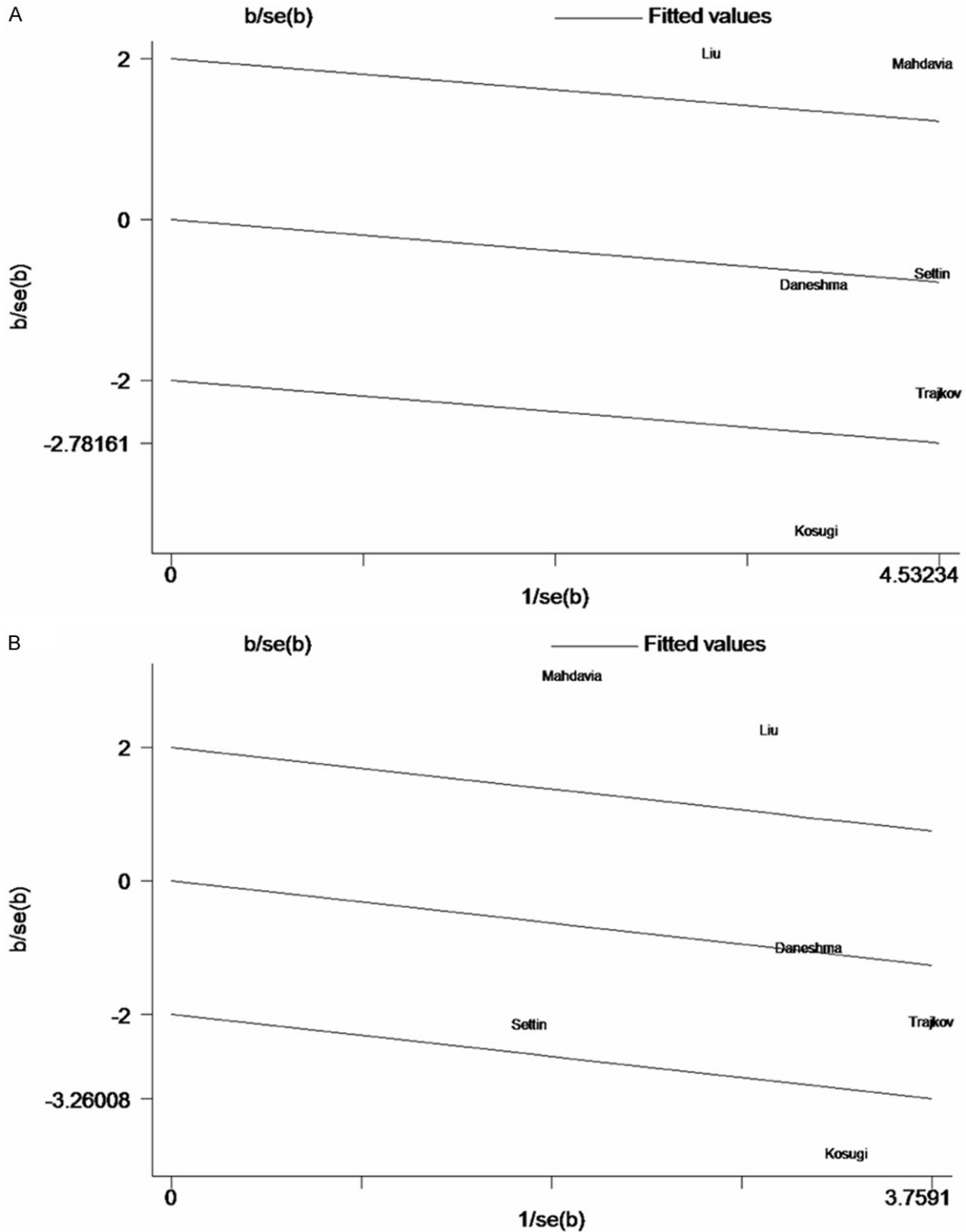


Figure 5. Galbraith plots for the association between IL-6 -174G/C polymorphism and bronchial asthma. A. C allele vs. G allele; B. CC + GC vs. GG.

In this study, our results indicated that IL-6 -174 CC genotype carriers had a reduced risk for bronchial asthma. Furthermore, analysis by ethnicity indicated that IL-6 -174 CC genotype

carriers had a significantly reduced risk for asthma in Caucasian. There was only one study [19] in Asian, in which the CC genotype was not found, so no subgroup analysis was performed.

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Table 3. Results of publication bias test

Polymorphism	Compared genotype	Begg's test		Egger's test	
		z value	P value	t value	P value
-174G/C	CC vs. GC + GG	0.73	0.462	-1.38	0.261
	CC vs. GG	-0.24	1.000	-0.26	0.815
	C allele vs. G allele	0.38	0.707	0.33	0.755
	CC + GC vs. GG	0.75	0.452	0.70	0.525

In addition, analysis by age indicated that IL-6 -174 CC genotype carriers had a markedly reduced risk for asthma in adults. We could not perform analysis in children due to only one study [17] included.

To our knowledge, this is the first meta-analysis about IL-6 gene polymorphism and bronchial asthma susceptibility. In the present meta-analysis, we have combined six eligible studies with 479 cases and 894 controls to yield summary results, indicating that IL-6 -174 G/C polymorphism might be related to asthma risk in the overall population. Furthermore, we considered that CC genotype was a protective factor against asthma in Caucasian according to ethnicity and a protective factor against asthma in adults according to age. Our results are supported by several studies, which found that IL-6 -174G/C polymorphism modified transcriptional regulation and IL-6 levels [13], meanwhile IL-6 might be involved in the pathophysiology of bronchial asthma [10, 33]. However, some other studies did not find evidence for association between IL-6 -174G/C polymorphism and circulating IL-6 Level and considered IL-6 a byproduct of ongoing inflammation in the airways [34-37]. It is suggested that studies based on larger well-designed populations are still needed to clarify the relationships between IL-6 gene polymorphism and bronchial asthma susceptibility.

The heterogeneity needs to be mentioned when interprets the meta-analysis results. For the stable results of -174G/C polymorphism in recessive model (CC vs. GC + GG) and homozygote comparison (CC vs. GG), there was no or low heterogeneity (indicated by I^2 -statistics) among studies. However, obvious heterogeneity was observed in allele model (C allele vs. G allele) and dominant model (CC + GC vs. GG). After stratifying by ethnicity and age respectively, relatively significant heterogeneity was still observed in Caucasian and adults, which may have been responsible for the negative results.

Furthermore, Galbraith plot was performed to explore the source of heterogeneity. As shown in **Figure 5**, it is possible that three studies [14, 16, 19] may have been the main source of heterogeneity.

Some limitations should be addressed when interpreting the results: i) the limited number of

bronchial asthma cases and control subjects may lead to a relatively small power; ii) in some cases, heterogeneity was not resolved after subgroup analyses, suggesting that other factors such as the differences in gender, lifestyle factors or clinical characteristics might have caused heterogeneity; not all the control subjects were age or sex matched to cases, which was likely one of the causes for heterogeneity; iii) it is well acknowledged that many other factors, such as gene-gene or gene-environment interactions, may affect the risk for bronchial asthma; and iv) only published studies with sufficient data were included and publication bias may have occurred even though the result of Begg's test or Egger's test did not detect it.

In conclusion, the current meta-analysis indicates that IL-6 -174 CC genotype may be a protective factor against asthma in Caucasian and adults. Larger and well-designed studies based on different ethnic groups are needed to confirm our result.

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Disclosure of conflict of interest

None.

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