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ORIGINAL PAPER

The −159C/T polymorphism in the *CD14* gene and the risk of asthma: a meta-analysis

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Abstract The −159C/T polymorphism in the CD14 gene has been implicated in susceptibility to asthma, but a large number of studies have reported inconclusive results. The aim of this study is to investigate the association between the −159C/T polymorphism in the CD14 gene and the risk of asthma by meta-analysis. We searched Pubmed, Embase, CNKI database, Wanfang database, Weipu database, and Chinese Biomedical database, covering all publications (last search been performed on April 20, 2010). Statistical analysis was performed by using the softwares Revman 4.2 and STATA 10.0. A total of 17 case–control studies in 17 articles (4,246 cases and 3,631 controls) were included in this meta-analysis. There was no association between this polymorphism and asthma risk in combined analyses (odds ratio (OR)=0.86 and 95% confidence interval (95% CI)=0.72–1.02, P=0.09 for TC+TT vs. CC). In the subgroup analysis by age, ethnicity, and atopic status, no significant associations of asthma risks were obtained from age groups, ethnic groups, and atopic groups for TC+TT vs. CC comparison. For atopic population, significant decreased atopic asthma risks were found among Asian population (OR=0.69, 95% CI 0.52–0.92, P=0.01) and children population (OR=0.69, 95% CI 0.54–0.89, P=0.0004) for TC+TT vs. CC comparison. This meta-analysis suggests that *CD14* is a candidate gene for atopic asthma susceptibility. The −159C/T polymorphism may be a protective factor for atopic asthma in Asian and children. More studies are needed to validate these associations.

Keywords Asthma · CD14 · Meta-analysis · Polymorphism

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Abbreviations

HWE Hardy–Weinberg equilibrium
OR Odds ratio
CI Confidence interval

Introduction

Asthma is a complex inflammatory disease affecting nearly 300 million individuals worldwide (Gupta et al. 2009). It is characterized by airway hyperresponsiveness, hypertrophy, and hyperplasia of smooth muscle, hypersecretion of mucus, bronchial epithelial desquamation, and structural remodeling (Mahn et al. 2010; Zhang et al. 2010). Previous studies have indicated that asthma is a complex disorder with multiple determinants that include genetic variations, environmental exposures, and gene–environment interactions (Carroll et al. 2009; Weiss et al. 2009). Numerous published studies have focused on the association of genetic variants with asthma susceptibility (Hattori et al. 2009; Jung et al. 2009; Kabesch 2010; Møller-Larsen et al. 2008), and among them, *CD14* gene has been extensively studied (Bernstein et al. 2006; Chen et al. 2009; Cui et al. 2003; de Faria et al. 2008; Heinzmann et al. 2003; Hong et al. 2007; Kedda et al. 2005; Kowal et al. 2008; Leung et al. 2003; Sharma et al. 2004; Smit et al. 2007, 2009; Tan et al. 2006; Wang et al. 2009; Woo et al. 2003; Wu et al. 2010; Zambelli-Weiner et al. 2005).

The *CD14* gene is localized on chromosome 5q31.1, a region that is linked to both asthma and total serum IgE concentration. It encodes two protein isoforms: a membrane molecule (mCD14) on the surface of monocytes, macrophages, and neutrophils and a soluble form in serum (sCD14; Buckova et al. 2003). CD14 is a membrane recognition factor involved in the binding of bacterial components or inhaled endotoxin, a potent inducer of lung inflammation which may activate immune pathways that promote Th1 differentiation and Th2-dependent immunoglobulin E responses (Kedda et al. 2005). As previously shown in genetic studies, a polymorphism in the *CD14* gene, −159C/T (rs2569190), might interact with environmental factors in the development of asthma and asthma phenotypes (Bernstein et al. 2006; Chen et al. 2009; Cui et al. 2003; de Faria et al. 2008; Heinzmann et al. 2003; Hong et al. 2007; Kedda et al. 2005; Kowal et al. 2008; Leung et al. 2003; Sharma et al. 2004; Smit et al. 2007, 2009; Tan et al. 2006; Wang et al. 2009; Woo et al. 2003; Wu et al. 2010; Zambelli-Weiner et al. 2005). This polymorphism is in the promoter region of *CD14* gene and has been associated with altered CD14 and IgE levels (Zambelli-Weiner et al. 2005). There have been a large number of studies investigating this polymorphism with asthma risk; however, the results were inconsistent and inconclusive. Considering a single study may lack the power to provide reliable conclusion, we performed a meta-analysis to investigate these associations. This is, to our knowledge, the most comprehensive meta-analysis of genetics studies on the association between asthma susceptibility and the −159C/T polymorphism in *CD14* gene.

Methods

Publication search

Two reviewers independently searched Pubmed, Embase, China National Knowledge Infrastructure (CNKI), Wanfang Database, Weipu Database, and Chinese Biomedical (CBM) database, to identify studies that had investigated the association between asthma susceptibility and *CD14* polymorphisms, with the last updated search being performed on 20 April 2010. The search terms were used as follows: "*asthma* or *asthmatic*" and "*CD14*" in combination with "*polymorphism* or *variant* or *mutation*". Studies published in English and Chinese were all included. Articles reporting on the association between asthma and *CD14* polymorphism were identified. Studies included in our meta-analysis had to meet the following inclusion criteria: (1) evaluation of the −159C/T polymorphism in *CD14* gene and asthma risk, (2) using a case–control design, (3) genotype distributions in both cases and controls should be available for estimating an odds ratio (OR) with 95% confidence interval (CI), and (4) genotype distribution of control population must be consistent with Hardy–Weinberg equilibrium (HWE). Accordingly, the following exclusion criteria were also used: (1) abstracts, reviews, and repeat studies; (2) genotype frequency not reported; and (3) genotype distribution in the control population not consistent with HWE.

Data extraction

Two independent reviewers checked all potentially relevant studies and reached a consensus on all studies. In case of disagreement, a third author also assessed those articles. A standardized data form was used and included first author, year of publication, country of origin, ethnicity of the study population, definition of cases, source of control, genotyping methods, total number of cases and controls, and genotype distribution in cases and controls.

Statistical analysis

The strength of the association between the −159C/T polymorphism and asthma risk was measured by OR and

95% CI. The statistical significance of summary OR was determined with Z test. We first estimated with the dominant model (TT+TC vs. CC) and recessive model (TT vs. TC+CC) and then evaluated variant genotype TT and compared with the wild-type CC homozygote (TT vs. CC). We also estimated the risks of T vs. C and TC vs. CC. Heterogeneity was evaluated by a χ^2-based Q statistic and was considered statistically significant at P value less than 0.10. When the P value is greater than 0.10, the pooled OR of each study was calculated by the fixed-effects model; otherwise, a random-effects model was used, as this was more appropriate when there was significant heterogeneity. The significance of the pooled OR was determined by the Z test, and P less than 0.05 was considered as statistically significant. To evaluate the ethnicity-specific, age-specific, and atopic-specific effects, subgroup analyses were performed by ethnic, age, and atopic status. To evaluate the ethnicity–atopic status and age–atopic status associations, the atopic asthma populations were stratified analyzed by ethnicity and age.

Sensitivity analysis was performed through sequentially excluding individual studies to assess the stability of the results (Zhang et al. 2010). Asymmetry funnel plots were used to assess potential publication bias. The Begg's test and Egger's test were also used to assess publication bias statistically (Zhang et al. 2010).

Hardy–Weinberg equilibrium was tested by using a web-based program (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl). All statistical tests were performed by using the Revman 4.2 software and STATA 10.0 software.

Results

Study included in the meta-analysis

Figure 1 outlines the process of selecting studies. Briefly, a total of 254 articles were identified after an initial search from the Pubmed, Embase, CNKI database, Wanfang database, Weipu database, and CBM database. After reading the titles and abstracts, 217 articles were excluded for being not relevant to *CD14* polymorphisms and asthma risk, or abstracts and reviews. After reading full texts of the remaining 38 articles, two studies which did not concern −159C/T polymorphism were excluded. Thus, 36 articles were left for data extraction. Of the 36 articles, 15 did not report the genotype frequencies and were excluded. Thus, a total of 21 case–control studies were extracted from 21 articles. Among 21 case–control studies, genotype frequencies for control group in two studies were not consistent with HWE, and data in two studies were overlapped. So these four case–control studies were excluded. Finally, a total of 17 case–controls in 17 articles were identified for meta-analysis (Bernstein et al. 2006; Chen et al. 2009; Cui et al. 2003; de Faria et al. 2008; Heinzmann et al. 2003; Hong et al. 2007; Kedda et al. 2005; Kowal et al. 2008; Leung et al. 2003; Sharma et al. 2004; Smit et al. 2007, 2009; Tan et al. 2006; Wang et al. 2009; Woo et al. 2003; Wu et al. 2010; Zambelli-Weiner et al. 2005). The characteristics of each case–control studies are shown in Table 1. Genotype and allele distributions for each case–control studies are listed in Table 2. There were eight case–controls of Asians (Chen et al. 2009; Cui et al. 2003; Hong et al. 2007; Leung et al. 2003; Sharma et al. 2004; Tan et al. 2006; Wang et al. 2009; Wu et al. 2010), seven of Caucasians (Bernstein et al. 2006; Heinzmann et al. 2003; Kedda et al. 2005; Kowal et al. 2008; Smit et al. 2007, 2009; Woo et al. 2003), and two were mixed (de Faria et al. 2008; Zambelli-Weiner et al. 2005). Nine studies were performed in adults (Bernstein et al. 2006; Chen et al. 2009; Kedda et al. 2005; Kowal et al. 2008; Sharma et al. 2004; Smit et al. 2007, 2009; Woo et al. 2003; Zambelli-Weiner et al. 2005), while eight were performed in children (Cui et al. 2003; de Faria et al. 2008; Heinzmann et al. 2003; Hong et al. 2007; Leung et al. 2003; Tan et al. 2006; Wang et al. 2009; Wu et al. 2010).

Quantitative data synthesis

All studies As shown in Fig. 2, we analyzed the heterogeneity of TT+TC vs. CC for all 17 studies and the value of χ^2 was 44.78 with 16° of freedom and P=0.0002 in a random-effects model. Additionally, I-square value is another index of the test of heterogeneity. In Fig. 2, the I-square was 64.3%, suggesting a present of heterogeneity. Thus, we chose the random-effects model to synthesize the data. Overall, OR was 0.88 (95% CI=0.73–1.07) and the test for overall effect Z value was 1.26 (P=0.21). The results suggested that the TT homozygote and TC heterozygote carriers did not have an increased risk of asthma compared with those individuals with the CC homozygote. Summary of the results of other genetic comparisons are listed in Table 3.

Subgroup analyses

In the subgroup analysis by ethnicity (Supplement Fig. 1), no associations were found among Asians (OR 0.80, 95% CI 0.56–1.15, P=0.23) and Caucasians (OR 1.01, 95% CI 0.77–1.34, P=0.94) in dominant model (TT+TC vs. CC). Similarly, in the subgroup analysis by age (Supplement Fig. 2), no associations were found among adults (OR 0.84, 95% CI 0.63–1.10, P=0.21) and children (OR 0.94, 95% CI 0.71–1.25, P=0.67). Subgroup analyses were also

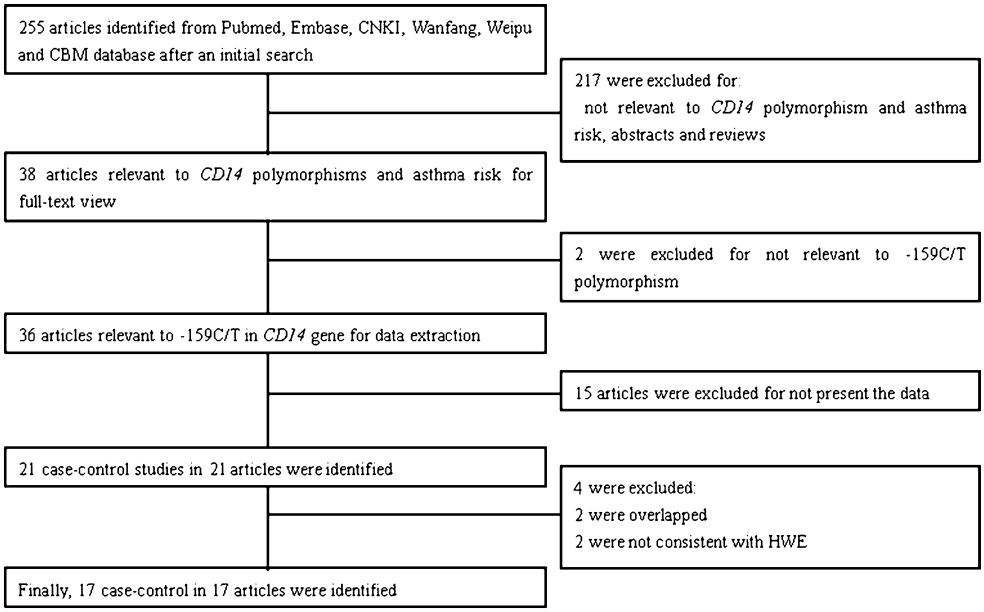

Fig. 1 Flow diagram of included/excluded studies

performed by atopic status (Supplement Fig. 3); no associations were found among atopic asthma patients, non-atopic asthma patients, and mixed atopic status asthma patients in dominant model (Table 3). Summary of the results of other genetic comparisons are listed in Table 3.

Atopic asthma patients A total of eight case–control studies performed among atopic asthma patients were identified in the meta-analysis (Cui et al. 2003; de Faria et al. 2008; Hong et al. 2007; Kedda et al. 2005; Kowal et al. 2008; Leung et al. 2003; Sharma et al. 2004; Woo et al. 2003). Four studies were performed among Asians (Cui et al. 2003; Hong et al. 2007; Leung et al. 2003; Sharma et al. 2004), three among Caucasians (Kedda et al. 2005; Kowal et al. 2008; Woo et al. 2003), and one among mixed ethnicities (de Faria et al. 2008). Five studies were performed in children (Cui et al. 2003; de Faria et al. 2008; Hong et al. 2007; Leung et al. 2003; Sharma et al. 2004), while three were performed in adults (Kedda et al. 2005; Kowal et al. 2008; Woo et al. 2003). Subgroup analyses were also performed according to ethnicity and age. As shown in Supplement Fig. 4, significant decreased risk of asthma was found among children (OR=0.69, 95% CI 0.54–0.89, P=0.0004). The results suggested that the T allele carriers (TT+TC) have a 31% deceased risk of atopic asthma compared with those individuals with the CC homozygote in children population. In the subgroup analysis by ethnicity (Supplement Fig. 5), significant decreased risks of atopic asthma were found among Asians (OR=0.69, 95% CI 0.52–0.92, P=0.01). The results suggested that the T allele carriers (TT+TC) have a 31% deceased risk of atopic asthma compared with those individuals with the CC homozygote in Asian population. Summary of the results of other genetic comparisons are listed in Table 3.

Publication bias

Publication bias was assessed by Begg's funnel plot and Egger's test. The shape of the funnel plots seemed symmetrical in the TT+TC vs. CC comparison genetic model, suggesting the absence of publication bias (Fig. 3). Then, the Egger's test was performed to provide statistical evidence of funnel plots asymmetry. The results indicated a lack of publication bias of the current meta-analysis (t=−1.31, P=0.211).

Sensitivity analysis

As describe previously (Zhang et al. 2010), in order to assess the stability of the results, sensitivity analysis was performed by sequentially excluding each study. Statistically similar results were obtained after sequentially excluding each case–control study, suggesting the stability of the results.

Discussion

Common variants in genes in the pathway of pathogenesis may alter protein function and individual's susceptibility to disease (Contopoulos-Ioannidis et al. 2005; Gao et al. 2006;

Table 1 Characteristics of the 17 case–control studies included in meta-analysis

First author	Year	Country	Ethnicity	Age of cases	Cases (*n*)	Control (*n*)	Genotyping method	Asthma definition	Atopic status
Smit, LA (Smit et al. 2009)	2009	France	Caucasian	–	223	554	Taqman or 1536-plex Illumina Golden Gate assay	Questionnaire	Atopic asthma and non-atopic
Bernstein, DI (Bernstein et al. 2006)	2006	Canada	Caucasian	–	62	75	RFLP	Gold standard for occupational asthma	Atopic asthma and non-atopic
Smit, LA (Smit et al. 2007)	2007	Denmark	Caucasian	–	100	88	SSP and PCR	Questionnaire	Atopic asthma and non-atopic
Heinzmann, A (Heinzmann et al. 2003)	2003	Germany	Caucasian	5–18	182	261	RFLP	Clinical symptom and lung function	–
Sharma, M (Sharma et al. 2004)	2004	India	Asian	29.23±14.6	187	227	RFLP	ATS	Atopic asthma
Woo, JG (Woo et al. 2003)	2003	Canada	Caucasian	48.2±14.9	175	61	RFLP	ATS	Atopic asthma and non-atopic[a]
Zambelli-Weiner, A (Zambelli-Weiner et al. 2005)	2005	USA	Mixed	24.1±13.0	293	454	RFLP	–	Atopic asthma and non-atopic
Hong, SJ (Hong et al. 2007)	2007	Korea	Asian	9.27±2.63	626	153	RFLP	ATS	Atopic asthma and non-atopic[a]
Wu, X (Wu et al. 2010)	2010	China	Asian	8.8±3.2	252	227	RFLP	ATS	Atopic asthma and non-atopic
Wang, JY (Wang et al. 2009)	2009	China	Asian	7.82±3.81	447	509	Taqman	History, symptom, and lung function	Atopic asthma and non-atopic
Tan, CY (Tan et al. 2006)	2006	China	Asian	–	120	120	RFLP	History, symptom, and lung function	Atopic asthma and non-atopic
Kowal, K (Kowal et al. 2008)	2008	Poland	Caucasian	25 (23–26)	372	160	RFLP	GINA	Atopic asthma
de Faria, IC (de Faria et al. 2008)	2008	Brazil	Mixed	10.3±2.79	88	202	RFLP	GINA	Atopic asthma
Leung, TF (Leung et al. 2003)	2003	China	Asian	9.8±4.2	258	92	RFLP	ATS	Atopic asthma and non-atopic[a]
Kedda, MA (Kedda et al. 2005)	2005	Australian	Caucasian	–	568	226	RFLP	Questionnaire and spirometric test	Atopic asthma and non-atopic[a]
Chen, M (Chen et al. 2009)	2009	China	Asian	14–71	150	150	RFLP	Prevention of Chinese preventive guidelines for asthma 2003	–
Cui, TP (Cui et al. 2003)	2003	China	Asian	2–16	143	72	RFLP	Allergic asthma definition	Atopic asthma

RFLP restriction fragment length polymorphism, *SSP* single-specific primer, *PCR* polymerase chain reaction, *ATS* American Thoracic Society, *GINA* Global Initiative for Asthma

[a] Data for atopic and non-atopic asthma patients could be separately extracted

Table 2 Distribution of *CD14* genotype and allele among asthma patients and controls

First author	Case			Control			Case		Control		HWE
	CC	CT	TT	CC	CT	TT	C	T	C	T	
Bernstein, D I (Bernstein et al. 2006)	17	33	12	15	45	15	67	57	75	75	Yes
Chen, M (Chen et al. 2009)	63	62	25	40	68	42	188	112	148	152	Yes
Cui, TP (Cui et al. 2003)	27	67	49	10	42	20	121	165	62	82	Yes
de Faria, IC (de Faria et al. 2008)	32	42	14	58	112	32	106	70	228	176	Yes
Heinzmann, A (Heinzmann et al. 2003)	51	89	42	79	124	58	191	173	282	240	Yes
Hong, SJ (Hong et al. 2007)	113	284	229	22	71	60	510	742	115	191	Yes
Kedda, MA (Kedda et al. 2005)	148	284	136	75	104	47	580	556	254	198	Yes
Kowal, K (Kowal et al. 2008)	141	152	79	42	73	45	434	310	157	163	Yes
Leung, TF (Leung et al. 2003)	55	123	80	18	45	29	233	283	81	103	Yes
Sharma, M (Sharma et al. 2004)	43	92	52	30	112	85	178	196	172	282	Yes
Smit, LA (Smit et al. 2007)	34	47	19	26	47	15	115	85	99	77	Yes
Smit, LA (Smit et al. 2009)	49	107	67	145	276	133	205	241	566	542	Yes
Tan, CY (Tan et al. 2006)	17	56	47	24	55	41	90	150	103	137	Yes
Wang, JY (Wang et al. 2009)	57	230	160	96	236	177	344	550	428	590	Yes
Woo, JG (Woo et al. 2003)	46	94	35	20	35	6	186	164	75	47	Yes
Wu, X (Wu et al. 2010)	54	117	81	31	121	75	225	279	183	271	Yes
Zambelli-Weiner, A (Zambelli-Weiner et al. 2005)	138	137	18	198	206	50	413	173	602	306	Yes

Ohar et al. 2010; Pabst et al. 2010). CD14 is a membrane recognition factor involved in binding of bacterial components and plays a central role in innate immunity. One polymorphism in the *CD14* gene, 159C/T (rs2569190), might interact with environmental factors in the development of asthma and asthma phenotypes. Correlation of this polymorphism and asthma risk has been studied, but the results remain controversial. Therefore, we performed a meta-analysis to clarify the relationship between this polymorphism and susceptibility to asthma.

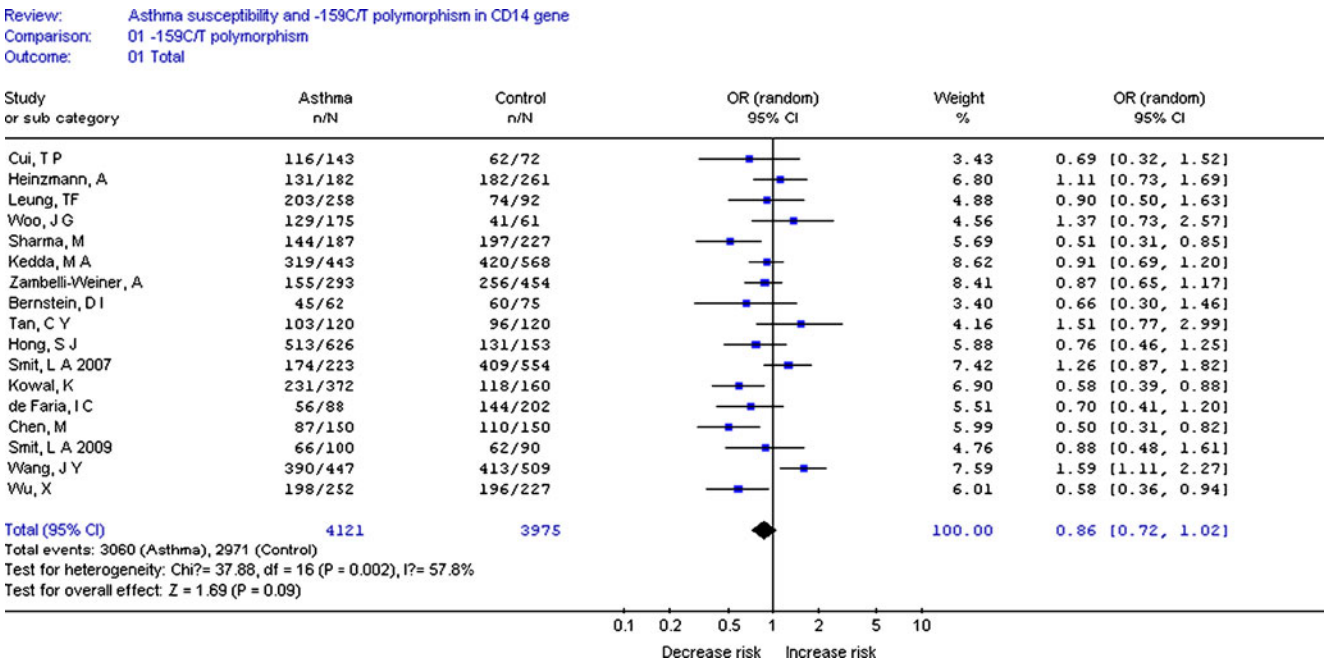

Fig. 2 Meta-analysis with a random-effects model for the association between asthma risk and the *CD14* −159C/T polymorphism (TT+TC vs. CC)

Table 3 Summary of different comparative results

	TT+TC vs. CC		TT vs. TC+CC		TT vs. CC		TC vs. CC		T vs. C	
	OR (95% CI)	P^a	OR (95% CI)	P^a	OR (95% CI)	P^a	OR (95% CI)	P^a	OR (95% CI)	P^a
Total	0.88 (0.73, 1.07)	0.21	0.96 (0.83, 1.12)	0.60	0.88 (0.68, 1.14)	0.33	0.89 (0.74, 1.06)	0.20	0.94 (0.84, 1.06)	0.32
Subgroup by ethnicity										
Asian	0.80 (0.56, 1.15)	0.23	0.91 (0.76, 1.10)	0.35	0.79 (0.53, 1.17)	0.24	0.82 (0.58, 1.15)	0.25	0.89 (0.74, 1.07)	0.22
Caucasian	1.01 (0.77, 1.34)	0.94	1.11 (0.88, 1.40)	0.38	1.11 (0.76, 1.61)	0.59	0.99 (0.77, 1.26)	0.92	1.04 (0.86, 1.26)	0.68
Mixed	0.83 (0.64, 1.07)	0.15	0.71 (0.38, 1.32)	0.28	0.60 (0.38, 0.96)	0.03	0.88 (0.66, 1.17)	0.37	0.83 (0.69, 1.01)	0.06
Subgroup by age										
Adults	0.84 (0.63, 1.10)	0.21	0.89 (0.66, 1.19)	0.43	0.80 (0.52, 1.23)	0.31	0.86 (0.68, 1.09)	0.21	0.90 (0.73, 1.10)	0.29
Children	0.94 (0.71, 1.25)	0.67	1.03 (0.89, 1.19)	0.72	1.00 (0.77, 1.30)	0.98	0.92 (0.68, 1.24)	0.58	1.00 (0.90, 1.12)	0.94
Subgroup by atopic status										
Atopic	0.81 (0.60, 1.09)	0.16	0.95 (0.80, 1.12)	0.53	0.84 (0.58, 1.23)	0.37	0.80 (0.61, 1.05)	0.11	0.92 (0.76, 1.11)	0.38
Asian	**0.69 (0.52, 0.92)**	**0.01**	0.88 (0.70, 1.11)	0.27	**0.68 (0.47, 0.99)**	**0.05**	**0.70 (0.51, 0.95)**	**0.02**	0.85 (0.71, 1.03)	0.10
Caucasian	0.99 (0.52, 1.86)	0.97	1.04 (0.79, 1.36)	0.78	1.12 (0.47, 2.66)	0.80	0.96 (0.55, 1.69)	0.89	1.02 (0.66, 1.59)	0.93
Children	**0.69 (0.54, 0.89)**	**0.004**	0.89 (0.72, 1.11)	0.30	**0.69 (0.51, 0.93)**	**0.02**	**0.69 (0.53, 0.91)**	**0.007**	**0.85 (0.73, 0.99)**	**0.03**
Adults	0.99 (0.52, 1.86)	0.97	1.04 (0.79, 1.36)	0.78	1.12 (0.47, 2.66)	0.80	0.96 (0.55, 1.69)	0.89	1.02 (0.66, 1.59)	0.93
Non-atopic	1.17 (0.73, 1.89)	0.51	0.97 (0.70, 1.35)	0.87	1.17 (0.56, 2.47)	0.67	1.20 (0.82, 1.76)	0.35	1.08 (0.77, 1.49)	0.66
Mixed	0.92 (0.69, 1.23)	0.56	1.04 (0.90, 1.20)	0.59	0.96 (0.69, 1.35)	0.83	0.91 (0.68, 1.21)	0.50	0.97 (0.83, 1.14)	0.70

The bold values mean that their association is significant

[a] *P* value for *Z* test

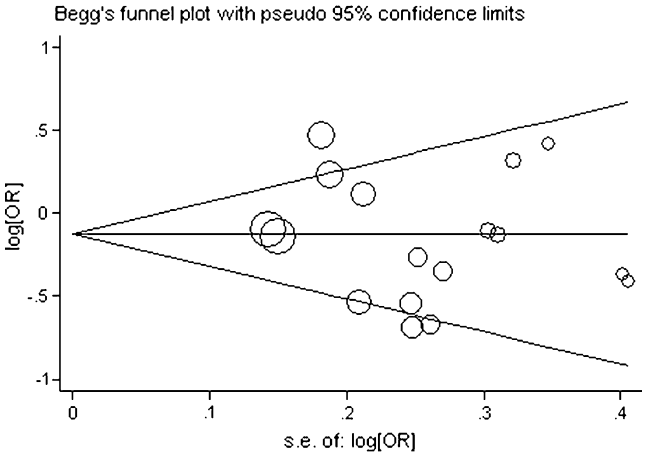

Fig. 3 Begg's funnel plot for publication bias in selection of studies on the *CD14* −159C/T polymorphism (TT+TC vs. CC)

A total of 17 case–control studies were included in the meta-analysis. The strength of the present analysis was based on the accumulation of published data giving information to detect more precise conclusion. In this study, the effect of allele frequency and the effect of dominant and recessive models were all estimated. In addition, the consistency of genetic effects across populations from different ethnicities and ages were investigated. The consistency of atopic status was also investigated. Main and subgroup analyses for ethnicity, age, and atopic status for all genetic contrasts produced no significant results, and the heterogeneity ranged from none to high. For the atopic asthma patients, subgroup analysis was performed by ethnicity and age. Significant decreased risks of asthma were found among Asian and children groups.

In this study, we did not find a clear association between the −159C/T polymorphism and risk of asthma in the total combined analysis. This may be related to the fact that the functionality of the polymorphism, at least with respect to the extent of the influence on CD14 plasma levels among asthma, has not been definitively established. Although an effect on transcription and CD14 levels was described (Zambelli-Weiner et al. 2005) and the potential effect on asthma was also described in some studies (Fageras et al. 2004; Woo et al. 2003), it is possible that that effect may be affected by several polymorphisms, rather than one individual polymorphism. This implies that the solitary −159C/T polymorphism might influence plasma levels but not in a substantial way.

In this study, subgroup analysis was also performed among atopic status patients. Significant decreased risk of asthma was found among atopic status patients in Asian and children, but not in Caucasians and adults, suggesting a possible role of ethnic differences in genetic backgrounds and etiology in different age. In addition, there is no reported study using Asian adults and Caucasian children in atopic asthma patients. So it is likely that the observed ethnic and age differences may be due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect. Therefore, additional studies are warranted to further validate ethnic and age differences in the effect of this polymorphism on asthma susceptibility, especially in atopic status patients.

We have to mention two studies which were based on Hong Kong Chinese. These two studies were from almost the same investigators based on the same ethnic population. The first publication was based on atopic population, and the second publication was based on atopic and non-atopic population. The second publication included more cases and controls than the first publication. There may be some potential overlapped for cases or controls. Thus, we excluded one study. In order to include more cases and controls for atopic population, we just included the first publication in this meta-analysis, which is not according with our previous study. However, if we included this later study instead of the previous study for data analysis, the same no associations were found for overall analysis (data not shown).

Since 1990s, host genetic variants and their associations with susceptibility to asthma have been extensively studied, and many variants have been suggested as determinants of susceptibility to asthma. In recently years, the genome-wide association studies (GWAS) has become an important scientific focus in asthma genetic studies (Barnes 2010; DeWan et al. 2010; Kabesch 2010; Moffatt et al. 2010; Weidinger et al. 2010). Up to now, several loci have been suggested as asthma risk factors by GWAS (Barnes 2010; DeWan et al. 2010; Kabesch 2010; Moffatt et al. 2010; Weidinger et al. 2010), such as DENND1B, RAD50/IL13, HLA-DQB1, ORMDL3, PDE11A, SMAD3, and et al. (Barnes 2010; DeWan et al. 2010; Moffatt et al. 2010; Weidinger et al. 2010), and a few have also been replicated in different ethnic populations (Barnes 2010; Kabesch 2010; Weidinger et al. 2010). Although a few GWAS reported some loci which were associated with total IgE such as RAD50/IL13 and HLA-DQB1 (Barnes 2010; Weidinger et al. 2010), clearly none of these GWAS reported the significant association with −159C/T (rs2569190) polymorphism. This can be partly explained by the slight effects of this polymorphism on asthma susceptibility. In the future, more GWAS should be performed in atopic asthma patients to resolve whether the −159C/T polymorphism shows significant association with asthma susceptibility.

There are several limitations in this study that need to be addressed. First, only publications in Chinese and English included by the selected electronic databases were identified in this meta-analysis; it is possible that some relevant

published studies in other languages or unpublished studies which had null results were not included, which might bias the results, while our statistical test might not show it clearly. Second, the number of studies and the number of subjects in the studies included in the meta-analysis by specific subgroups were small. This may not have enough power to explore the association between the −159C/T polymorphism and the disease; thus, caution should be adopted when explaining our results. Third, there is heterogeneity among studies, maybe owing to ages, ethnicity, atopic status, or environmental factors and so on. Fourth, most of the studies were performed in Asian and Caucasian populations; further studies are needed in other ethnic population because of possible ethnic differences of the −159C/T polymorphism.

To our knowledge, this is the most comprehensive meta-analysis to date to have assessed the relationship between the −159C/T polymorphism in *CD14* gene and asthma risk. Our results revealed that the −159C/T polymorphism was significantly associated with decreased risk of asthma among Asian atopic population. This finding suggests that the −159C/T polymorphism may be a low-penetrance susceptibility marker of asthma. In the future, more studies in different ethnic population or ages should be performed to assess these associations.

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Conflict of interest None.

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