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Association of CD14 −159 (−260C/T) polymorphism and asthma risk: an updated genetic meta-analysis study

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Abstract

Background: It has been reported that the cluster of differentiation 14 (*CD14*) gene *−159C/T* variant may be associated with asthma risk. However, some studies yielded conflicting results. Therefore, a comprehensive meta-analysis was designed to assess the precise association.

Methods: A systematic search in PubMed, Embase (Ovid), China National Knowledge Internet (CNKI), and Wan fang databases was conducted up to August 15, 2015. Odds ratio (OR) and 95% confidence interval (CI) were used to pool the effect size. We used I^2 to assess heterogeneity, and a funnel plot and Egger test to assess publication bias.

Results: In total, 34 studies involving 15,641 subjects were included in this meta-analysis. There was a statistically significant association between *CD14 −159C/T* polymorphism and asthma risk observed in dominant model (TT+TC vs CC: OR=0.86, 95% CI=0.77–0.97, P=0.012) and codominant model (TC vs CC: OR=0.88, 95% CI=0.78–0.99, P=0.035) in adults. However, there may be no significant association between *CD14 159C/T* and atopic and nonatopic asthma risk.

Conclusion: In summary, the overall results suggested that the *CD14 −159C/T* variant may decrease the risk of asthma susceptibility in adults. However, no significant association between *CD14 159C/T* and atopic and nonatopic asthma susceptibility was identified. More studies with larger sample size are needed to validate the findings from this study.

Abbreviations: 95% CIs = 95% confidence intervals, CD14 = cluster of differentiation 14, CNKI = China National Knowledge Internet, ESR1 = estrogen receptor 1, GWAS = genome-wide linkage studies, HWE = Hardy–Weinberg equilibrium, LPS = lipopolysaccharides, OR = Odds ratio, TGF-β1 = transforming growth factor beta 1.

Keywords: asthma, CD14, meta-analysis, polymorphism

1. Introduction

Characterized by airway hyperreactivity to some environmental stimuli, mucus hypersecretion, reversible airway obstruction, and bronchial epithelial desquamation, resulting in airway structural remodeling, asthma is a complex respiratory disease with a multifactorial etiology.[1,2] Asthma is in high prevalence worldwide with an estimated 300 million affected people, leading to significant mortality and morbidity.[3,4] Especially, atopic asthma accounted for 56% of all asthma population in the United States, which is triggered by aeroallergens and endotoxin.[5] Although the precise etiology of asthma remains unclear, a combination of genetic predisposition and environmental exposures is believed to contribute to pathogenesis of asthma.[1,6] With numerous recent advances in genetic research, many genes that are related to asthma susceptibility have been identified as candidates in multiple populations, including transforming growth factor beta 1 (TGF-β1), prostaglandin-endoperoxide synthase 1 (PTGS1), and estrogen receptor 1 (ESR1), especially the CD14.[6–11]

The *CD14* gene, located on chromosome 5q31.3, is presented in 2 exons and linked to asthma in genome-wide association studies (GWAS).[12] It encodes 2 glycoprotein isoforms expressed as a membrane-bound form on the surface of monocytes, macrophages, and neutrophils and a soluble form in the serum.[11,13]*CD14* acts as a multifunctional high-affinity receptor for the binding of endotoxins, lipopolysaccharides (LPS), and other bacterial wall components, involved in primary immune and inflammatory responses.[14,15] Studies have demonstrated that *−159C/T* variant in *CD14* may change *CD14* protein structure and associated with *CD14* and immunoglobulin E level.[16]*CD14* may activate innate immune system pathways that influence the balance of the Th1 versus Th2 cytokines, thereby affecting IgE responses, inducing lung inflammation, and triggering allergic conditions such as atopic asthma.[11,17]

According to published data, the *−159C/T* variant in the *CD14* gene was found to be involved in pathogenesis of asthma.[18–20] Nevertheless, some other studies failed to replicate

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the association of *CD14 −159C/T* variation with asthma risk.[21–23] So far, 2 earlier meta-analyses based on different strategies have tried to detect the possible association of *CD14 −159C/T* polymorphisms with asthma.[24,25] Unfortunately, the former had several noteworthy errors pertaining to study inclusion, data abstraction.[24] The latter had included 3 articles which deviated from Hardy–Weinberg equilibrium (HWE).[25] Thereafter, some new studies have been reported about diverse ethnic populations and phenotypes of asthma. Therefore, the data needs to be updated and more reliable evaluates of *CD14 −159C/T* variant with asthma risk are warranted.

Due to the inconsistency of past studies and the critical role of *CD14 −159C/T* variant in the pathogenesis of asthma, we conducted an updated meta-analysis to investigate the association between *CD14 −159C/T* polymorphism and asthma risk by precise results.

2. Materials and methods

The PRISMA protocol was prospectively performed. Ethical approval was unnecessary in this study because it was a meta-analysis analyzing existing articles and did not involve handling of individual patient data.

2.1. Study selection

Two independent reviewers exhaustively searched PubMed, Embase (Ovid), China National Knowledge Internet (CNKI), and Wan fang database to identify studies, which had detected the association of *CD14* polymorphisms and asthma susceptibility. The latest electronic search was carried out on August 15, 2015. The search terms were used as follows: "asthma" or "asthmatic" and "*CD14*" or "cluster of differentiation 14" and "polymorphism" or "variant" or "mutation" or "polymorphisms" or "variants" or "mutations." No language restrictions were imposed. Studies eligible for this meta-analysis fulfilled the following inclusion criteria: using a case–control design, investigating the association between *−159C/T* polymorphism in *CD14* gene and asthma risk, genotype distributions should be available for estimating the odds ratio (OR) with 95% confidence interval (CI), and genotype distribution of control groups should be consistent with HWE. Exclusion criteria were as follows: conference, review, and overlapping publications; study with no available genotype distributions; genotype distribution in the control population is not consistent with HWE. We also inspected the reference list of review or past meta-analysis for potentially relevant publications. Two investigators independently screened all abstracts and citations to extract potentially eligible studies.

2.2. Data extraction

Two independent investigators collected the information of each eligible study based on the inclusion criteria. First author, publication year, country, ethnicity, genotype and allele distributions, case and control size, and type of diseases were extracted. In case of dispute, 2 investigators would check the collected data and reach a consensus through discussion. The information is presented in Tables 1 and 2.

2.3. Statistical method

In this meta-analysis, all data were presented as OR with 95% CI to assess the association between *−159C/T* polymorphism in the *CD14* gene and asthma risk. Heterogeneity was evaluated using χ^2-based Q-test and I^2 statistics. If no or low heterogeneity existed ($I^2 > 50\%$ and $P < 0.10$), the random-effects model was applied to estimate pooled OR. Otherwise, the fixed-effects model was used. The genetic models were evaluated for the pooled OR of the CD14 −159C/T polymorphism in allele, dominant, recessive, codominant model. To explore the source of the heterogeneity and evaluate the ethnicity-specific and age-specific effects, subgroup analyses were conducted based on ethnicity and age. In addition, subjects were divided into different classifications according to asthma phenotype definition: atopic asthma, nonatopic asthma, and mixed asthma (atopic asthma not mentioned). Moreover, we also performed a subgroup analysis to further assess the ethnicity-specific, age-specific effects for atopic, nonatopic, and mixed asthma.

In order to assess the stability of the results, we performed a sensitivity analysis by sequentially excluding each study. Potential publication bias was tested by several methods. Visual inspection of asymmetry in funnel plots was carried out. Furthermore, Egger regression and Begg test were also utilized to detect publication bias, and a P-value <0.05 was considered statistically significant. Moreover, to obtain further evidence, HWE was recalculated in control groups by Pearson χ^2 test before this meta-analysis was conducted. All data analysis was performed with STATA 11.0 software (Stata Corp LP, College Station, TX).

3. Results

3.1. Included study characteristics

In total, 437 articles (393 articles in English and 44 papers in Chinese) based on the inclusion criteria were identified after we systematically searched PubMed, Embase (Ovid), CNKI, and Wan fang databases. After reading titles and abstracts, 62 articles were screened in full-text review (Fig. 1). Three articles were excluded because they did not evaluate the association of *CD14 −159C/T* variant and asthma susceptibility, but other gene polymorphisms. Three articles were excluded because the genotype frequencies for the controls deviated from HWE.[8–10] Seventeen articles were excluded because of insufficient data, and 5 studies were overlapped for 4 data sets. We retained the studies with the largest number of subjects.[22,26–28] Therefore, in total, 34 studies from 34 articles[11,17–23,26–51] (31 articles in English, 2 papers in Chinese, and 1 article in Polish) were identified, which contained 15,641 subjects (7535 cases and 8106 controls) to investigate the relationship between *CD14 −159C/T* variant and the risk of asthma. The characteristics of included studies are shown in Tables 1 and 2.

3.2. Quantitative data synthesis

All 34 studies[11,17–23,26–51] involving 15,641 subjects (7535 cases and 8106 controls) were pooled to investigate association between *CD14 −159C/T* variant and asthma risk. For presence of a moderate heterogeneity, random-effects model was used in allele, codominant model and fixed-effects model in other genetic models. The overall results suggested that no significant association of *CD14 −159C/T* polymorphism and asthma susceptibility was observed in any genetic model (Table 3).

Then, we found no statistically significant relationship between *CD14 −159C/T* and asthma risk in any model when studies were subset by ethnicity (Caucasian and Asian) (Table 3). In the subgroup analysis done on the basis of age, however, a significant

Table 1

Characteristics of studies included in meta-analysis.

Author	Year	Country	Ethnicity	Age	Case/control	Atopic status	Asthma definition
Hakonarson	2001	Iceland	Caucasian	Adults	94/94	AA	ATS
Koppelman	2001	Netherlands	Caucasian	Adults	159/158	MA	Clinical symptom, lung function
Lis	2001	Poland	Caucasian	Children	50/73	AA	Clinical symptom
Heinzmann	2003	Germany	Caucasian	Children	182/261	MA	Clinical symptom, lung function
Woo	2003	Canada	Caucasian	Adults	175/61	AA, NA*	ATS
Cui	2003	China	Asian	Children	143/72	AA	Allergic asthma definition
Sharma	2004	India	Asian	Adults	187/227	AA	ATS
Kedda	2005	Australia	Caucasian	Adults	568/443	AA, NA*	Questionnaire, spirometric test
Bernstein	2006	Canada	Caucasian	Adults	62/75	MA	Gold standard for occupational asthma
Barnes	2006	Barbados	Mixed	Adults	322/451	MA	Clinical symptom
Park	2006	Korea	Asian	Adults	85/550	MA	Clinical symptom, lung function
Smit	2007	Denmark	Caucasian	Adults	100/88	MA	Questionnaire
Hong	2007	Korea	Asian	Children	626/153	AA, NA*	ATS
Chan	2008	China	Asian	Children	269/141	MA	ATS
Kowal	2008	Poland	Caucasian	Adults	372/160	AA	GINA
Wang	2009	China	Asian	Children	447/509	MA	GINA
Smit	2009	France	Caucasian	Adults	223/554	MA	Questionnaire
Chen	2009	China	Asian	Adults	150/150	MA	Chinese preventive guideline
Bjornvold	2009	Norway	Caucasian	Children	103/479	AA	History, clinical symptom
Wu	2010	China	Asian	Children	252/227	MA	ATS
Kuo Chou	2010	China	Asian	Children	116/232	MA	ATS
Murk	2011	USA	Caucasian	Children	97/473	AA	History, clinical symptom
Wu	2011	China	Asian	Adults	188/60	AA	History, clinical symptom
Perin	2011	Slovenia	Caucasian	Children	247/158	AA, NA*	ATS
Micheal	2011	Pakistan	Asian	Adults	110/120	AA	History, clinical symptom
Rennie	2013	Canada	Caucasian	Children	90/434	MA	History, clinical symptom
Hussein	2013	Egypt	Mixed	Children	500/150	AA, NA*	ATS
Bose	2013	India	Asian	Adults	20/50	MA	History, clinical symptom
Kljaic-Bukvic	2014	Croatia	Caucasian	Children	397/372	MA	History, clinical symptom
Wang	2014	China	Asian	Adults	126/126	MA	GINA
Sahin	2014	Turkey	Caucasian	Adults	131/75	AA, NA*	GINA
Zhang	2015	China	Asian	Children	362/384	AA	History, clinical symptom
Feng	2015	China	Asian	Adults	152/116	AA, NA*	History, clinical symptom
Martinez-Aguilar	2015	Mexico	Caucasian	Children	421/430	MA	GINA

AA = atopic asthma, ATS = American Thoracic Society, GINA = Global Initiative for Asthma, MA = mixed asthma (atopic asthma not mentioned), NA = nonatopic asthma.
* The data for atopic asthma and nonatopic asthma could be separately extracted.

association of *CD14 −159C/T* and asthma risk was found in dominant model (TT+TC vs CC: OR = 0.86, 95% CI = 0.77–0.97, $P = 0.012$) (Fig. 2) and codominant model (TC vs CC: OR = 0.88, 95% CI = 0.78–0.99, $P = 0.035$) in adults (Table 3). Other genetic models are also summarized in Table 3.

3.3. Subgroup analysis

3.3.1. Atopic asthma. All 18 studies[11,17–19,22,23,33,35–38,42,44,47,48,50,51] containing 7029 subjects reported the association between *CD14 −159C/T* polymorphism and atopic asthma risk. No statistically significant association of *CD14 −159C/T* polymorphism and atopic asthma risk was identified in dominant model (TT+TC vs CC: OR = 0.95, 95% CI = 0.84–1.06, $P = 0.351$) (Fig. 3) and any other genetic models (Table 3).

Subgroup analyses were performed to investigate the potential effect of ethnicity and age. We found no statistically significant relationship of *CD14 −159C/T* polymorphism and atopic asthma risk in either Asian or Caucasian subjects. Additionally, in the subgroup analysis of age, *CD14 −159C/T* variant was also found with no significant association with the risk of atopic asthma in all genetic models (Table 3).

3.3.2. Mixed asthma. A total of 3420 cases and 4808 controls from 17 studies[20–22,26–28,30–32,34,39–41,43,45,46,49] were included in our meta-analysis. Random-effects model was used to calculate the pooled OR and 95% CI because of the presence of moderate heterogeneity in dominant and codominant model (TC vs CC) ($I^2 = 57.2\%$, $P < 0.05$), fixed-effects model in other models (Table 4). By total analysis, the overall gene effect showed no significant association of *CD14 −159C/T* polymorphism and mixed asthma susceptibility in any model (Table 3).

Subgroup analyses were also performed according to ethnicity and age. We found no statistically significant association of *CD14 −159C/T* polymorphism and mixed asthma risk in any genetic model in either Asian or Caucasian subjects (Table 3). Moreover, in subgroup analysis based on age, we found a strong association between the heterozygote (TC) and mixed asthma susceptibility in adults (TC vs CC: OR = 0.84, 95% CI = 0.71–1.00, $P = 0.047$, $I^2 = 3.3\%$). Other genetic models are also showed in Table 3.

3.3.3. Nonatopic asthma. A total of 7 case–control studies[11,17,22,23,33,36,47] conducted among nonatopic asthma were included in this meta-analysis. Overall, the pooled results indicated that there was no significant relationship of *CD14 −159C/T* and nonatopic asthma risk in dominant model (TT+TC vs CC: OR = 1.05, 95% CI = 0.82–1.33, $P = 0.700$) (Fig. 3) and any other genetic comparisons (Table 3). Further subgroup analysis of

Table 2

Distributions of *CD14* −*159C/T* allele and genotypes in different groups.

		Case					Control					
Author	**Year**	**TT**	**TC**	**CC**	**T (%)**	**C (%)**	**TT**	**TC**	**CC**	**T (%)**	**C (%)**	**HWE**
Hakonarson	2001	17	46	31	80 (42.55)	108 (57.45)	19	46	29	84 (44.68)	104 (55.32)	0.92
Koppelman	2001	32	76	51	140 (44.03)	178 (55.97)	42	85	31	169 (53.48)	147 (46.52)	0.31
Lis	2001	6	24	20	36 (36.00)	64 (64.00)	11	34	28	56 (38.36)	90 (61.64)	0.9
Heinzmann	2003	42	89	51	173 (47.53)	191 (52.47)	58	124	79	240 (45.98)	282 (54.02)	0.48
Woo	2003	35	94	46	164 (46.86)	186 (53.14)	6	35	20	47 (38.52)	75 (61.48)	0.1
Cui	2003	49	67	27	165 (57.69)	121 (42.31)	20	42	10	82 (56.94)	62 (43.06)	0.11
Sharma	2004	52	92	43	196 (52.41)	178 (47.59)	85	112	30	282 (62.11)	172 (37.89)	0.47
Kedda	2005	136	284	148	556 (48.94)	580 (51.06)	93	226	124	412 (46.50)	474 (53.50)	0.59
Bernstein	2006	12	33	17	57 (45.97)	67 (54.03)	15	45	15	75 (50.00)	75 (50.00)	0.08
Barnes	2006	15	147	160	177 (27.48)	467 (72.52)	47	204	200	298 (33.04)	604 (66.96)	0.64
Park	2006	30	39	16	99 (58.24)	71 (41.76)	193	267	90	653 (59.36)	447 (40.64)	0.88
Smit	2007	19	47	34	85 (42.50)	115 (57.50)	15	47	26	77 (43.75)	99 (56.25)	0.42
Hong	2007	229	284	113	742 (59.27)	510 (40.73)	60	71	22	191 (62.42)	115 (37.58)	0.89
Chan	2008	80	134	55	294 (54.65)	244 (45.35)	38	77	26	153 (54.26)	129 (45.74)	0.23
Kowal	2008	79	152	141	310 (41.67)	434 (58.33)	45	73	42	163 (50.94)	157 (49.06)	0.27
Wang	2009	160	230	57	550 (61.52)	344 (38.48)	177	236	96	590 (57.96)	428 (42.04)	0.27
Smit	2009	67	107	49	241 (54.04)	205 (45.96)	133	276	145	542 (48.92)	566 (51.08)	0.94
Chen	2009	25	62	63	112 (37.33)	188 (62.67)	42	68	40	152 (50.67)	148 (49.33)	0.25
Bjornvold	2009	15	49	39	79 (38.35)	127 (61.65)	85	233	161	403 (42.07)	555 (57.93)	0.96
Wu	2010	81	117	54	279 (55.36)	225 (44.64)	75	121	31	271 (59.69)	183 (40.31)	0.1
Kuo Chou	2010	35	64	17	134 (57.76)	98 (42.24)	69	118	45	256 (55.17)	208 (44.83)	0.67
Murk	2011	11	55	31	77 (39.69)	117 (60.31)	100	236	137	436 (46.09)	510 (53.91)	0.93
Wu	2011	75	90	23	240 (63.83)	136 (36.17)	25	30	5	80 (66.67)	40 (33.33)	0.33
Perin	2011	64	101	82	229 (46.36)	265 (53.64)	39	70	49	148 (46.84)	168 (53.16)	0.17
Micheal	2011	32	53	25	117 (53.18)	103 (46.82)	31	49	40	111 (46.25)	129 (53.75)	0.06
Rennie	2013	16	53	30	85 (42.93)	113 (57.07)	79	229	126	387 (44.59)	481 (55.41)	0.16
Hussein	2013	75	215	210	365 (36.50)	635 (63.50)	12	70	68	94 (31.33)	206 (68.67)	0.3
Bose	2013	5	12	3	22 (55.00)	18 (45.00)	13	29	8	55 (55.00)	45 (45.00)	0.22
Kljaic-Bukvic	2014	121	201	75	443 (55.79)	351 (44.21)	97	197	78	391 (52.55)	353 (47.45)	0.23
Wang	2014	41	62	23	144 (57.14)	108 (42.86)	40	61	25	141 (55.95)	111 (44.05)	0.84
Sahin	2014	42	63	26	147 (56.11)	115 (43.89)	24	36	15	84 (56.00)	66 (44.00)	0.82
Zhang	2015	99	163	100	361 (49.86)	363 (50.14)	74	190	120	338 (44.01)	430 (55.99)	0.94
Feng	2015	56	76	20	188 (61.84)	116 (38.16)	42	60	14	144 (62.07)	88 (37.93)	0.29
Martinez-Aguilar	2015	97	206	118	400 (47.51)	442 (52.49)	116	198	116	430 (50.00)	430 (50.00)	0.1

HWE = Hardy–Weinberg equilibrium.

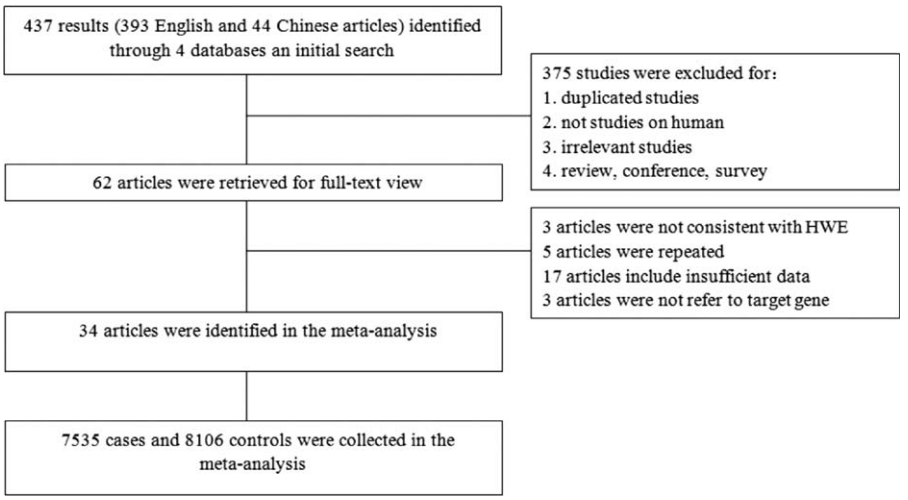

Figure 1. Flow diagram of included and excluded studies.

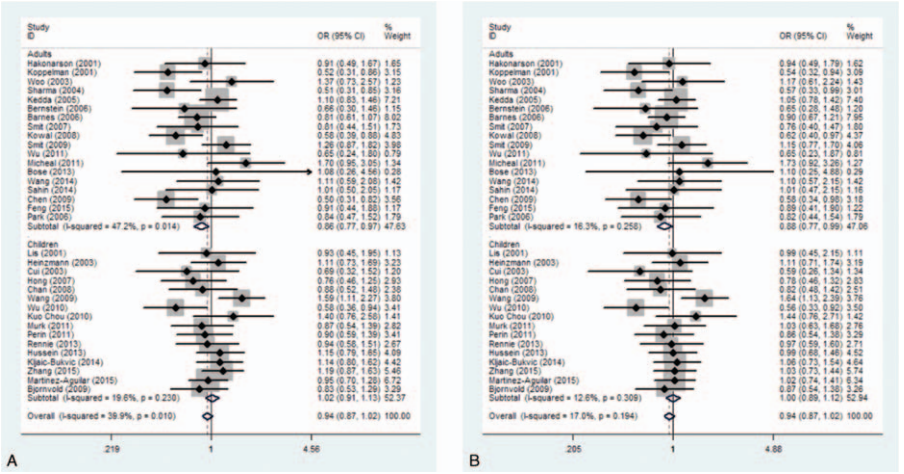

Figure 2. Meta-analysis of ORs and 95% CIs of each study and pooled data for the association of *CD14 −159C/T* variant and asthma risk: subgroup analysis by age. (A) For dominant model: TT+TC versus CC. (B) For heterozygous model: TC versus CC. CI = confidence interval, I-squared = measure to quantify the degree of heterogeneity in meta-analyses, OR = odds ratio.

studies comparing nonatopic asthmatics and nonasthmatics by ethnicity and age did not meaningfully change the results.

3.4. Sensitivity analysis

In order to examine the influence of the individual data set on the pooled ORs and evaluate the stability of the results, in this current meta-analysis, we carried out a sensitivity analysis by sequentially excluding individual studies to assess the stability of the results. The corresponding pooled ORs were similar in all genetic models, indicating that the results were stable (data not shown).

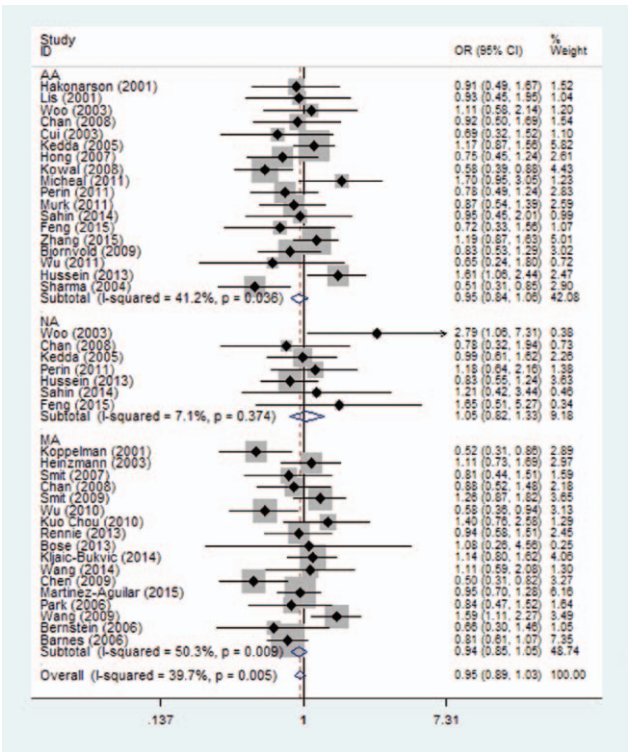

Figure 3. Meta-analysis of ORs and 95% CIs of each study and pooled data for the association of *CD14 −159C/T* variant and asthma risk: subgroup analysis by atopic status (AA, NA, and MA) in dominant model: TT+TC versus CC. AA = atopic asthma, CI = confidence interval, I-squared = measure to quantify the degree of heterogeneity in meta-analyses, MA = mixed asthma, NA = nonatopic asthma, OR = odds ratio.

3.5. Publication bias

Publication bias was assessed through the Begg funnel plot and Egger regression intercept tests. The shape of the Begg funnel plot did not reveal basically asymmetric distribution in all comparisons of the overall population. Moreover, the result of Egger test ($P = 0.203$) further provided no evidence of significant publication bias. Our observation of symmetric funnel plots and nonsignificant statistical tests confirmed no publication bias (Fig. 4).

4. Discussion

Asthma is a complex disease caused by many genetic and environmental risk factors, leading to heterogeneous clinical features.[1,52] Although the exact etiology of asthma remains incompletely clear, there is accumulating evidence showing that the initiation and progression of asthma are affected by *CD14 −159C/T* polymorphism.[23,29,53] Recently, many new case–control studies on this subject have been published. However, the data have yielded conflicting results.[11,21,30–36] Therefore, we performed this updated meta-analysis to investigate the more precise association between the *CD14 −159C/T* variant and asthma risk.

In this meta-analysis, we investigated the *CD14 −159C/T* polymorphism with 34 separate case–control studies (7535 cases and 8106 controls) regarding the association of this gene to the risk of asthma. No significant overall association was detected between *CD14 −159C/T* and asthma. Nevertheless, a moderate heterogeneity was detected in this meta-analysis, which may be attributed to different characteristics of the cohort, intrinsic complexity of asthma architecture, and different asthma definitions. Therefore, we carried out subgroup analysis to investigate heterogeneity by ethnicity, age, and asthma subtypes.

Strongly and significantly decreased risk of asthma was observed when the analysis was restricted to adults in dominant

Table 3

Summary of overall results and subgroup for the association between *CD14 −159C/T* and asthma.

	N	TT+TC vs CC OR (95% CI)	P*	TT vs TC+CC OR (95% CI)	P*	TT vs CC OR (95% CI)	P*	TC vs CC OR (95% CI)	P*	T vs C OR (95% CI)	P*
Overall	34	0.94 (0.87–1.02)	0.136	0.99 (0.92–1.08)	0.921	0.91 (0.78–1.07)	0.264	0.94 (0.87–1.02)	0.147	0.96 (0.89–1.03)	0.282
Ethnicity											
Caucasian	17	0.94 (0.85–1.05)	0.29	0.99 (0.88–1.11)	0.884	0.92 (0.76–1.14)	0.391	0.95 (0.85–1.06)	0.336	0.96 (0.87–1.05)	0.373
Asian	15	0.95 (0.83–1.08)	0.426	1.01 (0.90–1.13)	0.871	0.92 (0.71–1.19)	0.514	0.93 (0.81–1.08)	0.349	0.97 (0.86–1.09)	0.567
Age											
Adults	18	0.86 (0.77–0.97)†	0.012†	0.93 (0.83–1.05)	0.25	0.82 (0.63–1.06)	0.131	0.88 (0.78–0.99)†	0.035†	0.91 (0.81–1.03)	0.142
Children	16	1.02 (0.91–1.13)	0.775	1.05 (0.94–1.16)	0.386	1.02 (0.85–1.23)	0.805	1.00 (0.89–1.12)	0.972	1.02 (0.94–1.10)	0.674
Atopic status											
Atopic											
Overall	18	0.95 (0.84–1.06)	0.351	1.05 (0.86–1.28)	0.646	0.96 (0.73–1.26)	0.764	0.91 (0.80–1.02)	0.114	0.99 (0.87–1.12)	0.82
Caucasian	9	0.89 (0.76–1.05)	0.16	0.94 (0.73–1.21)	0.648	0.86 (0.64–1.17)	0.341	0.90 (0.76–1.06)	0.19	0.93 (0.80–1.07)	0.298
Asian	8	0.92 (0.76–1.11)	0.396	1.02 (0.81–1.28)	0.88	0.89 (0.61–1.31)	0.554	0.88 (0.72–1.08)	0.214	0.97 (0.81–1.15)	0.706
Adults	9	0.90 (0.76–1.06)	0.212	0.95 (0.76–1.17)	0.615	0.87 (0.60–1.27)	0.478	0.90 (0.75–1.08)	0.239	0.94 (0.78–1.12)	0.473
Children	9	0.99 (0.85–1.16)	0.907	1.14 (0.86–1.51)	0.436	1.04 (0.69–1.57)	0.839	0.91 (0.77–1.08)	0.288	1.03 (0.86–1.11)	0.738
Nonatopic											
Overall	7	1.05 (0.82–1.33)	0.7	0.96 (0.73–1.26)	0.749	1.05 (0.61–1.79)	0.863	1.09 (0.85–1.41)	0.496	1.01 (0.86–1.18)	0.944
Caucasian	4	1.22 (0.88–1.71)	0.239	1.01 (0.71–1.44)	0.944	1.32 (0.67–2.62)	0.426	1.25 (0.88–1.78)	0.208	1.13 (0.84–1.51)	0.432
Asian	2	1.06 (0.52–2.15)	0.869	1.11 (0.66–1.86)	0.697	1.08 (0.34–3.40)	0.896	1.07 (0.51–2.25)	0.865	1.05 (0.61–1.82)	0.86
Adults	4	1.28 (0.88–1.88)	0.197	1.19 (0.83–1.69)	0.346	1.62 (0.73–3.60)	0.24	1.27 (0.85–1.88)	0.246	1.16 (0.93–1.14)	0.18
Children	3	0.91 (0.66–1.24)	0.546	0.69 (0.44–1.07)	0.099	0.67 (0.39–1.18)	0.164	0.98 (0.71–1.37)	0.925	0.87 (0.69–1.08)	0.204
Mixed											
Overall	17	0.94 (0.85–1.05)	0.278	0.97 (0.87–1.08)	0.589	0.89 (0.71–1.11)	0.297	0.96 (0.86–1.07)	0.464	0.95 (0.86–1.05)	0.309
Caucasian	8	0.96 (0.79–1.15)	0.629	1.03 (0.88–1.20)	0.726	0.97 (0.75–1.26)	0.819	0.97 (0.82–1.13)	0.657	0.98 (0.86–1.12)	0.802
Asian	8	0.92 (0.66–1.29)	0.637	0.98 (0.84–1.14)	0.77	0.91 (0.64–1.30)	0.612	0.98 (0.80–1.18)	0.796	0.95 (0.81–1.12)	0.537
Adults	9	0.80 (0.63–1.01)	0.056	0.89 (0.74–1.07)	0.21	0.73 (0.49–1.09)	0.122	0.84 (0.71–1.00)†	0.047†	0.87 (0.73–1.04)	0.129
Children	8	1.04 (0.85–1.28)	0.684	1.02 (0.89–1.16)	0.809	1.05 (0.84–1.31)	0.678	1.06 (0.91–1.24)	0.438	1.02 (0.94–1.12)	0.586

CI = confidence interval, OR = odds ratio, TC vs CC = heterozygote, TT vs CC = homozygote, TT vs TC+CC = recessive model, TT+TC vs CC = dominant model.

* The *P*-values of Z test for odds ratios test.

† Significant difference.

(TT+TC vs CC) and codominant (TC vs CC) models. In the subgroup of asthma subtypes, these results suggested that the heterozygote (TC) may strongly decrease the risk for developing mixed asthma in adults. But we found no statistically significant association of *CD14 −159C/T* variant and asthma susceptibility in either atopic or nonatopic asthma. However, we must be careful when we refer to the finding. The mixed asthma was an overly broad collection of different phenotypes, which may have unknown underlying confounding factors to not reveal a credible relationship. Interestingly, the pooled results of this study were inconsistent with the results of previous meta-analysis,[24,25] which showed that the TT and TC genotypes were associated with decreased risk of atopic asthma compared with CC in Asian and children. The following reasons may be plausible explanation of the contradictory results: the small sample was included in the 2 meta-analyses, so the results may reveal an unreliable association, also there are 18 case–control studies including 7029 subjects eligible for this meta-analysis among atopic asthma, therefore the result of this meta-analysis may be closer to the real value; there is a lack of golden standard for asthma phenotype definitions, resulting in the misclassification of cases and reduction of statistical power, besides, as we know, several other risk factors, including different environmental exposure, clinical information, and further subtypes, may have an effect on the results and contribute to moderate heterogeneity; and different genotyping methods and various experimental protocols, and different life backgrounds may make these results incredible. Nevertheless, no sufficient data were utilized to conduct further analysis by these factors.

CD14 is an essential membrane receptor for LPS and plays a role in innate immunity and inflammatory response.[14,15,29] One variant on the *CD14* gene in the pathway of pathogenesis, *159C/T* (rs2569190), may alter the structure and function of protein and influence the *CD14–LPS* interactions and sCD14 levels.[54] But *CD14 −159C/T* variant plays no clear role in developing all asthma, atopic and nonatopic asthma, based on this review. The results were consistent with some recent studies.[11,21,23,36] However, this may be due to the mediating environmental conditions and the unclear relationship between *−159C/T* variant and sCD14 levels. It was demonstrated that the association of the *−159C/T* polymorphism and asthma is dependent on different degrees of endotoxin exposure: individuals with TT genotypes were protective for asthma at low levels of endotoxin, but were at risk at high levels of endotoxin exposure. Conversely, carriers of C allele upon exposure to high levels of endotoxin showed a reversed protective effect.[55] Furthermore, some studies have reported that *−159C/T* variant was correlated with sCD14 levels and the potential effect on asthma was described,[16,47] but the effect may be affected by several polymorphisms and many additional regulatory elements influencing the gene expression. Consequently, only increasing the number of populations, without taking gene–environment and gene–gene interaction into account, will not guarantee the validity of the results. In addition, some GWAS have reported some loci were correlated with total IgE, such as HLA-DQB1, but no *CD14 −159C/T* variant.[56] This may be due to the slight effect of this polymorphism on asthma risk. When subgroup analysis was stratified based on adults, the genotype-specific ORs showed a protective effect. This result was in line with the

Table 4

Summary of the between-study heterogeneity for the association between *CD14 −159C/T* and asthma.

		TT+TC vs CC		TT vs TC+CC		TT vs CC		TC vs CC		T vs C	
	N	I^2 (%)*	P_{het}†	I^2 (%)*	P_{het}†	I^2 (%)*	P_{het}†	I^2 (%)*	P_{het}†	I^2 (%)*	P_{het}†
Overall	34	39.9	0.01	38.2	0.014	56	<0.001	17	0.194	51	<0.001
Ethnicity											
Caucasian	17	14.1	0.288	27.1	0.145	41.9	0.036	0	0.739	41.6	0.037
Asian	15	58.9	0.002	25	0.178	59.7	0.002	49.1	0.016	56.4	0.004
Age											
Adults	18	47.2	0.014	42.2	0.031	61.4	<0.001	16.3	0.258	60.2	0.001
Children	16	19.6	0.23	31.9	0.107	42.7	0.036	12.6	0.309	24.9	0.173
Atopic status											
Atopic											
Overall	18	41.2	0.036	61.3	< 0.001	66.8	<0.001	0	0.503	65.5	<0.001
Caucasian	9	3.3	0.408	40.4	0.098	44.1	0.074	0	0.645	41.6	0.09
Asian	8	49.3	0.055	46.2	0.072	61.6	0.011	24.1	0.237	59.5	0.016
Adults	9	54.7	0.024	33.5	0.15	62.1	0.007	31.2	0.169	62	0.007
Children	9	24.4	0.227	72.4	< 0.001	71.5	<0.001	0	0.794	68.9	0.001
Nonatopic											
Overall	7	7.1	0.374	43.3	0.102	52.6	0.049	0	0.727	41.9	0.111
Caucasian	4	14.4	0.32	39.3	0.176	54	0.089	0	0.586	45.2	0.14
Asian	2	0	0.323	52.3	0.148	49.1	0.161	0	0.563	55.8	0.133
Adults	4	19.3	0.293	44.9	0.142	56.2	0.077	0	0.579	49.3	0.116
Children	3	0	0.606	0	0.443	12.7	0.318	0	0.671	0	0.592
Mixed											
Overall	17	50.3	0.009	29.5	0.122	57.2	0.002	37.3	0.061	51.1	0.008
Caucasian	8	30.7	0.183	19.6	0.275	42.5	0.095	2.6	0.41	44.2	0.084
Asian	8	66.2	0.004	0	0.549	59.6	0.016	61.4	0.011	54.8	0.03
Adults	9	40.7	0.096	54	0.026	63.6	0.005	3.3	0.408	60.9	0.009
Children	8	47.2	0.066	0	0.744	34.6	0.152	47.5	0.064	6.6	0.379

CI = confidence interval, OR = odds ratio, TC vs CC = heterozygote, TT vs CC = homozygote, TT vs TC+CC = recessive model, TT+TC vs CC = dominant model.

* The value of I^2 statistics for heterogeneity test.

† *P*-value of the Q-test for heterogeneity test.

hypothesis at low endotoxin exposure levels by Martinez.[55] Some studies reported that serum sCD14 might be increased at specific time points, suggesting a time window at which adults may be more vulnerable for exposure.

There were several potential limitations in this meta-analysis. First, several risk factors, such as environment–gene/gene–gene interaction, different characteristics of the cohort, and life style, may affect the susceptibility to asthma. However, no further analysis could be conducted due to lack of original information. Second, a majority of studies were conducted regarding Asian and Caucasian populations and the pooled results may be only applicable to the 2 ethnic populations. Therefore, we need to verify the association in other ethnicities. Despite these limitations, a strict protocol, data identification, and statistical analysis were performed to reduce potential bias through the whole process. Thus, the objectivity and reliability of the results are guaranteed.

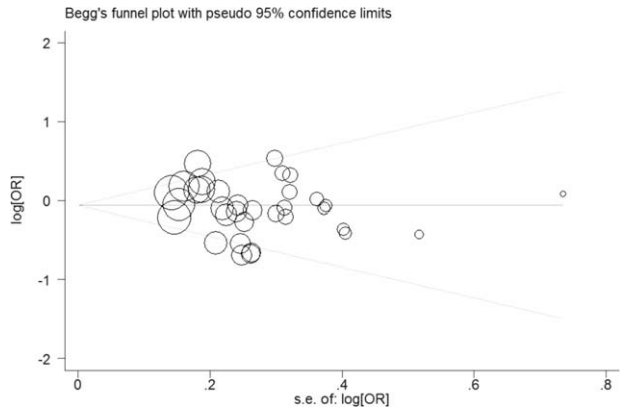

Figure 4. Funnel plot for evaluation of publication bias on the association between asthma risk and the *CD14 −159C/T* variant (dominant model: TT+TC vs CC). Each point represents a separate study for the indicated association. Log (OR) = natural logarithm of OR; horizontal line: mean effect size.

5. Conclusion

The meta-analysis results suggested *CD14 −159C/T* polymorphism may be significantly associated with decreased risk of asthma in adults. However, there may be no significant association between *CD14* −159C/T and atopic and nonatopic asthma risk. In the future, there is a need for larger sample size and more ethnic groups to further validate the results of the current meta-analysis.

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