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META-ANALYSIS

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A Meta-Analysis of IL-13 Polymorphisms and Pediatric Asthma Risk

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: *IL13*–1112C/T and +2044A/G polymorphisms have been reported to be correlated with pediatric asthma susceptibility, but study results were still debatable. Thus, a meta-analysis was conducted.

Material/Methods: PubMed and EMBASE databases were searched. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to calculate the strength of association in the random-effects model or fixed-effects model.

Results: Fourteen case-control studies with 4710 asthma cases and 6086 controls were included in this meta-analysis. *IL13*–1112C/T and +2044A/G polymorphisms were significantly associated with an increased risk of pediatric asthma (OR=1.14, 95% CI 1.01–1.28, P=0.04, I^2=0%; OR=1.20, 95% CI 1.09–1.32, P<0.01, I^2=0%), respectively. In the subgroup analysis by ethnicity, *IL13*–1112C/T polymorphism was significantly associated with pediatric asthma risk in whites (OR=1.29, 95% CI 1.02–1.63, P=0.03, I^2=16%). *IL13* +2044A/G polymorphism was significantly associated with pediatric asthma risk in Asians (OR=1.21, 95% CI 1.10–1.34, P<0.01, I^2=24%).

Conclusions: The results of this meta-analysis suggest that *IL13*–1112C/T and +2044A/G polymorphisms contribute to the development of pediatric asthma.

MeSH Keywords: Asthma • Interleukin-13 • Meta-Analysis • Pediatrics • Polymorphism, Genetic

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Background

Asthma affects nearly 300 million people in the world, and its prevalence has been increasing in most developed countries [1]. It is commonly thought that asthma is a multifactorial disease caused by complex interactions between a variety of genetic and environmental factors.

The Th2 cytokine interleukin-13 (IL-13), which shares significant pathways and many biological activities with IL-4, plays an important role in the development of asthma. It has been also demonstrated that expression of IL-13 is high in bronchial asthma lesions [2]. Blease et al. demonstrated that ablating IL-13 production via delivery of a human IL-13 coupled to a derivative of *Pseudomonas* exotoxin to kill IL-13 producing cells *in vivo* inhibited all features of *Aspergillus*-induced airway disease [3]. Walter et al. demonstrated that allergen challenge of IL-13-deficient mice failed to develop allergen-induced AHR, despite the presence of vigorous, Th2-biased, eosinophilic inflammation [4].

Recently, the association between the *IL13* polymorphisms and susceptibility of pediatric asthma has been investigated extensively [5–18], but the results are conflicting and inconclusive. A previous meta-analysis suggested that *IL13*–1112C/T and +2044A/G polymorphisms were risk factors for asthma [19], but it did not assess the association between the *IL13* polymorphisms and risk of pediatric asthma. Therefore, we performed this meta-analysis to precisely estimate the association between the *IL13*–1112C/T and +2044A/G polymorphisms and susceptibility to pediatric asthma.

Material and Methods

Publication search

Online electronic databases (PubMed and EMBASE) were searched using the search terms: (interleukin-13 or IL-13) and (polymorphism or variant or variation) and (asthma or asthmatic). The last search was performed on 10 June 2014. We also searched the reference lists of all retrieved articles and relevant reviews. There was no language restriction.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) the study must have evaluated the association between the *IL13* polymorphisms and pediatric asthma risk (age <18 years); (2) the study must have a case-control design; and (3) sufficient data should have been provided to calculate odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following conditions applied: (1) only abstracts or reviews were available, without sufficient data; (2) animal studies; and (3) studies were repeated or publications overlapped.

Data extraction and qualitative assessment

The following data were recorded from each article: first author, year of publication, ethnicity of participants, atopic status, numbers of cases and controls, and genotype number in cases and controls. The data were extracted by 2 of the authors independently (Liu and Li). Any discrepancy was resolved by discussion (Liu and Li).

Two authors (Liu and Li) completed the quality assessment independently. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality, which scored studies by the selection of the study groups, the comparability of the groups, and the ascertainment of the outcome of interest. We considered a study awarded 0–3, 4–6, or 7–9 as a low-, moderate-, or high-quality study, respectively. Discrepancies were resolved by consensus and discussion (Liu and Li).

Statistical analysis

The strength of association between the *IL13* polymorphisms and pediatric asthma risk was assessed by calculating OR with 95% CI. The pooled ORs were performed for the dominant model since most of the studies reported the results in this genetic model. Departure from Hardy-Weinberg equilibrium (HWE) in controls was tested by the chi-square test. A statistical test for heterogeneity was performed based on the Q statistic. The $P>0.10$ of the Q test indicated a lack of heterogeneity among studies. If heterogeneity was observed among the studies, the random-effects model was used to estimate the pooled OR (the DerSimonian and Laird method). Otherwise, the fixed-effects model was adopted (the Mantel-Haenszel method). Stratified analysis was performed by ethnicity and atopic status, if possible. Potential publication bias was examined by Egger's test [20]. All statistical tests were performed with the software STATA version 11.0 (Stata Corporation, College station, TX, USA). A P value <0.05 was considered statistically significant.

Results

Study characteristics

Figure 1 outlines the study selection process. Briefly, a total of 276 articles were identified after an initial search. After removing duplications, 55 articles were excluded. After reading the titles and abstracts, 197 articles were excluded because of abstracts, reviews, and irrelevant to pediatric asthma risk or *IL-13* polymorphisms. After reading full texts of the remaining 24 articles, 10 studies were then excluded and 14 studies

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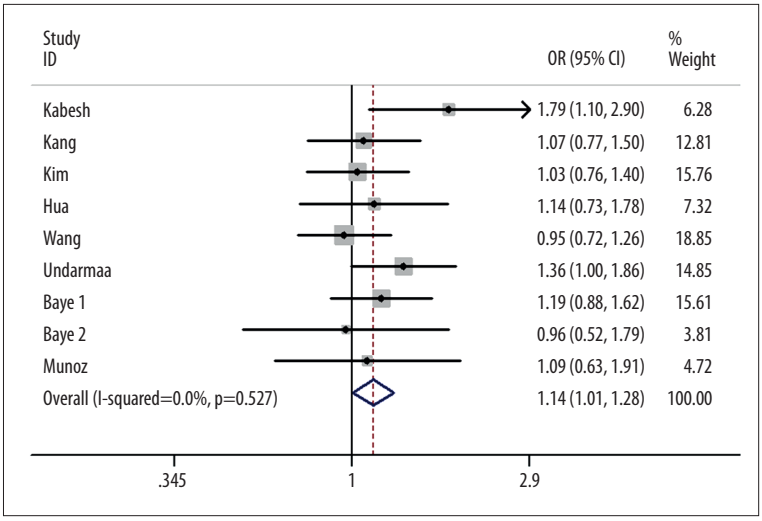

Figure 1. Meta-analysis of the association between the *IL13*–1112C/T polymorphism and pediatric asthma risk.

Table 1. Characteristics of the studies.

Study	Year	Ethnicity	Atopic status	Case number	Control number	Quality score
Leung	2001	Asian	Mixed*	157	54	6
Xi	2004	Asian	NA	43	31	6
Kabesch	2006	Caucasian	NA	73	773	7
Kang	2007	Asian	NA	374	242	8
Chan	2008	Asian	Mixed	273	141	8
Kim	2008	Asian	Mixed*	715	240	7
Hua	2009	Asian	NA	192	192	6
Wang	2009	Asian	Mixed	446	511	8
Undarmaa	2010	Asian	Atopic	325	336	9
Wu	2010	Asian	NA	252	227	6
DeWan	2010	Mixed	Atopic	104	503	7
Baye 1	2011	Caucasian	NA	413	298	8
Baye 2	2011	African American	NA	315	51	8
Noguchi	2011	Asian	Mixed	938	2376	9
Munoz	2012	Caucasian	NA	90	111	6

* Both atopic and non-atopic data can be extracted. NA – not available.

remained [5–18]. One study reported 2 cohorts [16], and each cohort was considered as a case-control study. Finally, 4710 asthma cases and 6086 controls were included in this meta-analysis. Ten case-control studies included Asian populations, 3 studies were performed in white populations, and study included African-Americans. All studies were assessed by NOS. The quality scores ranged from 6 to 9, suggesting that the methodological quality was acceptable. All studies suggested that the distribution of genotypes in the controls was consistent with HWE. The characteristics of each case-control study and the genotype in each study are presented in Tables 1 and 2.

Results of meta-analysis

IL13–1112C/T polymorphism and pediatric asthma risk

The association between *IL13*–1112C/T polymorphism and pediatric asthma risk was investigated in 9 case-control studies,

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Table 2. Distribution of *IL13* genotype among patients and controls.

Study	Patient			Control			HWE
–1112C/T	**CC**	**CT**	**TT**	**CC**	**CT**	**TT**	
Kabesch	34	33	6	471	263	39	Yes
Kang	236	128	10	156	79	6	Yes
Kim	455	236	25	155	80	6	Yes
Hua	136	47	9	141	45	6	Yes
Wang	316	113	17	357	136	18	Yes
Undarmaa	186	119	20	227	98	11	Yes
Baye 1	242	149	22	187	98	13	Yes
Baye 2	116	152	49	18	25	8	Yes
Munoz	45	34	11	58	46	7	Yes
+2044A/G	**AA**	**AG**	**GG**	**AA**	**AG**	**GG**	
Leung	29	74	54	7	26	21	Yes
Xi	8	25	10	2	13	16	Yes
Kang	48	166	160	28	100	101	Yes
Chan	43	136	94	17	70	54	Yes
Kim	90	318	301	28	100	99	Yes
Wang	203	194	49	212	234	59	Yes
Undarmaa	36	144	145	34	149	156	Yes
Wu	36	111	105	18	84	125	Yes
DeWan	5	34	65	23	171	309	Yes
Baye 1	26	157	230	14	101	183	Yes
Baye 2	8	87	220	1	14	36	Yes
Noguchi	113	438	387	232	1033	1111	Yes
Munoz	21	52	17	23	65	23	Yes

HWE – Hardy-Weinberg equilibrium.

with a total of 2944 cases and 2754 controls. The TT and CT genotypes of *IL13*-1112C/T polymorphism was associated with a significantly increased risk of pediatric asthma when compared with CC genotype (OR=1.14, 95% CI 1.01–1.28, *P*=0.04, *I2*=0%; Figure 2). When stratified by ethnicity, a significantly elevated risk was observed in whites (OR=1.29, 95% CI 1.02–1.63, *P*=0.03, I^2=16%) but not in Asians (OR=1.09, 95% CI 0.94–1.26, *P*=0.24, I^2=0%). Subgroup analysis of the atopic status showed that no increased risk was found in atopic patients (OR=1.18, 95% CI 0.94–1.47, *P*=0.15, I^2=40%). Results of meta-analysis are listed in Table 3. Publication bias was assessed by funnel plot. The shape of the funnel plot was symmetric (Figure 3). No significant publication bias was detected by Egger's test (*P*=0.54).

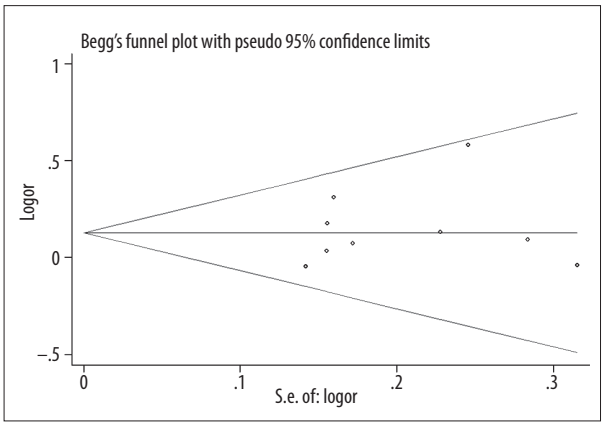

Figure 2. Funnel plot for the *IL13*–1112C/T polymorphism and pediatric asthma risk.

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Table 3. Detailed results of meta-analysis.

	Association		Heterogeneity	
	OR (95% CI)	*P* Value	*P* Value	I^2 (%)
–1112C/T				
Overall	1.14 (1.01–1.28)	0.04	0.53	0.0
Caucasian	1.29 (1.02–1.63)	0.03	0.31	16.0
Asian	1.09 (0.94–1.26)	0.24	0.56	0.0
Atopic	1.18 (0.94–1.47)	0.15	0.20	40.0
+2044A/G				
Overall	1.20 (1.09–1.32)	<0.01	0.44	0.0
Caucasian	1.24 (0.94–1.64)	0.13	0.76	0.0
Asian	1.21 (1.10–1.34)	<0.01	0.23	24.0
Atopic	1.05 (0.87–1.27)	0.62	0.64	0.0

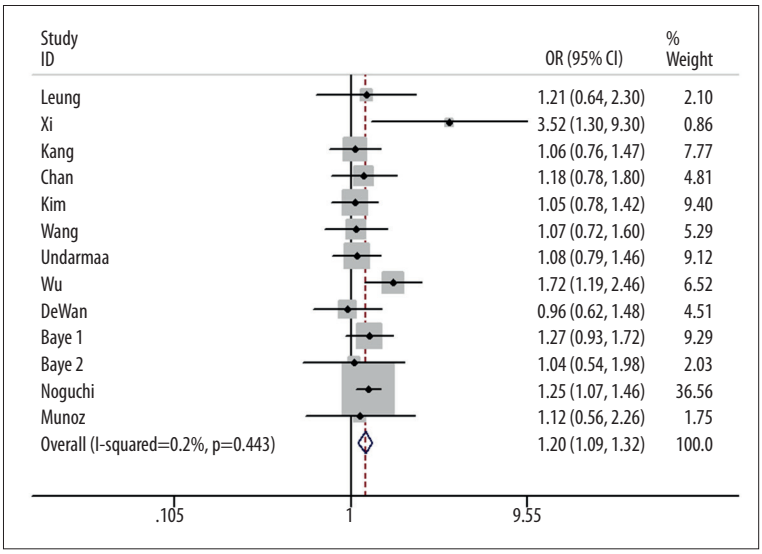

Figure 3. Meta-analysis of the association between the *IL13* +2044A/G polymorphism and pediatric asthma risk.

IL13 +2044A/G polymorphism and pediatric asthma risk

The association between *IL13* +2044A/G polymorphism and pediatric asthma risk was investigated in 13 case-control studies, with a total of 4439 cases and 5089 controls. The AA and AG genotypes of *IL13* +2044A/G polymorphism was associated with a significantly increased risk of pediatric asthma when compared with GG genotype (OR=1.20, 95% CI 1.09–1.32, *P*<0.01, I^2=0%; Figure 4). When stratified by ethnicity, a significantly elevated risk was observed in Asians (OR=1.21, 95% CI 1.10–1.34, *P*<0.01, I^2=24%) but not in whites (OR=1.24, 95% CI 0.94–1.64, *P*=0.13, I^2=0%). Subgroup analysis of the atopic status showed that no increased risk was found in atopic patients (OR=1.05, 95% CI 0.87–1.27, *P*=0.62, I^2=0%). Results of meta-analysis are listed in Table 3. Publication bias was assessed by funnel plot. The shape of the funnel plot was

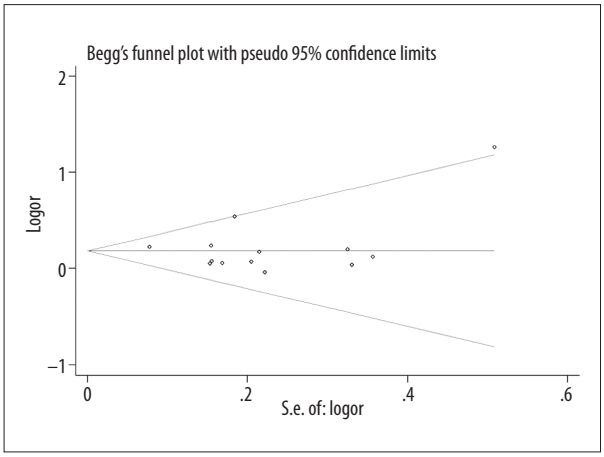

Figure 4. Funnel plot for the *IL13* +2044A/G polymorphism and pediatric asthma risk.

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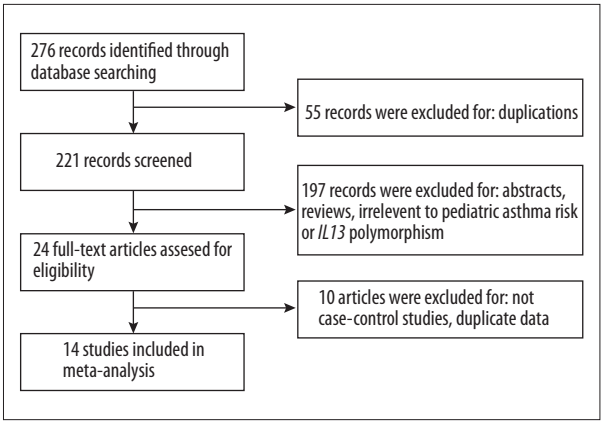

Figure 5. The process of study selection.

symmetric (Figure 5). No significant publication bias was detected by Egger's test (P=0.81).

Discussion

We believe this is the first meta-analysis to investigate the association between *IL13*–1112C/T and +2044A/G polymorphisms and susceptibility to pediatric asthma. We found that *IL13*–1112C/T and +2044A/G polymorphisms were risk factors for developing asthma in children. In the subgroup analysis by ethnicity, we noted that whites carrying the –1112TT or CT genotypes had an increased pediatric asthma risk, and Asians carrying the +2044AA or AG genotypes had an increased pediatric asthma risk. This result suggests a possible association between environmental exposures and different genetic backgrounds. The subgroup analysis based on atopic status showed that *IL13*–1112C/T and +2044A/G polymorphisms were not associated with allergic asthma risk in children. However, only a few studies provided data on atopic status. Therefore, the positive association between these polymorphisms and allergic asthma risk in children could not be excluded. Liu et al. found that +2044A/G polymorphism of the IL-13 gene might play an important role in total serum IgE production [21]. Thus, more studies with atopic subjects are needed.

IL-13 is produced by $CD4^+$ T cells, NK T cells, mast cells, basophils, eosinophils, and nuocytes. IL-13 is thought to be a central regulator in IgE synthesis, mucus hypersecretion, airway hyperresponsiveness (AHR), and fibrosis [22]. Polymorphisms in the IL-13 gene associated with asthma are described at –1112C/T and +2044A/G. It has been reported that the *IL13* +2044A/G polymorphism resulted in decreased affinity of IL-13 for IL-13Rα2, increased expression of IL-13, and phosphorylation of STAT6 [23]. Functional analysis of the -1112C/T polymorphism identified a Yin-Yang 1 binding site activator that overlapped with a STAT motif repressor. The Yin-Yang 1 binding site was hypothesized to increase IL-13 transcription as opposed to STAT6-mediated repression of IL-13 transcription in Th2 cells [24].

Heterogeneity is a potential problem that may affect the interpretation of the results. However, no significant heterogeneity existed in this meta-analysis. In addition, funnel plots and Egger's tests did not find potential publication bias. Altogether, these results suggest that the results of this meta-analysis are reliable.

Some limitations should be addressed. First, there was only 1 case-control study that investigated the association of IL-13 polymorphisms with pediatric asthma risk in African-Americans. Therefore, more studies with larger sample sizes are needed to investigate the association among African-Americans. Second, because small studies with negative results are less likely to published, the possibility of publication bias cannot be completely ruled out, even though the Egger's test and funnel plots did not show evidence of publication bias in this meta-analysis. Third, a lack of original data from the eligible studies limited evaluation of the effects of the gene-gene and gene-environment interactions during pediatric asthma development [25–28].

Conclusions

The results if this meta-analysis suggest that *IL13*–1112C/T and +2044A/G polymorphisms are associated with increased pediatric asthma risk. Further studies with large sample sizes were needed to confirm our findings.

Conflict of interest

The authors have no conflict of interest to disclose.

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