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ORIGINAL ARTICLE

No Association Between −*159C/T* Polymorphism of the *CD14* Gene and Asthma Risk: a Meta-Analysis of 36 Case-Control Studies

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Abstract—Numerous studies have evaluated the association between −*159C/T* polymorphism of the *CD14* gene and asthma risk; however, these studies have yielded inconsistent results. We performed meta-analyses to investigate the association between *CD14-159C/T* polymorphism and asthma risk. Studies were identified from PubMed, Embase, and two Chinese databases. Odds ratios (ORs) with 95 % confidence interval (CI) were used to evaluate the strength of association. Thirty-six studies were collected for meta-analysis, which involved 6954 cases and 7525 controls. In the overall populations, no significant association between the *CD14-159C/T* polymorphism and asthma risk was found for the dominant (OR=0.90, 95 % CI=0.81–1.01, *P*=0.08) or other models; stratified analyses indicated that the *CD14-159C/T* polymorphism was not associated with asthma risk in Caucasians or Asians or adults or children. Among the atopic asthma populations, no significant results were observed in the all-combined or subgroup analyses. This meta-analysis demonstrates that the *CD14-159C/T* polymorphism may not be a risk factor for asthma.

KEY WORDS: *CD14*; polymorphism; asthma; meta-analysis.

INTRODUCTION

Asthma is one of the most common chronic respiratory diseases worldwide, characterized by airway inflammation, airway hyper-responsiveness, variable airflow obstruction, and allergy [1]. Although environmental exposures such as allergens may be risk factors for asthma development, both family- and twin-based studies indicated the importance of genetic components [2]. Therefore, the etiology of asthma is considered to be interactions between environmental factors and genetic characteristics of an individual [3]. It is not surprising that numerous studies have investigated the associations between genetic polymorphisms and susceptibility to asthma, and among them, the cluster of differentiation 14 (*CD14*) gene has been widely studied [3, 4].

The gene-encoding *CD14* is located on chromosome 5q31, a region that is linked to asthma in genome-wide linkage studies [5]. Two protein forms are encoded by the *CD14* gene: (i) a membrane receptor expressed on the surface of monocytes, macrophages, and neutrophils and (ii) a soluble form in serum [6]. CD14 is the principal receptor for bacterial lipopolysaccharides (LPSs); upon binding, this complex together with co-receptors toll-like receptor 4 can activate the immune system [3]. The subsequent release of pro-inflammatory cytokines can promote Th1 differentiation of naive T cells resulting in a lower prevalence of allergies such as asthma [3, 7].

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Many studies have studied the associations between asthma susceptibility and polymorphisms in *CD14* gene, especially the *−159C/T* polymorphism which was first investigated as a candidate one for atopy [8]. However, inconsistent results were observed. This inconsistency may be attributed to the relatively small sample size of the individual studies. A meta-analysis can provide more reliable evidence by combining the data from different studies. Although there have been three meta-analyses concerning the association between the *CD14-159C/T* polymorphism and asthma risk [1, 9, 10], further investigations are required for the following reasons. The first meta-analysis only included the earlier studies, and no subgroup analyses were presented [10]. The second one had some significant errors in including studies and abstracting data [9]. The last meta-analysis was performed in 2011, and a number of new studies with more data have been published since 2011 [8, 11–19]. In light of this, we performed an updated meta-analysis to re-investigate the association of the *CD14-159C*/*T* polymorphism with asthma susceptibility.

MATERIALS AND METHODS

Identification of Eligible Studies

Relevant studies were identified from PubMed, Embase, and two Chinese databases (Wanfang and China National Knowledge Infrastructure (CNKI)) up to 8 May 2015. The search strategy was as follows: "*CD14*" and "asthma" or "asthmatic" and "mutation" or "polymorphism" or "variant." There was no restriction on languages or publication date. Also, the references of relevant reviews or meta-analyses were searched manually to identify additional studies. Studies that fulfilled the following criteria were incorporated into the meta-analysis: (1) evaluating *CD14-159C*/*T* polymorphism and asthma risk, (2) using a case-control design, and (3) providing enough data for calculating odds ratios (ORs) and 95 % confidence interval (CI). Exclusive criteria in this meta-analysis were (1) studies containing overlapping data; (2) design based on family or sibling pairs; and (3) some publication types such as comments, abstracts, reviews, and proceedings. For the studies with overlapping data, the one with the largest sample was selected.

Data Extraction

Two reviewers independently extracted the information from each included publication: author, year of publication, country of origin, ethnicity, age group, atopic status, sample size, asthma definition, and genotype distribution among cases and controls. Any discrepancy was resolved via discussing or consulting two additional authors.

Statistical Analysis

ORs and 95 % CI were employed to evaluate the strength of the associations between the *CD14-159C*/*T*

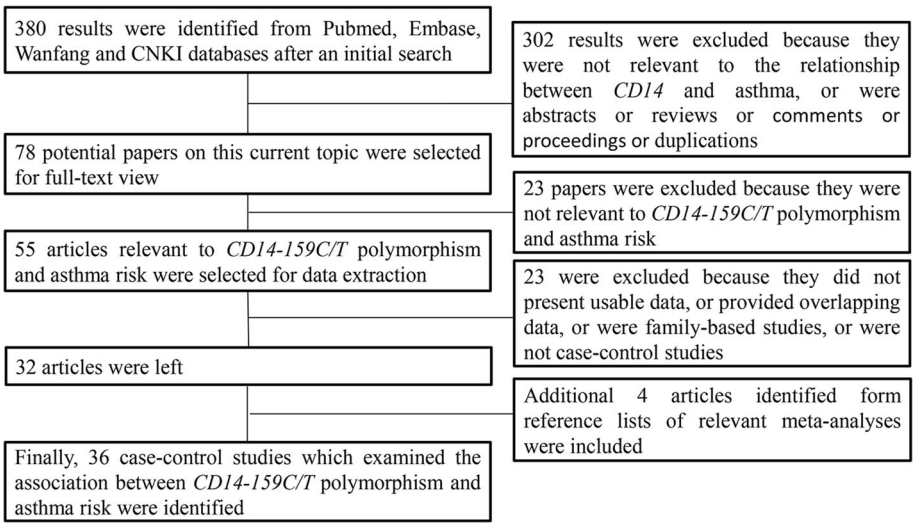

Fig. 1. Flow chart of included/excluded studies using the criteria before the meta-analysis.

Table 1. Main Characteristics of Studies Included in the Meta-Analysis

First author (year)	Country	Ethnicity	Age group	Atopic status	Case/control (*n*)	Asthma definition
Zhang *et al*. (2015)	China	Asian	Children	Atopic	362/384	Symptoms, physical examination, and history
Wang *et al*. (2014)	China	Asian	Adult	NM	126/126	GINA
Sahin *et al*. (2014)	Turkey	Caucasian	Adult	Atopic and non-atopic	131/75	GINA
Hussein *et al*. (2013)	Egypt	African	Children	Atopic and non-atopic	500/150	ATS
Bose *et al*. (2013)	India	Asian	Adult	NM	20/20	NM
Yazdani *et al*. (2012)	Iran	Asian	NM	NM	20/87	NM
Perin *et al*. (2011)	Slovenia	Caucasian	Children	Atopic and non-atopic	247/158	ATS
Micheal *et al*. (2011)	Pakistan	Asian	Adult	Atopic	110/120	Symptoms and history
Wu *et al*. (2011)	China	Asian	Adult	NM	188/60	History, symptoms, and lung function
Zaborowski *et al* (2011)	Poland	Caucasian	NM	Atopic and non-atopic	106/159	NM
Kuo Chou *et al*. (2010)	Taiwan	Asian	Children	Mixed	116/232	ATS
Wu *et al*. (2010)	China	Asian	Children	Mixed	252/227	ATS
Bjørnvold *et al*. (2009)	Norway	Caucasian	Children	Atopic	103/479	Symptoms, medication, and doctor's diagnosis
Smit *et al*. (2009)	France	Caucasian	Adult	Mixed	223/554	Questionnaire
Wang *et al*. (2009)	Taiwan	Asian	Children	Mixed	447/509	History, symptoms, lung function, and GINA
Kowal *et al*. (2008)	Poland	Caucasian	Adult	Atopic	372/160	GINA
de Faria *et al*. (2008)	Brazil	Mixed	Children	Atopic	88/202	GINA
Lachheb *et al*. (2008)	Tunisia	Caucasian	Children	Atopic and non-atopic	210/224	GINA
Smit *et al*. (2007)	Denmark	Caucasian	Adult	Mixed	100/88	Questionnaire
Bernstein *et al*. (2006)	Canada	Caucasian	NM	Mixed	62/75	Gold standard for occupational asthma
Hong *et al*. (2007)	Korea	Asian	Children	Atopic and non-atopic	626/153	ATS
Zambelli-Weiner *et al*. (2005)	USA	Mixed	NM	Mixed	293/454	NM
Kedda *et al*. (2005)	Australia	Caucasian	Adult	Atopic and non-atopic	568/443	Questionnaire and spirometric tests
Sharma *et al*. (2004)	India	Asian	NM	Atopic	187/227	ATS
Heinzmann *et al*. (2003)	Germany	Caucasian	Children	NM	182/261	History, medication, and lung function
Woo *et al*. (2003)	USA	Mixed	Adult	Atopic and non-atopic	175/61	ATS
Sengler *et al*. (2003)	German	Caucasian	Children	Mixed	84/119	History, physical examination, and lung function
Lis *et al*. (2001)	Poland	Caucasian	Children	Atopic	50/73	Wheezing and positive bronchial challenge test
Koppelman *et al*. (2001)	Netherlands	Caucasian	Adult	Mixed	159/158	Questionnaire, doctor's diagnosis, and lung function
Alexis *et al*. (2001)	USA	NM	Adult	Atopic	9/7	ATS
Hakonarson *et al*. (2001)	Iceland	Caucasian	Mixed	Atopic	94/94	ATS
Chan *et al*. (2008)	Hong Kong	Asian	Children	Atopic and non-atopic	269/141	ATS
Chen *et al*. (2009)	China	Asian	Mixed	NM	150/150	Prevention of Chinese preventive guideline for asthma 2003
Cui *et al*. (2003)	China	Asian	Children	Atopic	143/72	Allergic asthma definition
Murk *et al*. (2011)	USA	Mixed	Children	Atopic	97/473	Doctor's diagnosis, wheezing, medication use, and allergies
Park *et al*. (2006)	Korea	Asian	Adult	NM	85/550	History, symptoms, and lung function

Mixed data could not be separately extracted, except for the study by Woo *et al*., in which the data for Caucasians could be separately extracted; data for atopic asthma and non-atopic asthma patients could be separately extracted

NM not mentioned, *ATS* American Thoracic Society, *GINA* Global Initiative for Asthma

polymorphism and asthma risk in the dominant (TT+TC vs. CC), recessive (TT vs. TC+CC), codominant (TT vs. CC), and allelic models (T vs. C). The pooled ORs were calculated using a fixed-effect or random-effect model according to between-study heterogeneity, which was checked by Q test and I^2 statistics [20]. If the P value for the Q test was>0.10, the pooled OR was calculated with the fixed-effect model; otherwise, the random-effect model was used [9]. I^2 values were used to test the between-study heterogeneity quantitatively. I^2 values range between 0 and 100 %, and the values of 25, 50, and 75 % were nominally assigned as low, moderate, and high heterogeneity, respectively [21]. The statistical significance of the pooled ORs was analyzed by the Z test, and a P value of <0.05 was considered statistically significant. Subgroup analyses were conducted by ethnicity, age, and atopic status. For assessing the age—atopic and ethnicity—atopic associations, we further stratified the atopic asthma populations by age and ethnicity.

Hardy–Weinberg equilibrium (HWE) in controls was assessed with the chi-squared test (significance set at $P<0.05$). Sensitivity analysis was performed to check the stability of the results using two methods: (i) removing studies that deviated from HWE in controls and (ii)

Table 2. Genotype and Allele Distributions of *CD14-159C/T* Polymorphism in Cases and Controls

First author (year)	HWE	Cases			Controls			Cases		Controls	
		CC	CT	TT	CC	CT	TT	C	T	C	T
Alexis *et al*. (2001)	Yes	3	2	4	3	3	1	8	10	9	5
Bernstein *et al*. (2006)	Yes	17	33	12	15	45	15	67	57	75	75
Bjørnvold *et al*. (2009)[a]	Yes	39	49	15	161	233	85	127	79	555	403
Bose *et al*. (2013)	Yes	3	12	5	2	14	4	18	22	18	22
Chan *et al*. (2008)	Yes	55	134	80	26	77	38	244	294	129	153
Chen *et al*. (2009)	Yes	63	62	25	40	68	42	188	112	148	152
Cui *et al*. (2003)	Yes	27	67	49	10	42	20	121	165	62	82
de Faria *et al*. (2008)	No	27	41	20	63	131	8	95	81	257	147
Hakonarson *et al*. (2001)[a]	Yes	31	46	17	29	46	19	108	80	104	84
Heinzmann *et al*. (2003)	Yes	51	89	42	79	124	58	191	173	282	240
Hong *et al*. (2007)	Yes	113	284	229	22	71	60	510	742	115	191
Hussein *et al*. (2013)	Yes	210	215	75	68	70	12	635	365	206	94
Kedda *et al*. (2005)	Yes	148	284	136	124	226	93	580	556	474	412
Koppelman *et al*. (2001)	Yes	51	76	32	31	85	42	178	140	147	169
Kowal *et al*. (2008)	Yes	141	152	79	42	73	45	434	310	157	163
Kuo Chou *et al*. (2010)	Yes	17	64	35	45	118	69	98	134	208	256
Lachheb *et al*. (2008)	No	46	90	74	36	72	116	182	238	144	304
Lis *et al*. (2001)	Yes	20	24	6	28	34	11	64	36	90	56
Micheal *et al*. (2011)	Yes	25	53	32	40	49	31	103	117	129	111
Murk *et al*. (2011)	Yes	31	55	11	137	236	100	117	77	510	436
Park *et al*. (2006)	Yes	16	39	30	90	267	193	71	99	447	653
Perin *et al*. (2011)	Yes	82	101	64	49	70	39	265	229	168	148
Sahin *et al*. (2014)	Yes	26	63	42	15	36	24	115	147	66	84
Sengler *et al*. (2003)	No	23	43	18	26	72	21	89	79	124	114
Sharma *et al*. (2004)	Yes	43	92	52	30	112	85	178	196	172	282
Smit *et al*. (2007)	Yes	34	47	19	26	47	15	115	85	99	77
Smit *et al*. (2009)	Yes	49	107	67	145	276	133	205	241	566	542
Wang *et al*. (2009)	Yes	57	230	160	96	236	177	344	550	428	590
Wang *et al*. (2014)	Yes	23	62	41	25	61	40	108	144	111	141
Woo *et al*. (2003)	Yes	46	94	35	20	35	6	186	164	75	47
Wu *et al*. (2010)	Yes	54	117	81	31	121	75	225	279	183	271
Wu *et al*. (2011)	Yes	23	90	75	5	30	25	136	240	40	80
Yazdani *et al*. (2012)	Yes	7	9	4	15	34	38	23	17	64	110
Zaborowski *et al*. (2011)	Yes	32	53	21	53	73	33	117	95	179	139
Zambelli-Weiner *et al*. (2005)	Yes	138	137	18	197	206	51	413	173	600	308
Zhang *et al*. (2015)	Yes	100	163	99	120	190	74	363	361	430	338

HWE Hardy–Weinberg equilibrium

[a] Genotype frequencies were not reported in the original articles but were estimated by the meta-analysis [1]

excluding a single study each time if the statistically significant results were found. The potential publication bias was examined by visual inspection of Begg's funnel plots and Egger's test. All statistical tests were conducted with Revman 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 (StataCorp LP, College Station, TX, USA) software.

RESULTS

Main Characteristics of Included Studies

Figure 1 provides a flowchart detailing the procedure for study identification. Finally, 36 case-control studies were included [7, 8, 11–19, 22–46]. The main characteristics of the included studies and genotype distributions of *CD14-159C/T* polymorphism are presented in Tables 1 and 2, respectively. Except one study without ethnic information [40], 15 studies were performed in Asians, 15 in Caucasians, one in Africans, and four in the populations of mixed ethnicity. Thirteen studies were performed in adults, 16 in children, and seven in undefined or mixed age groups. Eleven studies only included atopic asthma populations; moreover, 18 studies included both non-atopic and atopic asthma populations; however, data could not be extracted separately in nine studies of them. Seven studies did not provide the atopic status of subjects. This information was summarized in Table 1. Based on the same data set, the genotype frequency data for atopic asthma subgroup in one included study [43] were abstracted from another study that had been excluded [47]. The distribution of the *CD14-159C/T* polymorphism in controls was inconsistent with HWE in three studies [28, 29, 37] (Table 2).

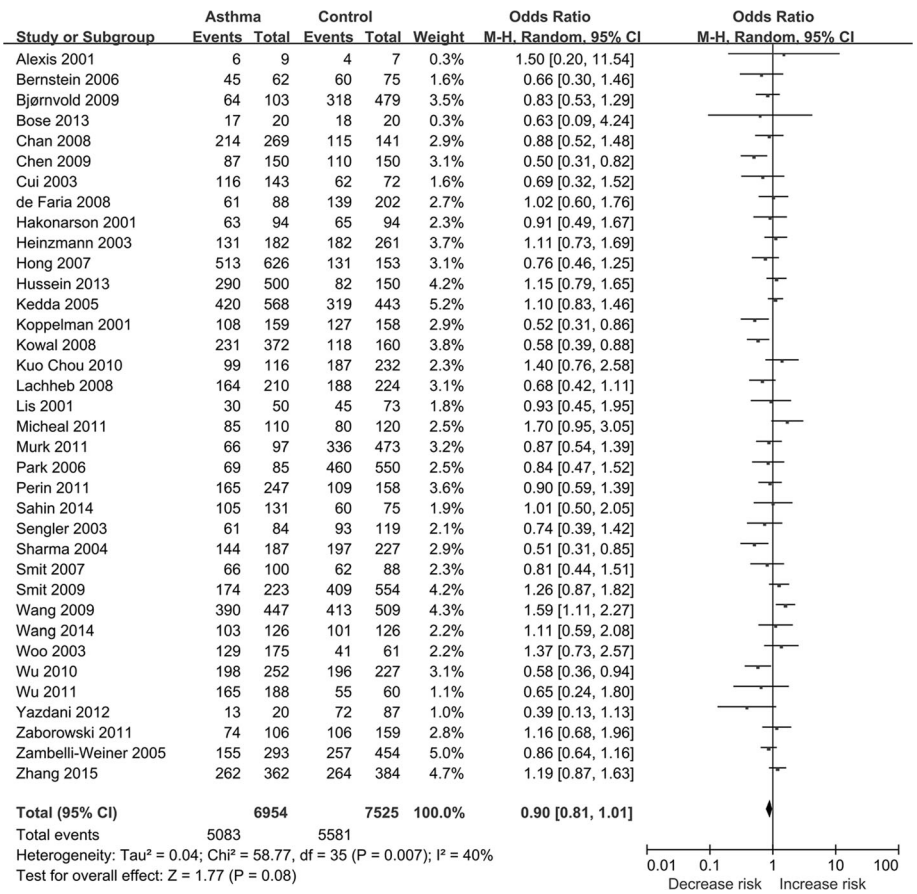

Fig. 2. Meta-analysis of the association between *CD14-159C/T* polymorphism and asthma risk among the overall populations in the dominant model, using a random-effect model. The *squares* and *horizontal lines* correspond to the odds ratios (ORs) and 95 % confidence interval (CI) in each study. The *black diamond* represents the pooled OR and 95 % CI.

Meta-Analysis of *CD14-159C/T* Polymorphism and Asthma Risk in the Overall Populations

A total of 6954 cases and 7525 controls in 36 case-control studies were included in meta-analysis. As shown in Fig. 2, the between-study heterogeneity of the dominant model (TT+TC vs. CC) for all 36 studies was tested by Q test and the corresponding P value was 0.007. Thus, a random-effect model was chosen for data synthesis. The pooled OR for all 36 studies was 0.90 (95 % CI=0.81–1.01, P=0.08; Fig. 2), indicating no significant association between this polymorphism and asthma risk in the dominant model. Similarly, no statistically significant associations were observed in the recessive, codominant, or allelic model. Summary results of all the genetic comparisons are listed in Table 3.

Stratified Analyses by Ethnicity, Age, and Atopic Status in the Overall Populations

For the subgroup analysis by ethnicity, no association was found between *CD14-159C*/*T* polymorphism and asthma risk among Caucasians (OR=0.91, 95 % CI=0.77–1.06, P=0.22) or Asians (OR=0.87, 95 % CI=0.68–1.10, P=0.25) in the dominant model; there were no significant results in the other models (Table 3). Stratification by age indicated no significant associations among adults (TT+TC vs. CC OR=0.95, 95 % CI=0.77–1.17, P=0.63) or children (TT+TC vs. CC OR=0.99, 95 % CI=0.88–1.11, P=0.81) in the dominant or other models (Table 3). The subgroup analysis by atopic status revealed no associations of this polymorphism with asthma risk among the atopic asthma patients, non-atopic asthma patients, or mixed atopic asthma patients in any model (Table 3).

Stratified Analyses in the Atopic Asthma Populations

Twenty eligible studies (3642 cases and 3806 controls) performed among the atopic asthma populations were identified for data analysis. Stratified analyses were conducted according to ethnicity and age. No matter which genetic comparison model we used, there were still no significantly statistical results in any subgroup analysis. Summary of the meta-analysis results is listed in Table 3.

Sensitivity Analysis

In the overall and stratified analyses, the conclusions of non-significance were stable in all the genetic models

Table 3. Meta-Analyses of the Associations Between *CD14-159C/T* Polymorphism and Asthma Risk

	n	Cases/controls (*n*)	TT+TC vs. CC			TT vs. TC+CC			TT vs. CC			T vs. C		
			OR [95 % CI]	*P*	I^2	OR [95 % CI]	*P*	I^2	OR [95 % CI]	*P*	I^2	OR [95 % CI]	*P*	I^2
Total	36	6954/7525	0.90 [0.81, 1.01]	0.08	40 %	0.99 [0.86, 1.13]	0.84	58 %	0.92 [0.76, 1.10]	0.35	63 %	0.95 [0.88, 1.03]	0.23	59 %
Subgroup by ethnicity														
Asian	15	3101/3058	0.87 [0.68, 1.10]	0.25	62 %	0.98 [0.84, 1.15]	0.82	37 %	0.87 [0.65, 1.16]	0.34	64 %	0.94 [0.82, 1.08]	0.37	63 %
Caucasian	16	2833/3169	0.91 [0.77, 1.06]	0.22	36 %	0.95 [0.80, 1.14]	0.59	43 %	0.90 [0.72, 1.14]	0.38	50 %	0.94 [0.83, 1.06]	0.32	58 %
Subgroup by age														
Adults	13	2266/2422	0.95 [0.77, 1.17]	0.63	42 %	1.07 [0.93, 1.24]	0.34	12 %	1.01 [0.76, 1.34]	0.94	49 %	1.00 [0.87, 1.15]	0.96	51 %
Children	16	3776/3857	0.99 [0.88, 1.11]	0.81	29 %	1.08 [0.87, 1.35]	0.48	70 %	1.04 [0.80, 1.35]	0.78 %	66	1.00 [0.89, 1.11]	0.95	56 %
Subgroup by atopic status														
Atopic	20	3642/3806	0.92 [0.79, 1.07]	0.28	41 %	1.09 [0.85, 1.40]	0.50	75 %	1.02 [0.76, 1.37]	0.91 %	73	0.98 [0.86, 1.13]	0.82	70 %
Atopic Asian	6	1531/1048	0.91 [0.64, 1.28]	0.57	61 %	1.06 [0.79, 1.42]	0.70	59 %	0.95 [0.60, 1.50]	0.83 %	70	1.00 [0.80, 1.24]	0.9	69 %
Atopic children	11	2119/2460	0.99 [0.85, 1.14]	0.88	8 %	1.22 [0.83, 1.79]	0.32	82 %	1.14 [0.75, 1.72]	0.53 %	76	1.03 [0.86, 1.23]	0.74	71 %
Atopic Caucasian	10	1667/1926	0.87 [0.75, 1.01]	0.08	20 %	0.89 [0.69, 1.15]	0.38	49 %	0.84 [0.62, 1.12]	0.23 %	45	0.89 [0.76, 1.04]	0.13	53 %
Atopic adults	6	1187/866	1.03 [0.73, 1.46]	0.87	55 %	1.11 [0.90, 1.36]	0.35	40 %	1.16 [0.72, 1.87]	0.54	61 %	1.06 [0.83, 1.37]	0.62	64 %
Non-atopic	9	781/1515	1.06 [0.72, 1.58]	0.75	67 %	0.86 [0.59, 1.23]	0.40	59 %	0.97 [0.54, 1.74]	0.92 %	74	0.98 [0.74, 1.29]	0.87	76 %
Mixed	18	9136/7960	0.95 [0.82, 1.10]	0.49	43 %	1.00 [0.86, 1.17]	0.97	48 %	0.97 [0.78, 1.21]	0.79 %	57	0.98 [0.89, 1.08]	0.66	53 %

n number of studies or subjects (cases and controls), *OR* odds ratio, *CI* confidence interval, *P* *P* value for *Z* test

when removing studies that deviated from HWE. We did not sequentially exclude a single study each time because no statistically significant results were observed.

Heterogeneity and Publication Bias

Between-study heterogeneity was observed during most of the meta-analyses in the overall and subgroup populations, which was indicated by I^2 values (Table 3). We used Begg's funnel plots to graphically estimate the publication bias, and found the relatively symmetric distribution of funnel plots in the dominant (Fig. 3) and other comparison models (figures not shown), which suggested the absence of publication bias. Moreover, the results of Egger's test also indicated lack of publication bias in the dominant (P_{Egger}=0.116), recessive (P_{Egger}=0.774), codominant (P_{Egger}=0.524), or allelic model (P_{Egger}=0.274).

DISCUSSION

Although multifactors contribute to asthma susceptibility, genetic predisposition is regarded as one of the important determinants. Many promising candidate genes for asthma have been identified on chromosome 5q31.1 [48], and *CD14* gene is such one. Variants in the promoter region of the *CD14* gene may modify the structure of the CD14 protein and influence the CD14-LPS interaction [19]. Baldini *et al*. first reported the *−159C/T* polymorphism in the promoter region of *CD14* gene [49], which was found to be associated with altered levels of soluble CD14 and IgE in various ethnic patients with asthma [15]. The above facts indicate that the *CD14-159C/T* polymorphism might be involved in the pathogenesis of asthma.

In order to investigate whether the *CD14-159C/T* polymorphism is associated with asthma risk, we have performed the current meta-analysis with 11 additional studies compared with previous meta-analyses [1, 9, 10]. The overall analysis and stratified analyses by ethnicity and age revealed no associations between this polymorphism and asthma risk. The findings were consistent with those in the previous meta-analyses. Maybe, the influence of *CD14-159C/T* polymorphism on soluble CD14 and IgE is not powerful enough so that the relationship between this polymorphism and asthma risk could not be detected. Another plausible explanation is that the solitary *CD14-159C/T* polymorphism merely influences the production of CD14 protein but does not play a key role in the subsequent pathway to asthma development.

When performing the stratified analysis by atopic status, there were still no significant results. However, the previous meta-analyses found a protective effect of the T-allele of *−159C/T* polymorphism for atopic asthma among the overall populations [1], Asians, and children [9]. Those results of those meta-analyses should be interpreted with caution because of a relatively small number of studies. Compared to previous meta-analyses [1, 9], the study inclusion of our meta-analysis is more comprehensive due to the largest sample size, suggesting more reliable results. Probably, this discrepancy reflects spurious relationship

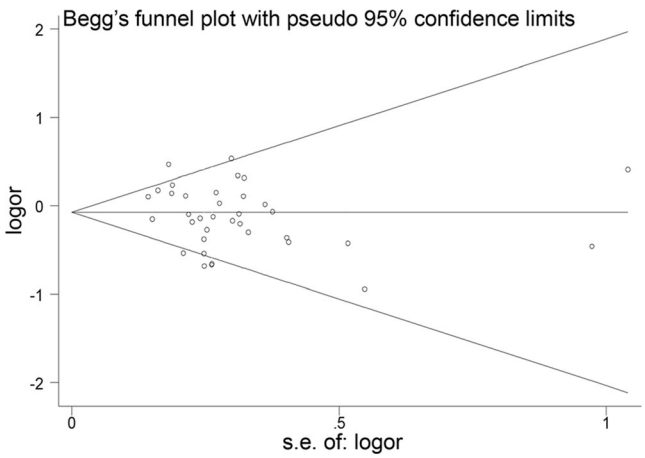

Fig. 3. Begg's funnel plot of *CD14-159C/T* polymorphism and asthma risk in the dominant model (TT+TC vs. CC).

caused by the relatively small sample size. We speculate that the *CD14-159C/T* polymorphism contribute little to risk of atopic asthma. More genetic association studies concerning the relationship between this polymorphism and atopic asthma are warranted to validate our findings.

Heterogeneity is a major issue that needs to be mentioned when interpreting the meta-analysis results. Although we performed a meticulous literature search, precise data extraction, and strict data analysis, there was low to moderate level heterogeneity in the overall populations (Table 3). After performing subgroup analyses, the heterogeneity was not effectively reduced or removed in most of genetic models, indicating that ethnicity, age, or atopic status might not be the source of heterogeneity. The heterogeneity, together with the stable negative results in sensitivity analysis, probably reflects the unclear association of this polymorphism with asthma risk.

Some limitations of the meta-analysis should be considered. First, although no significant publication bias was detected, some relevant studies published in other databases or unpublished negative studies may have been missed. Thus, potential bias could not be excluded. Second, our ethnic-specific meta-analyses were performed in Asians and Caucasians, so our results are applicable only to these ethnic groups. Our findings should be optimized by including other ethnic populations such as Africans and Latinos. Third, data could not be stratified by disease severity, sex, environmental factors, smoking status, or other variables attributing to insufficient original information in the included studies. Fourth, the lack of corresponding data did not allow us to conduct a meta-analysis of the gene-gene or gene-environment interactions. For these reasons, the interpretation of our meta-analysis results should be taken carefully.

In summary, the current study is the most comprehensive and latest meta-analysis concerning the *CD14-159C/T* polymorphism and asthma risk to date. Our results indicate that there is no evidence of significant association between the *CD14-159C/T* polymorphism and asthma risk either in Asians or Caucasians or adults or children. Moreover, the negative results are not influenced by atopic status. Due to the limitations showed above, our results should be viewed with caution and future large-scale studies with different ethnic populations and clinical subphenotypes are required for clarifying the role of the *CD14-159C/T* polymorphism in the pathogenesis of asthma.

Compliance with Ethical Standard

Conflict of Interest. The authors declare no conflicts of interest.

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