

Interleukin-13 +2044 G/A and +1923C/T polymorphisms are associated with asthma susceptibility in Asians

A meta-analysis

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Abstract

A number of studies have reported that the interleukin 13 (IL-13) gene is associated with asthma susceptibility. However, the reported relationships between the +2044G/A and +1923C/T polymorphisms and asthma susceptibility are inconsistent, especially in Asian adults and children with atopic status. Meta-analysis was used to analyze combined data.

The +2044G/A and +1923C/T polymorphisms were investigated using data from 18 and 11 studies, respectively. The results suggested that there was an association between asthma and the IL-13 +2044G/A polymorphisms: odds ratio (OR) 1.34, 95% confidence interval (CI) 1.03–1.75 for AA versus GG+GA and +1923C/T; OR 1.50, 95% CI 1.26–1.78 for TT versus CC; and OR 1.15, 95% CI 1.10–1.21 for TC versus CC. The subgroup meta-analysis demonstrated that IL-13 +2044G/A polymorphisms are associated with asthma: OR 1.47, 95% CI 1.06–2.04 for AA versus GG+GA and +1923C/T; OR 1.70, 95% CI 1.26–2.30 for TT versus CC; and OR 1.27, 95% CI 1.03–1.56 for TC versus CC. In particular, IL-13 +2044G/A polymorphisms are specifically associated with Asian ethnicity in both adults and children with atopic status. However, the 1923C/T polymorphisms were not significantly associated with age group or atopic status within the Asian subgroups. Further investigation using larger samples and meta-analysis is required. No publication bias was detected.

This meta-analysis indicates that the IL13 +2044G/A and +1923C/T polymorphisms are risk factors for asthma, especially among Asians.

Abbreviations: BHR = bronchial hyper-reactivity, HWE = Hardy-Weinberg equilibrium, IL-13 = interleukin 13, SNP = single-nucleotide polymorphism, Th1 = T helper cells 1, Th2 = T helper cells 2.

Keywords: +1923C/T polymorphisms, +2044 G/A polymorphisms, Asians, asthma, IL-13

1. Introduction

Asthma is a chronic inflammatory disease in which many cells of the innate and adaptive immune systems act together with inflammatory cells to cause bronchial hyper-reactivity (BHR), airway smooth muscle contraction, mucus overproduction, and airway remodeling. Worldwide, more than 300 million people are affected by asthma. The total cost of the disease is estimated to

exceed \$18 billion annually in the USA, including direct medical costs and indirect costs of lost productivity.^[1] The asymmetric functions of T helper cells 1 (Th1) and 2 (Th2) play an important role in causing asthma.^[2,3] Mice lacking key Th2 cytokines interleukin (IL)-4, IL-5, or IL-13 have reduced inflammation reactions in asthma features in the ovalbumin model.^[4] IL-13 is important for BHR and for goblet cell metaplasia, which can produce thick mucus containing the releasing mucins MUC5AC and MUC5B, which obstruct the airway lumen.^[5,6]

It is well-known that single-nucleotide polymorphisms (SNP) can be used to assess genetic disorders, on which basis multiple phenotypes have been associated with altered levels of IL-13. Two SNPs, positioned at regions +2044G/A and +1923C/T, have been linked to effective production of IL-13. Heinzmann et al^[7] first reported an association between the IL13 G+2044A variant and high asthma risk in Japanese and British populations. Recent studies have suggested that IL-13 +1923C/T polymorphism plays a critical role in the development of asthma. Although +2044G/A polymorphisms have been correlated with asthma susceptibility in several studies,^[8–10] neither the influences of age nor Asian populations have been described. One study^[11] reported a relationship between +1923C/T polymorphisms and asthma susceptibility; however, the influences of atopic phenotypes and age were not analyzed in Asians. Thus, pooled analysis of all available studies is necessary.

In this study, we sought to determine the association between IL-13 +2044G/A and +1923C/T polymorphisms and asthma susceptibility in Asian specifically, by including recently published studies, to evaluate the pathogenesis of asthma from a novel perspective.

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The authors declare that they have no conflicts of interest.

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2. Materials and methods

2.1. Search strategy and data extraction

This meta-analysis was not involved in an ethics committee or institutional review board. We considered all studies that examined the association between IL-13 and asthma, identified using PubMed, EMBASE, and China National Knowledge Infrastructure database (Wanfang database) from 2001 to 2014. Search terms were as follows: (gene or allele or polymorphism) and (IL-13), (+2044G/A), or (+1923C/T and asthma). Searches were performed in duplicate by 2 independent reviewers (QHM and JJQ). Only English and Chinese-language papers were included.

To explain the relationship between IL-13 and asthma susceptibility in Asians, different genotypes of +2044G/A and +1923C/T polymorphisms were extracted. The following information was extracted from each study: author, publication year, country, ethnicity, age group, positions, atopic status, and the number of cases. Disagreements were resolved by discussion between the authors.

2.2. Inclusion and exclusion criteria

All selected studies were evaluated for the following inclusion criteria: evaluation of the +2044G/A and +1923C/T polymorphisms in IL-13 gene and asthma risk; inclusion of odds ratio (OR) and 95% confidence interval (CI) estimates; use of a case-control design. Studies were excluded on the basis on the following criteria: not relevant to IL-13 +2044G/A and +1923C/T polymorphism or asthma risk; reviews or abstracts; sample size not reported; and animal study. For overlapping studies, the most recent or largest-sample report was selected.

2.3. Assessment of quality scores

The quality of the included studies was evaluated by JJQ using a standardized quality assessment scoring system for studies of genetic association with asthma, as recommended by

Thakkinstian et al.^[12] The criteria covered the representativeness of cases and controls, ascertainment of cases and controls, genotyping examination, Hardy-Weinberg equilibrium (HWE), association assessment, and response rate. Total scores ranged from 0 (worst) to 15 (best). Any disagreement was adjudicated by a third investigator (JJQ). Low-quality studies with scores of 4 or lower were excluded from analyses.

2.4. Statistical analysis

We used the meta-analysis method described by Thakkinstian et al.^[12] Briefly, ORs OR1, OR2, and OR3 were employed to calculate the genetic effects: AA versus GG (OR1), AG versus GG (OR2), and AA versus AG (OR3) for +2044G/A; TT versus CC (OR1), TC versus CC (OR2), and TT versus TC (OR3) for +1923C/T. We used a different method depending on the condition: OR1 = OR3 = 1 and OR2 = 1, recessive model; OR1 = OR2 = 1 and OR3 = 1, dominant model; OR2 = 1/OR3 = 1 and OR1 = 1, completely over-dominant model; and OR1 > OR2 > 1 and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1), codominant model.^[12] Heterogeneity of data was evaluated using the Q statistic and further analyzed by the I^2 test.^[13] If $I^2 < 50%$, a fixed-effect model was used^[14]; otherwise, a random-effect model was used as appropriate.^[15] Subgroup analysis was conducted to assess ethnicity, age, and atopic status. A funnel plot was used to verify the potential publication bias by Egger linear regression test. Statistical analyses were conducted using STATA 11.2 (Stata, College Station, TX). A P value < .05 was considered statistically significant.

3. Results

3.1. Study characteristics

The process of selection is shown in Fig. 1. A total of 712 articles were chosen after searching and screening. Ultimately, 25 eligible case-control studies were included, all of which assessed the

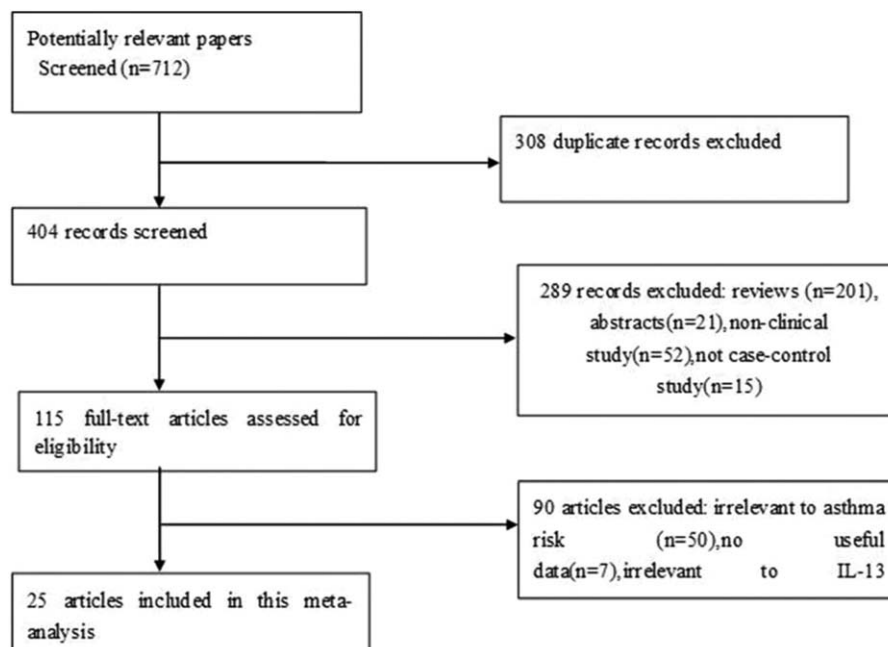


Figure 1. Study flow chart.

relationship between IL-13 +2044G/A and +1923C/T polymorphism and asthma risk; the studies represented 16,917 asthmatic cases and 32,522 controls.^[16–40] Of these 25 studies, 18 reported IL-13 +2044G/A and 11 reported IL-13 +1923C/T. Eleven studies were conducted on adults, 7 on children, and 4 on both adults and children. Regarding ethnicity among the included studies, 15 studies examined Asians, 9 studies examined Caucasians, and 1 study examined Africans. The major characteristics of each group are in Table 1. Genotype numbers and results of +2044G/A and +1923C/T HWE examination are listed in Tables 2 and 3.

3.2. Meta-analysis of available data

3.2.1. IL-13 +2044G/A. Table 4 shows results of the meta-analysis for IL-13 +2044G/A and asthma. We analyzed the OR1 (genotype AA vs GG), OR2 (genotype GA vs GG), and OR3 (genotype AA vs GA); we choose the recessive model of analysis (genotypes AA vs GG+GA; OR 1.34, 95% CI 1.03–1.75, *P* = .031), which indicated that IL-13 +2044G/A increased risk of asthma (Fig. 2). To further evaluate the relationship between IL-13 +2044G/A and asthma, we conducted subgroup analyses. IL-13 +2044G/A was significantly associated with Asians (OR 1.47, 95% CI 1.06–2.04, *P* = .020) (Fig. 2). Next, we conducted further analyses on age and atopic status within the Asian subgroups. Increased asthma risk was found in children (OR 1.59, 95% CI 1.05–2.40, *P* = .030), but not adults (OR 1.31, 95% CI 0.75–2.27, *P* = .344), in both atopic (OR 1.63, 95% CI 0.58–4.61, *P* = .355) and in nonatopic asthmatics (OR 1.41, 95% CI 0.97–2.05, *P* = .071).

In short, the IL-13 +2044G/A polymorphism was significantly associated with asthma. In the subgroup based on Asian ethnicity, there was association between the IL-13 +2044G/A polymorphism and asthma, especially in children, indicating that geographic and age difference may lead to heterogeneity among studies. IL-13 +2044G/A maybe a risk factor in Asian children.

3.2.2. IL-13 +1923C/T. The associations between IL-13 +1923C/T polymorphism and asthma are showed in Table 4. Exploring the comparisons between OR1 (genotype TT vs CC), OR2 (genotype TC vs CC), and OR3 (genotype TT vs TC), we determined that the genetic model was most likely dominant (genotypes TT vs CC OR 1.50, 95% CI 1.26–1.78, *P* = .000; TC vs CC OR 1.15, 95% CI 1.10–1.21, *P* = .000). This model showed that IL-13 +1923C/T increased asthma risk (Fig. 3). A fixed-effect model was chosen for subgroup analysis, on which significant associations were found between IL-13 +1923C/T and Asians (Fig. 3) (OR 1.70, 95% CI 1.26–2.30, *P* = .001), including both Asian adults (OR 2.51, 95% CI 1.16–5.42, *P* = .019) and children (OR 1.50, 95% CI 1.18–1.92, *P* = .001), and both atopic (OR 1.75, 95% CI 1.21–2.51, *P* = .003) and nonatopic asthmatics (OR 2.78, 95% CI 1.64–4.73, *P* = .000) for TT versus CC. Similarly, significant associations were also observed among Asians (OR 1.27, 95% CI 1.03–1.56, *P* = .025) for TC versus CC (Fig. 3). However, there was no significant association between Asian age and atopic status for TC versus CC.

In sum, the IL-13 +1923C/T polymorphism was associated with asthma risk in our meta-analysis. IL-13 +1923C/T was associated with asthma among Asians; for TT versus CC, IL-13

Table 1
Main characteristics of 25 case-control studies in asthmatic patients showing methods for analyzing IL-13 gene promoter +2044 and +1923 regions.

First author/reference	Year	Country	Ethnicity	Age group	Positions	Atopic status
Howard ^[17]	2001	Dutch	Caucasian	Adult	+2044	Nonatopic
Hakonarson ^[18]	2001	Iceland	Caucasian	Mixed	+1923	Atopic
					+2044	
Kauppi ^[19]	2001	Finland	Caucasian	NA	+2044	NA
Leung ^[16]	2001	China	Asian	Children	+2044	Mixed
Xj ^[20]	2004	China	Asian	Adult	+2044	Nonatopic
Liu ^[21]	2004	China	Asian	Adult	+2044	Nonatopic
Liu ^[22]	2004	China	Asian	Adult	+1923	Nonatopic
Donfack ^[23]	2005	American	Caucasian	NA	+1923	Mixed
					+2044	
Zhao ^[24]	2005	China	Asian	Adult	+2044	Nonatopic
Bernstein ^[25]	2006	American	Caucasian	NA	+2044	Atopic
Wei ^[26]	2007	China	Asian	Adult	+2044	Nonatopic
Hosseini-Farahabadi ^[27]	2007	Iran	Asian	Adult	+2044	Nonatopic
Battle ^[28]	2007	American	African	Mixed	+1923	NA
Kim ^[29]	2008	Korean	Asian	Children	+2044	Nonatopic
Wang ^[30]	2009	Taiwanese	Asian	Children	+2044	Nonatopic
Daley ^[31]	2009	Australia	Caucasian	Mixed	+1923	NA
Bottema ^[32]	2010	Dutch	Caucasian	Adult	+2044	Nonatopic
Wu ^[33]	2010	China	Asian	Children	+2044	Nonatopic
					+1923	
Yang ^[34]	2010	China	Asian	Children	+2044	Nonatopic
Moffatt ^[35]	2010	Mixed	Caucasian	Mixed	+1923	NA
Lj ^[36]	2010	American	Caucasian	Adult	+1923	NA
Xue-Xi Yang ^[37]	2011	China	Asian	Adult	+2044	Atopic
Noguchi ^[38]	2011	Japan	Asian	Children	+1923	Atopic
Yoon ^[39]	2012	Korean	Asian	Adult	+1923	NA
Liu ^[40]	2013	China	Asian	Children	+1923	Atopic
					+2044	

IL = interleukin.

Table 2**Distribution of IL-13 +2044G/A genotype among patients and controls.**

First author	n	GG	Asthma GA	AA	n	Control GG	GA	AA	HWE (P)
Howard ^[17]	152	89	52	11	120	67	64	9	.636
Hakonarson ^[18]	94	66	25	3	94	64	27	3	.941
Kauppi ^[19]	163	64	82	17	132	62	51	19	.119
Leung ^[16]	157	54	74	29	54	21	26	7	.812
Xi ^[20]	43	10	25	8	31	16	13	2	.765
Liu ^[21]	100	27	54	19	100	44	46	10	.822
Donfack ^[23]	126	78	41	7	205	127	73	5	.194
Zhao ^[24]	130	18	60	52	100	8	42	50	.842
Bernstein ^[25]	62	32	26	4	75	48	24	7	.046
Wei ^[26]	32	18	8	6	20	15	3	2	.030
Hosseini-Farahabadi ^[27]	30	11	13	6	50	34	10	6	.006
Kim ^[29]	709	301	318	90	227	99	100	28	.769
Wang ^[30]	466	203	194	49	505	212	234	59	.696
Bottema ^[32]	114	57	51	6	89	62	24	3	.706
Wu ^[33]	252	105	111	36	227	125	84	18	.495
Yang ^[34]	178	71	60	47	158	73	66	19	.500
Xue-Xi Yang ^[37]	41	20	15	6	204	90	80	33	.040
Liu ^[40]	384	180	154	50	384	199	169	21	.001

HWE = Hardy-Weinberg equilibrium, IL = interleukin.

+1923C/T associated with Asian adults and children, and with atopic status, indicating that the T allele plays an important role in asthma.

3.3. Study heterogeneity and publication bias

Sensitivity analyses did not change the initial results. There was little modification of the estimates after exclusion of individual studies. Publication bias in the included literature did not show evidence of remarkable asymmetry (Fig. 4), as supported by Egger test (all $P > .1$).

4. Discussion

Asthma is 1 of the most common chronic airway inflammations in humans. Asthma is estimated to cause over 3000 deaths and cost over \$56 billion annually in medical expenses.^[41] The imbalance of type 1 and type 2 immune responses is the main cause of asthma. Th2 cells mainly secrete cytokines IL-4, IL-5, and IL-13, which stimulate type 2 immunity to induce an immune response.^[42,43] IL-13 is an important mediator of asthma exacerbations. Clinical trial data for IL-13-directed therapies show a strong effect on decreasing asthma exacerbation,

implicating IL-13 as a mediator of inflammation in asthma.^[44] In addition, many experimental results have demonstrated that IL-13 may direct increased airway inflammation and is involved in airway remodeling in asthma. Introduction of exogenous IL-13 into murine airways results in eosinophilic and lymphocytic increases, airway muscle contraction, and airway hyper-responsiveness.^[5,6] Furthermore, the inhibition of IL-13 alone in vivo prevents and reverses established mucus cell changes, indicating that IL-13 plays an important role in mucus hyperproduction.^[45,46] These cumulative results suggest that IL-13 is the major effector of asthma exacerbation. Moreover, in the Human Genome Project, it was very popular to use SNPs to detect the localization of the genetic determinants of human disease. Numerous studies have revealed that the IL-13 +2044A/G SNP markedly increases the risk of developing asthma.^[16–21,23–27,29,30,32–34,37,40] Meanwhile, many studies have found that the IL-13 +1923C/T polymorphism is associated with asthma risk.^[18,22,23,28,31,33,35,36,38–40] Thus, it is interesting to study the +2044A/G and +1923C/T polymorphisms associated with asthma.

In this study, we included 25 case-control studies with specific information about the relationship between the +2044A/G and

Table 3**Distribution of IL-13 +1923C/T genotype among patients and controls.**

First author	n	CC	Asthma CT	TT	n	Control CC	CT	TT	HWE (P)
Hakonarson ^[18]	94	65	27	2	94	64	27	3	.942
Liu ^[21]	100	24	55	21	100	43	47	10	.583
Donfack ^[23]	126	72	45	9	205	120	77	8	.310
Battle ^[28]	264	31	117	113	176	21	77	72	.953
Daley ^[31]	644	422	199	23	751	516	213	22	.997
Wu ^[33]	252	106	114	32	227	126	85	16	.794
Moffatt ^[35]	10365	6306	3558	501	16110	10310	5156	644	.984
Li ^[36]	473	257	183	33	1892	1217	601	74	.985
Noguchi ^[38]	938	387	439	112	2376	1125	1025	226	.735
Yoon ^[39]	44	20	17	7	7450	3583	3127	731	.202
Liu ^[40]	384	174	164	46	384	179	169	36	.505

HWE = Hardy-Weinberg equilibrium, IL = interleukin.

Table 4

Meta-analysis of the IL-13 polymorphisms in asthma.

SNP	Comparison	Subgroup	Meta OR (95% CI)	Analysis P	Heterogeneity I ² (%)	Test P	
+2044G/A	AA vs GG	All	1.49 (1.11–2.01)	.009	53.0	.004	
		All	1.25 (1.04–1.49)	.015	38.3	.051	
		All	1.18 (0.98–1.42)	.087	55.1	.003	
		All	1.34 (1.03–1.75)	.031	50.0	.008	
		Asian	1.47 (1.06–2.04)	.020	61.0	.003	
		Age (Asian)					
		Adult	1.31 (0.75–2.27)	.344	44.7	.107	
		Children	1.59 (1.05–2.40)	.030	71.1	.004	
		Atopic status (Asian)					
		Atopic	1.63 (0.58–4.61)	.355	73.3	.053	
+1923C/T	TT vs CC	All	1.50 (1.26–1.78)	0.000	33.2	0.133	
		All	1.17 (1.06–1.29)	0.001	0.0	0.854	
		All	1.15 (1.10–1.21)	0.000	28.3	0.175	
		Asian	1.70 (1.26–2.30)	.001	34.9	.189	
		Age (Asian)					
		Adult	2.51 (1.16–5.42)	.019	34.0	.218	
	TT vs TC	Children	1.50 (1.18–1.92)	.001	34.9	.318	
		Atopic status (Asian)					
		Atopic	1.75 (1.21–2.51)	.003	0.0	.742	
		Nonatopic	2.78 (1.64–4.73)	.000	0.0	.420	
		TC vs CC	Asian	1.27 (1.03–1.56)	.025	41.6	.160
			Age (Asian)				
	TC vs CC	Adult	1.43 (0.68–3.04)	.347	63.3	.097	
		Children	1.23 (1.00–1.52)	.051	41.6	.160	
		Atopic status (Asian)					
		Atopic	1.00 (0.74–1.35)	.991	0.0	.468	
		Nonatopic	1.72 (1.24–2.38)	.001			

CI=confidence interval, IL=interleukin, OR=odds ratio, SNP=single-nucleotide polymorphisms.

+1923C/T polymorphisms in IL-13 and asthma in a meta-analysis. Although 4 meta-analyses have revealed evidence that these 2 polymorphisms are associated with significantly increased risk of asthma in overall analyses,^[8–11] none reported the relationship between these polymorphisms within specific Asian age groups and atopic status. Wang et al^[10] did not analyze whether +2044A/G was associated with Asian ethnicity. Our

findings are in agreement with linkage studies showing that these 2 polymorphisms are associated with asthma risk factors, especially in Asians. The difference between the other meta-analyses and ours is that we focused specifically on Asian subgroups. The results of our meta-analysis suggest that there is an association between the IL-13 +2044G/A and +1923C/T polymorphisms, and asthma susceptibility. Our subgroup meta-

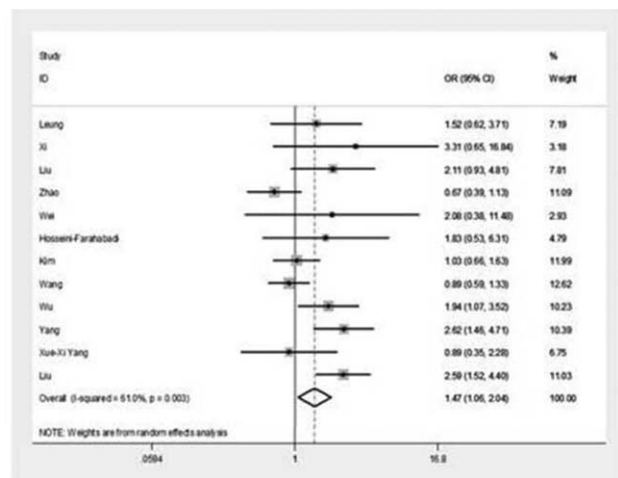
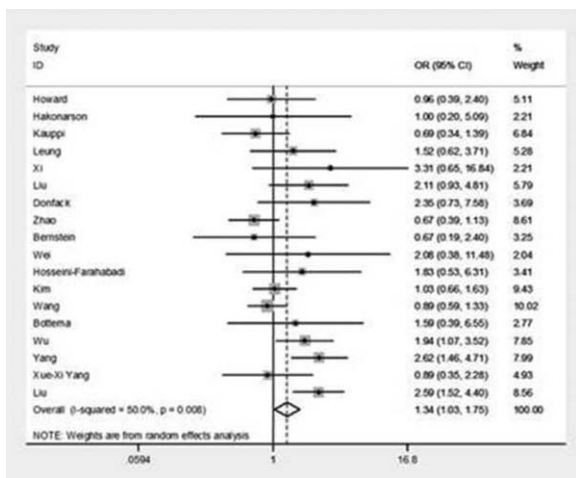


Figure 2. Forest plot of ORs and 95% CIs of +2044G/A between asthmatics and controls in studies related to HWE (A), Asian (B) for AA versus GG + GA test. CI=confidence interval, HWE=Hardy-Weinberg equilibrium, OR=odds ratio.

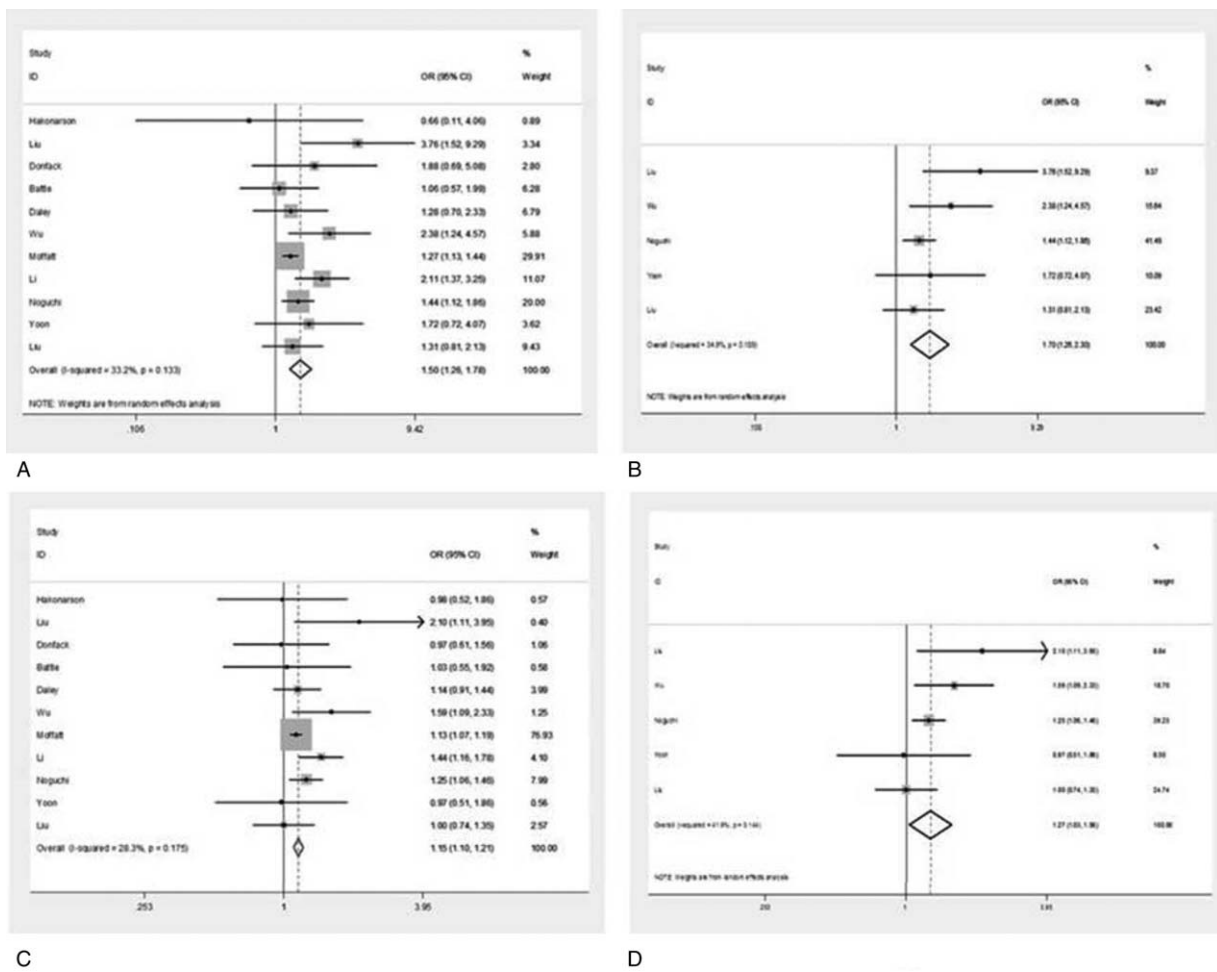


Figure 3. Forest plot of ORs and 95% CIs for +1923C/T between asthmatics and controls in studies including HWE (A), Asian (B) for TT versus CC test; ORs and 95% CIs for +1923C/T between asthmatics and controls in studies including HWE (C), Asian (D) for TC versus CC test. CI=confidence interval, HWE=Hardy-Weinberg equilibrium, OR=odds ratio.

analysis also demonstrates that the IL-13 +2044G/A and +1923C/T polymorphisms are associated with Asian ethnicity; in particular, the IL-13+2044G/A polymorphism is associated with participants who were Asian adults or children, and with Asians who had atopic status. However, the +1923C/T polymorphisms were not associated with Asian age group or atopic status. We also carried out sensitivity analysis to assess the

stability of this meta-analysis. Sequential removal of each study did not alter the conclusions regarding increased asthma risk, suggesting that these results are reliable. Thus, there is no publication bias in our meta-analysis.

There are several limitations to our meta-analysis. First, the number of published studies was insufficient for comprehensive analysis, particularly for the +1923C/T polymorphism; there

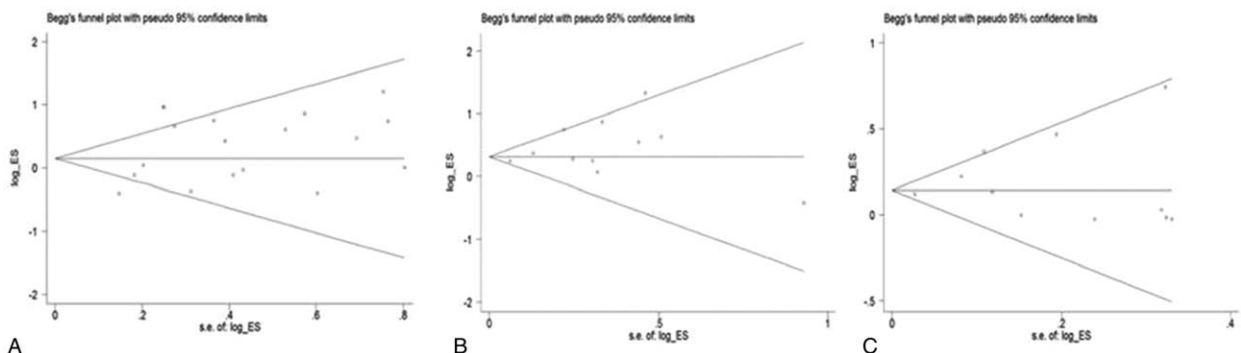


Figure 4. Funnel plot for asthma risk and the IL-13 2044G/A (A) or +1923C/T (B, C) polymorphisms. IL=interleukin.

were only 2 studies that included atopic and nonatopic status within Asians for the +1923C/T polymorphisms analysis. Second, heterogeneity may have affected the meta-analysis. Third, because it was not included in these studies' original data, we were unable to evaluate of the effects of gene-gene and gene-environment interactions within the asthma patient population.

5. Conclusions

To the best of our knowledge, this is the first meta-analysis to explain the relationships between the +2044A/G and +1923C/T polymorphisms, and age and atopic status, specifically within Asian samples. Our study results suggest that the IL-13 +2044A/G and +1923C/T polymorphisms are significantly associated with asthma risk; specifically, IL-13 +2044A/G is associated with Asian ethnicity among adults and children with atopic status. Further investigations should also consider gene-gene and gene-environment interactions, and well-designed studies with larger samples should be considered.

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