

Accepted Manuscript

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PII: S0198-8859(14)00401-7

DOI: <http://dx.doi.org/10.1016/j.humimm.2014.08.202>

Reference: HIM 9420

To appear in: *Human Immunology*

Received Date: 11 March 2014

Accepted Date: 18 August 2014



Please cite this article as: Zhao, Y-F., Luo, Y-M., Xiong, W., Wu, X-L., Genetic variation in *ORMDL3* gene may contribute to the risk of asthma: A meta-analysis, *Human Immunology* (2014), doi: <http://dx.doi.org/10.1016/j.humimm.2014.08.202>

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Genetic variation in *ORMDL3* gene may contribute to the risk of asthma: A meta-analysis

Running title: *ORMDL3* gene and asthma risk

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ABSTRACT

Background: Since the first genome-wide association study report of an association between the *ORMDL3* rs7216389 polymorphism and asthma, many studies have been carried out to establish its role in asthma susceptibility among different ethnic groups. However, results have not been consistent across all studies, compelling us to conduct the present meta-analysis.

Methods: A literature search for eligible studies published before January 20, 2014 was conducted in the MEDLINE, EMBASE, and CNKI databases. The association was assessed using pooled crude odds ratios (ORs) with their corresponding 95% confidence intervals (CIs).

Results: A total of 18 individual studies in 15 publications (total 7,904 asthma patients and 10,874 healthy controls) were included in the meta-analysis. A meta-analysis of all included studies suggested that there was a highly significant risk effect conferred by the rs7216389*T allele on asthma susceptibility. In addition, we performed stratified analyses to evaluate ethnicity-specific and age-specific effects. Our subgroup analyses based on ethnicity and age-of-onset confirmed the role of the *ORMDL3* rs7216389 polymorphism in conferring susceptibility to both childhood- and adult-onset asthma, especially in Caucasians and Asians.

Conclusions: The results of this meta-analysis firmly established that genetic variation at the rs7216389 locus, which controls the expression of the *ORMDL3*, may be a major, independent predisposing factor for asthma in ethnically diverse populations. However, further systematic studies are needed to determine the underlying mechanisms of this association.

Key words: *ORMDL3* gene, asthma, children, adults, genetics, meta-analysis.

1. Introduction

Asthma is one of the most common chronic inflammatory respiratory disorders in children. It is most prevalent during preschool age and is characterized by recurrent episodes of reversible air way obstruction and increased bronchial hyper-responsiveness [1]. It occurs in at least 5% of the general population [2] and approximately 10% of patients with asthma are prone to severe exacerbations [3]. Although the exact mechanism of the disease is still not fully elucidated, it is recognized as a complex disease triggered by complex interactions of genetic predisposition and environmental factors [4]. Over the past decade, the genetic basis involved in the pathogenesis of asthma has been extensively investigated; more than 200 candidate genes have been proposed to harbor sequence variants associated with asthma or related phenotypes, although few studies have been robustly replicated. [5-8] Recently, Moffatt et al. published the first genome-wide association (GWA) study of 317,000 single-nucleotide polymorphisms (SNPs) in a cohort of 994 white patients with childhood onset asthma and 1,243 non-asthmatics, using family and case-referent panels [9]. They identified a novel susceptibility locus on chromosome 17q12-21, containing multiple genes and associated markers, to be strongly and reproducibly associated with childhood-onset asthma, and replicated these results in two large Caucasian cohorts [9]. Further analyses found that markers of the 17q21 locus regulated the expression of ORM1-like 3 (*ORMDL3*) in Epstein-Barr viruses transformed lymphoblastoid cell lines in asthmatic children, suggesting that the *ORMDL3* gene might be a determinant for susceptibility to asthma [9].

ORMDL3, located at 17q21.1, belongs to the *ORMDL* gene family (*ORMDL1*, *ORMDL2*, and *ORMDL3*), which encodes transmembrane proteins anchored in the endoplasmic reticulum (ER) [10]. Although present knowledge of the *ORMDL3* function is limited, it was found to inhibit the sarco-endoplasmic reticulum Ca^{2+} pump (SERCA) and thus increase the unfolded-protein response (UPR) [11], which is considered as an endogenous inducer of chronic inflammatory diseases such

as asthma [12]. Several potential asthma-associated SNPs in the *ORMDL3* gene were identified. Among them, the SNP rs7216389, as one of the most frequently studied polymorphisms, showed the smallest *P* value for association with childhood asthma and transcription levels of *ORMDL3*. [9] Since the first report of an association with this SNP, many candidate gene association studies have been carried out to establish its role in asthma susceptibility among ethnically diverse populations [13-19]. However, results have not always been consistent across all studies. Conflicts in these studies' findings might be partially due to their different selection criteria of asthmatics and non-asthmatics. Most studies investigated the association in childhood-onset asthma or childhood atopic asthma [13,14,16,18,20], whereas others focused on asthma in adults [17,21,22]. In addition, it was found that the linkage disequilibrium (LD) within the SNP rs7216389 is high, which encompasses not only the *ORMDL3*, but also the gasdermin-A (*GSDMA*), gasdermin-B (*GSDMB*), zona pellucida binding protein 2 (*ZPBP2*), and IKAROS family zinc finger 3 (*IKZF3*) genes [23]. Thus, the differing patterns of LD between the populations may also explain the differences observed in their associations with asthma.

Based on these observations, we performed a meta-analysis to evaluate whether the SNP rs7216389 in the *ORMDL3* gene is a genetic risk factor for the development of asthma. Given that asthma, as a complex human disease, has variable ages of onset, we conducted this meta-analysis modified by enrolled patients (i.e., childhood- and adult-onset asthma). In addition, subgroup analyses on the basis of ethnicity were also conducted. To the best of our knowledge, this study is the first meta-analysis attempt to explore the interaction between the SNP rs7216389 in the *ORMDL3* gene and asthma risk. We hypothesized that the rs7216389 SNP at chromosome 17q21 region is associated with asthma.

2. Materials and methods

The present meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Supplement S1).

2.1 Publication search

We performed an exhaustive search for studies that evaluated the association between the *ORMDL3* rs7216389 polymorphism and asthma. Relevant studies were identified through a computerized search of MEDLINE, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) (Last search was updated on January 20, 2014) with the following medical subject heading (MeSH) terms and/or text words: (“asthma” or “bronchial asthma” or “asthmatic”) and (“*ORMDL3* protein, human” or “ORM1-like 3” or “*ORMDL3*” or “rs7216389”) and (“single nucleotide polymorphism” or “SNP” or “variation” or “genetic polymorphism”). There were no restrictions in language, publication status, race or geographic area. Review articles and bibliographies of identified relevant studies were also searched for additional literature that may not retrieved by our computer-assisted search.

2.2 Selection criteria

All included candidate studies complied with the following three criteria: (1) used a case-control or family-based design; (2) evaluated the *ORMDL3* rs7216389 polymorphism and asthma risk, regardless of subjects’ type of asthma or age; (3) published original data for calculating odds ratios (ORs) with 95% confidence intervals (CIs). Studies were excluded if they met any of the following three criteria: (1) editorials, reviews or reports; (2) not relevant to the rs7216389 polymorphism and asthma; (3) genotype or allele frequencies could not be ascertained. For repeating or overlapping studies, only the one with the most extensive data was included.

2.3 Data extraction

The following data were independently extracted from each study by two investigators: the surname of first author, year of publication, country of subject recruitment, ethnicities, number of asthmatics and non-asthmatics, mean age (or range whenever possible), the type of asthma, study

design, detection methods, allelic and genotypic frequencies information for rs7216389 polymorphism, etc. Asthma was categorized as either childhood- or adult-onset asthma. Subjects' ethnicities were classified as Caucasian, Asian or African. When studies included subjects of more than one ethnicity [13], data were extracted separately according to ethnicity for subgroup analyses. For data not provided in the main text, the required information was obtained by contacting corresponding authors when possible.

2.4 Quality score assessment

The methodological qualities of all included studies were assessed by the Newcastle-Ottawa Scale (NOS) criteria (Supplement S2) [24]. The NOS criteria uses a “star” rating system to judge methodological quality with scores ranging from 0 stars to 9 stars. A score of more than 5 stars indicates a moderate-high quality. Two investigators assessed the quality of all included studies. Discrepancies over quality scores were resolved through discussion between all the authors and subsequent consensus.

2.5 Statistical analysis

All the statistical analyses were conducted using STATA software version 12.0 (Stata Corp, College Station, TX). We first used the Chi-square test to test whether the observed genotype frequencies in controls conformed to Hardy-Weinberg equilibrium (HWE) [25]. Cochran's Q statistic and the I^2 metric (ranging from 0 to 100%) were also used to assess within- and between study heterogeneity [26,27]. When a $P > 0.10$ for Q-test and $I^2 < 50\%$ indicated of the absence of heterogeneity across the studies, a fixed-effects model with the *Mantel-Haenszel* method was used on the pool data; otherwise, a random-effects model with the *DerSimonian-Laird* method was used. A meta-analysis of the association between the *ORMDL3* rs7216389 polymorphism and asthma risk was conducted using the pooled ORs with their corresponding 95% CIs under five genetic models, including the allelic (T allele vs. C allele), dominant (TT + TC vs. CC), recessive (TT vs. TC + CC), homozygous (TT vs. CC), and heterozygous (TT vs. TC) contrasts. In addition to an overall

analysis, stratified analyses were performed to evaluate ethnicity-specific and age-specific effects. To assess the stability of the results, a one-way sensitivity analysis was conducted by sequentially excluded individual studies. In addition, the Begg's funnel plot and Egger's linear regression test were used to statistically assess publication bias [28]. A P -value of < 0.05 was considered statistically significant for the pooled data, except for tests of heterogeneity where a level of 0.10 was used.

3. Results

3.1 Baseline characteristics of included studies

The flow diagram in Fig. 1 showed the study identification and selection process. A total 90 references were preliminarily identified after eliminating 55 duplicate records. Of these, 67 publications were excluded based on a review of titles and abstracts, and the remaining 23 publications were given a full-text evaluation. 8 publications were then excluded for not reporting detailed genotype frequencies [8,23,29-34] and 15 publications that completely met the inclusion criteria were incorporated into the pooled analysis with a total sample size of 7,904 asthmatics and 10,874 non-asthmatics [9,13-22,35-38]. In two publications [13,37], more than one study was presented, each of which was considered separately for analysis. Thus, a total of 18 studies from 15 publications were involved in this meta-analysis. The characteristics and methodological qualities of the included studies are presented in Table 1. The publication years of the 15 publications are: 2007 ($n = 1$), 2008 ($n = 3$), 2009 ($n = 2$), 2010 ($n = 2$), 2011 ($n = 3$), and 2012 ($n = 4$). Of the 18 included studies, 6 studies were conducted in Caucasian populations [9,13,15,16,37], 11 studies in Asian populations [13,14,17-22,35,36,38], and one study in an African population [13]. Age of onset was also considered as a restricted variable. For the 15 publications, 11 publications were performed in children [9,13-16,18-20,35,36,38], 3 in adults [17,21,22], and one in both children and

adults [37]. To profile the rs7216389 polymorphism, the classical polymerase chain reaction-restriction fragment length polymorphism (PCR-RELP) and TaqMan methods were performed in the majority of publications, while the RT-PCR, AS-PCR, and MassARRAY methods were applied in the remaining three publications. The genotype distributions of the controls were in HWE in all but 3 publications [20,21,35]. Table 1 and Fig. 2 summarize NOS assessments. The quality scores of all the included publications were moderate-high, with NOS stars greater than 5.

3.2 Quantitative data synthesis

A summary of our meta-analysis findings on the association between the *ORMDL3* rs7216389 polymorphism and asthma in the overall population and subgroups based on ethnicity and age-of-onset is provided in Table 2. The T nucleotide allele at rs7216389 had an average frequency of 69.6% in asthmatics compared with 63.8% in non-asthmatics. Since two publications did not provide a detailed number of each genotype in case and control groups, they were only included in the allelic comparison (T allele vs. C allele). Meta-analysis of all studies indicated that there was a highly significant risk effect conferred by the rs7216389*T allele on asthma, with an approximately 30-50% increase in the ORs (T allele vs. C allele: OR = 1.31, 95%CI: 1.21-1.41, $P < 0.001$; TT + TC vs. CC: OR = 1.39, 95%CI: 1.25-1.55, $P < 0.001$; TT vs. TC + CC: OR = 1.46, 95%CI: 1.36-1.56, $P < 0.001$; TT vs. CC: OR = 1.48, 95%CI: 1.21-1.81, $P < 0.001$; TT vs. TC: OR = 1.42, 95%CI: 1.32-1.53, $P < 0.001$) (Fig. 3).

Since population stratification is a consideration in studying genetic susceptibility, we conducted a subgroup analysis based on ethnicity. Since only one study conducted in an African population [13] was included in this meta-analysis, an ethnicity-specific meta-analysis was only conducted on Caucasian and Asian populations. Subgroup analysis by ethnicity indicated that the rs7216389*T allele was significantly correlated with increased risk of asthma in both Caucasian populations (T allele vs. C allele: OR = 1.32, 95%CI: 1.10-1.58, $P = 0.003$; TT + TC vs. CC: OR = 1.72, 95%CI: 1.19-2.49, $P = 0.004$; TT vs. TC + CC: OR = 1.44, 95%CI: 1.10-1.88, $P = 0.008$; TT

vs. CC: OR = 2.03, 95%CI: 1.27-3.24, $P = 0.003$; TT vs. TC: OR = 1.68, 95%CI: 1.21-2.30, $P < 0.001$) and Asian populations (T allele vs. C allele: OR = 1.28, 95%CI: 1.20-1.37, $P < 0.003$; TT vs. TC + CC: OR = 1.44, 95%CI: 1.32-1.57, $P < 0.008$; TT vs. CC: OR = 1.32, 95%CI: 1.12-1.56, $P = 0.001$; TT vs. TC: OR = 1.28, 95%CI: 1.17-1.40, $P < 0.001$) (Fig. 4).

Because the age-of-onset is likely to be genetically mediated, we assessed the strength of the association with the rs7216389*T allele stratified by age at onset of asthma by dividing the asthmatic patients into childhood-onset (before or at 18 years of age, $n = 6,585$) and adult-onset subgroups (at or after 19 years of age, $n = 1,319$). Our results showed that the effects of the rs7216389*T allele in childhood-onset asthma cases (T allele vs. C allele: OR = 1.34, 95%CI: 1.22-1.46, $P < 0.001$; TT + TC vs. CC: OR = 1.54, 95%CI: 1.37-1.74, $P < 0.001$; TT vs. TC + CC: OR = 1.46, 95%CI: 1.35-1.59, $P < 0.001$; TT vs. CC: OR = 1.68, 95%CI: 1.35-2.09, $P < 0.001$; TT vs. TC: OR = 1.39, 95%CI: 1.28-1.52, $P < 0.001$) was similar to that seen for adult-onset cases (T allele vs. C allele: OR = 1.20, 95%CI: 1.07-1.35, $P = 0.002$; TT vs. TC + CC: OR = 1.42, 95%CI: 1.22-1.66, $P < 0.001$; TT vs. TC: OR = 1.52, 95%CI: 1.29-1.78, $P < 0.001$) (Fig. 5).

3.3 Sensitivity analysis and publication bias

To determine the stability of the results of this meta-analysis, one-way sensitivity analyses were performed by sequentially excluding individual studies. The pooled ORs of the rs7216389 polymorphism and asthma were not influenced by the results of any individual study, indicating the stability of the results. Furthermore, the potential publication bias of the included studies was assessed by Begg's funnel plot and Egger's linear regression test. The shapes of the funnel plot did not reveal obvious asymmetry. Egger's test also did not show any statistical evidence of publication bias ($t = 1.64$; $P = 0.124$).

4. Discussion

Asthma is a common chronic respiratory disorder that results from a combination of genetic predetermination and environmental factors [4]; it affects at least 5% of the general population [2]. Over the past decade, candidate gene studies have been carried out to identify genetic causes of asthma in various ethnic populations. Many putative SNP markers have been identified by GWA studies [9, 39, 40], which may help improve the prevention and treatment of this difficult to manage condition. The first reported GWA study of asthma in European subjects resulted in the identification of a novel susceptibility locus on chromosome 17q12 [9]. Among asthma-associated SNPs on 17q21 in the initial study, the rs7216389 SNP in the *ORMDL3* gene showed the strongest correlation with childhood asthma and transcription levels of *ORMDL3*, leading the authors to suggest *ORMDL3* as the most likely disease candidate gene [9]. Since then, this finding on the rs7216389 SNP in *ORMDL3* as a candidate polymorphism for childhood-onset asthma susceptibility has been replicated in Puerto Rican [13], Japanese [14], British [15,37], Danes [16], and Korean [18,38] populations, but not in African-American [13], and Chinese [20,35,36] populations. To date, several other studies have also replicated this association for adult-onset asthma in Chinese populations [17,19,22], but not in British populations [37]. These inconsistent findings led us to undertake the present meta-analysis to provide a robust estimate of the effect of this variant on asthma. To the best of our knowledge, this is the first meta-analysis on the topic.

This meta-analysis, including 7,904 asthma patients and 10,874 healthy controls from 18 studies, investigated the association between a functional polymorphism in the *ORMDL3* gene and asthma risk. As shown in Table 2, our results demonstrated a significant risk correlation between the *ORMDL3* rs7216389 polymorphism and asthma in an overall meta-analysis. Although the underlying mechanisms of the associations between the rs7216389 locus on chromosome 17q12 and asthma have not yet been elucidated, there are several possible mechanisms that could be responsible for this connection. First, the rs7216389 SNP controls the expression of the *ORMDL3* gene, which facilitates endoplasmic reticulum mediating inflammatory responses and thereby

influences the regulation of allergen sensitization [18]. In addition, there is evidence that the rs7216389 SNP is associated with increased IgE levels and the severity of bronchial hyper-responsiveness, which are the most important intermediate phenotypes of asthma, as well as with asthma susceptibility [18,38]. It is also possible that our findings are the result of mutations within a large LD block, which includes not only *ORMDL3* but also *GSDMB*, *ZPBP2*, *IKZF3*, *GSDMA*, and *TOP2* genes, suggesting that other genes and mechanisms may also contribute to the association [34].

In addition to an overall analysis, stratified analyses were performed to evaluate ethnicity-specific and age-specific effects. Since only one study conducted in an African population was included in this meta-analysis, ethnicity stratification was just performed for Caucasian and Asian populations. Our results indicated that the rs7216389*T allele is significantly correlated with an increased risk of asthma both in Caucasian and Asian populations, suggesting that the mutation might have the same effects across ethnically and racially distinct populations. However, it is noteworthy that there may be no significant association between the rs7216389*T allele and asthma in African-American patients [13]. For African populations, therefore, caution must be taken in applying these findings and replication is needed for further confirmation. Furthermore, asthmatic patients were also stratified separately according to age-of-onset. We found that individuals who carried the rs7216389*T variant allele not only had an increased risk for developing asthma in childhood, but also presented a substantial risk for the onset of asthma in adulthood, suggesting that childhood- and adult-onset asthma may share certain disease mechanisms. However, further exploration of interaction between the rs7216389 variant and age of onset is warranted since subjects' age of onset supplies important information about the etiology of asthma [16].

Several limitations of this meta-analysis should not be ignored when interpreting these results. First, most of the studies included in this meta-analysis were carried out in Caucasian and Asian populations and thus may not reflect genetic effects in African populations, which demand further

study. Second, in addition to its effects on asthma susceptibility, several studies showed that the rs7216389 polymorphism was also a major risk factor for asthma exacerbations [15,16], a finding that has the potential to improve treatment and prevention. However, the biologic mechanism behind this association remains to be explained. Third, since only one of the included studies focused on childhood atopic asthma [14], we could not examine the association between the rs7216389 SNP and atopic asthma. A detailed characterization of the atopic condition is very important and might explain controversial results, especially when *ORMDL3* gene could influence the regulation of allergen sensitization. Therefore, further studies examining associations for severe asthmatics and atopy status are wanted. The association between the rs7216389 variant and asthma has also been reported to be significantly enhanced by early exposure to tobacco smoke exposure and pet fur, a finding which our study did not evaluate [32,34]. Aside from the limitations listed above, our meta-analysis also has its strengths. Stratified analyses were performed to evaluate ethnicity-specific and age-specific effects, which accounted for population stratification and age-of-onset effects. To the best of our knowledge, this is the first meta-analysis to investigate the correlation between the *ORMDL3* rs7216389 polymorphism and asthma.

In summary, evidence from this meta-analysis confirms the role of the *ORMDL3* rs7216389 polymorphism as a locus conferring susceptibility to childhood- and adult-onset asthma. However, further large, well-designed epidemiological studies are still required to investigate the functional role of this polymorphism and to delineate the pathogenesis of asthma for therapeutic interventions.

Conflict of interest

The authors have no financial or non-financial conflict of interest to declare.

Acknowledgements

The authors thank all subjects enrolled in this study. The present study was supported by the Pudong New Area Health Bureau Foundation of Shanghai (Grant no. PWRd 2012-07 to Yun-feng Zhao) and Key Specialty Construction Project of Pudong Health and Family Planning Commission of Shanghai (Grant no. PWZz 2013-07 to Yun-feng Zhao), and the National Natural Science Foundation of China (Grant no. 81070056 and 81270130 to Xue-ling Wu).

Supporting Information

Supplement S1 The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

Supplement S2 Newcastle-Ottawa Quality Assessment Scale.

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Figure Legends

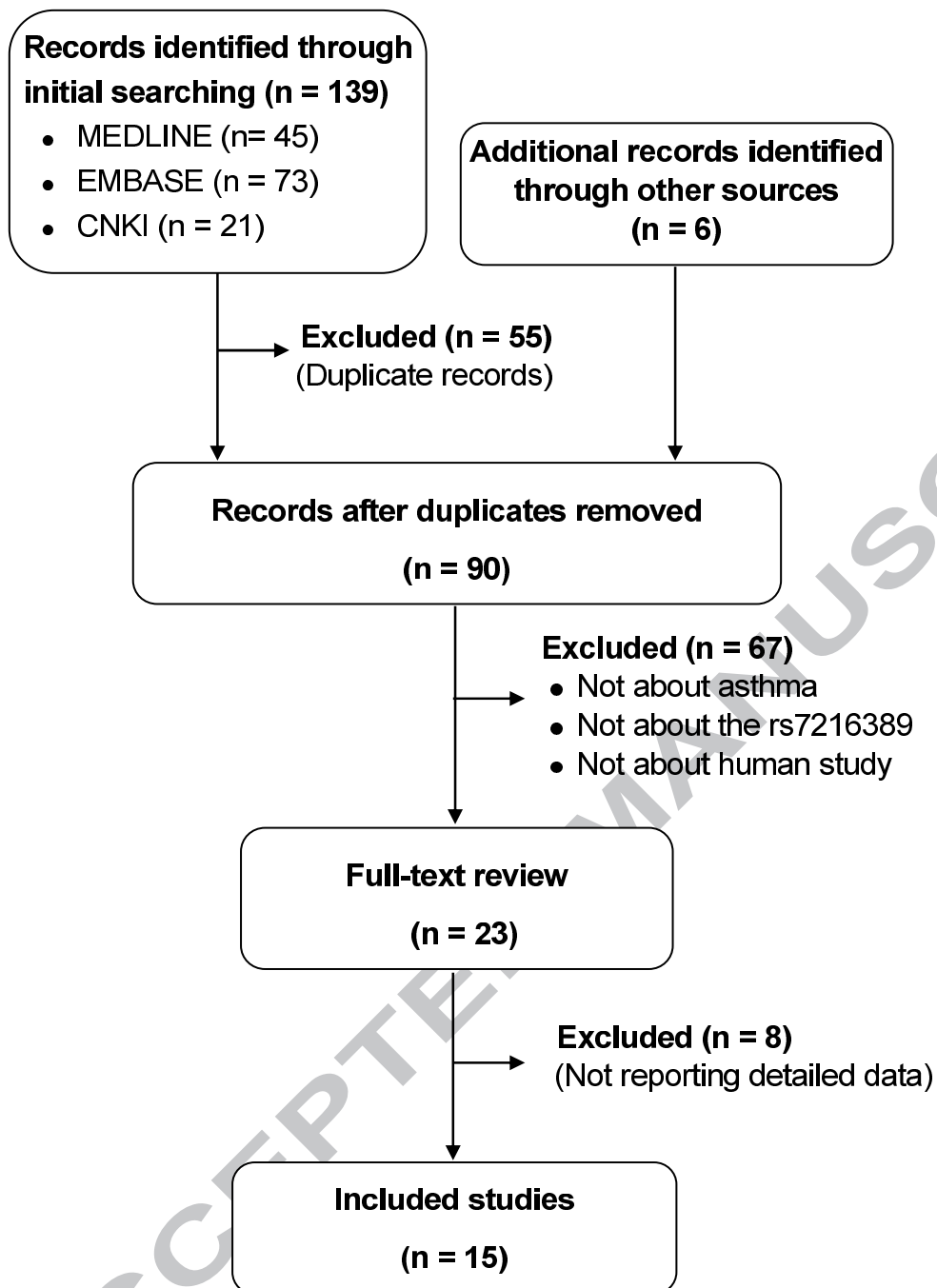
Fig. 1. Flow diagram of study selection and specific reasons for exclusion from the present meta-analysis.

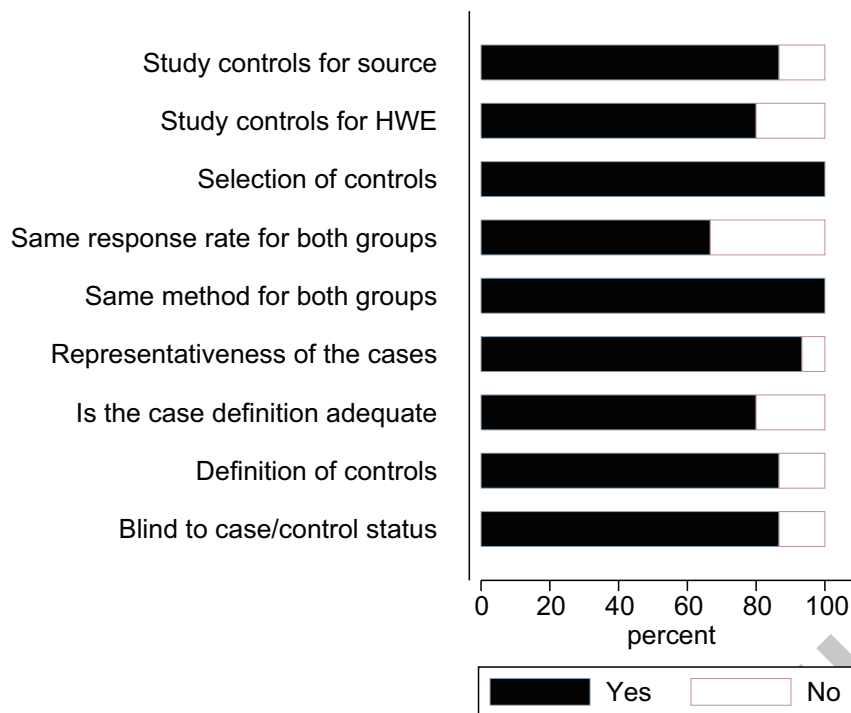
Fig. 2. Quality assessment scale for studies included in this meta-analysis.

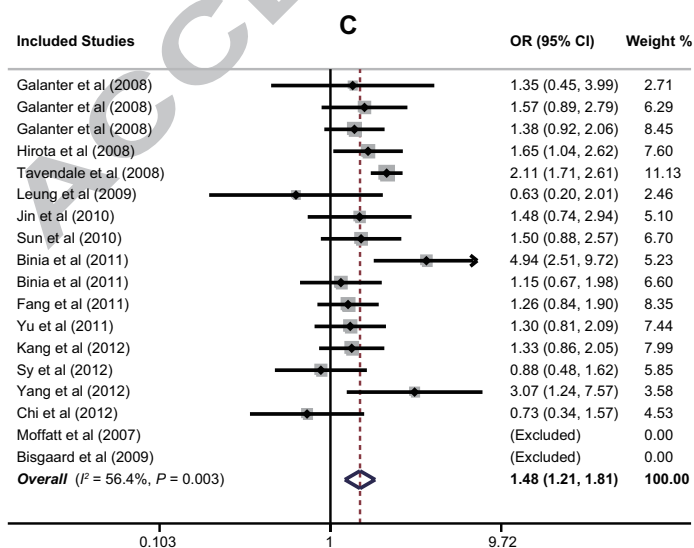
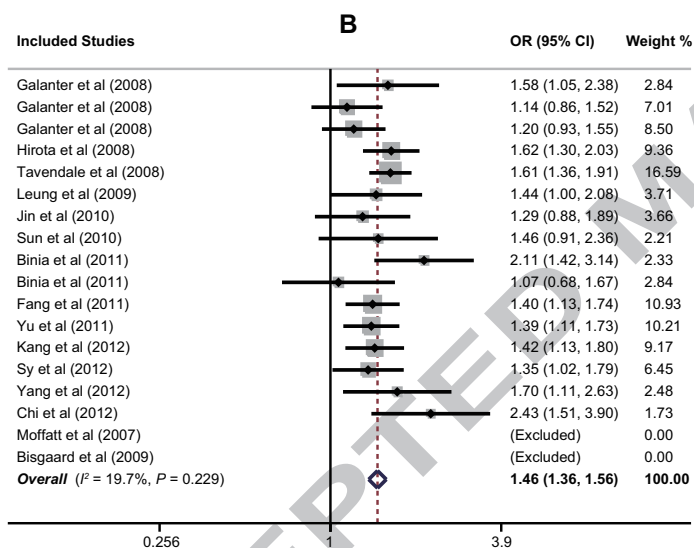
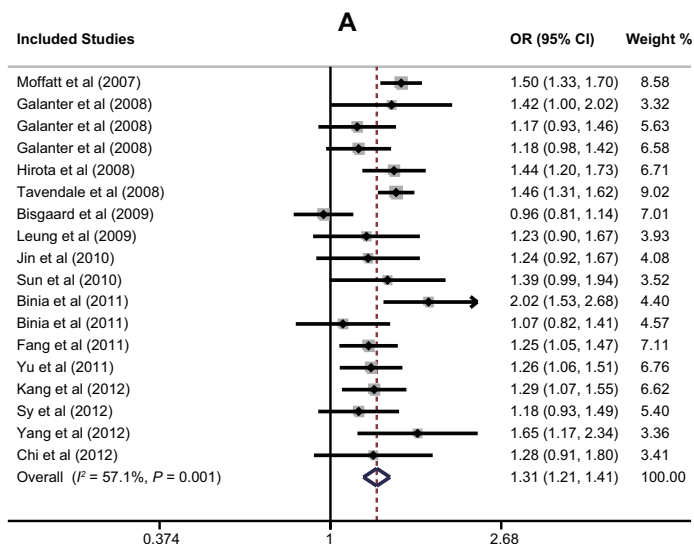
Fig. 3. Forest plot of ORs for the association between the rs7216389 SNP and overall asthma risk (A: T allele vs. C allele; B: TT vs. TC + CC; C: TT vs. CC).

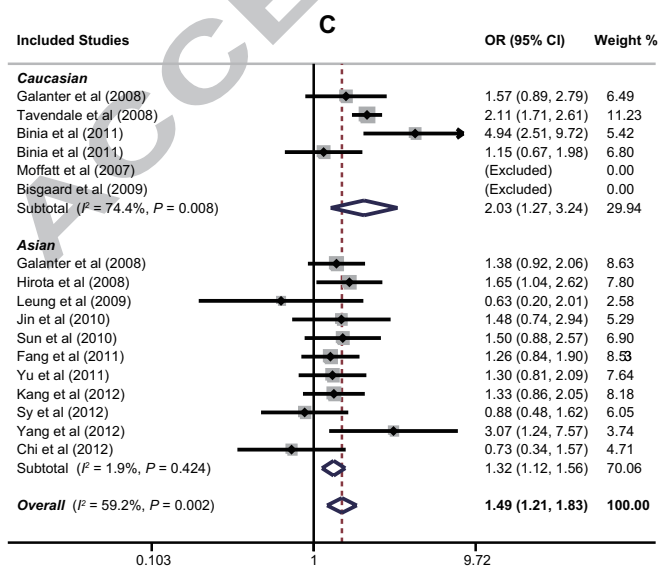
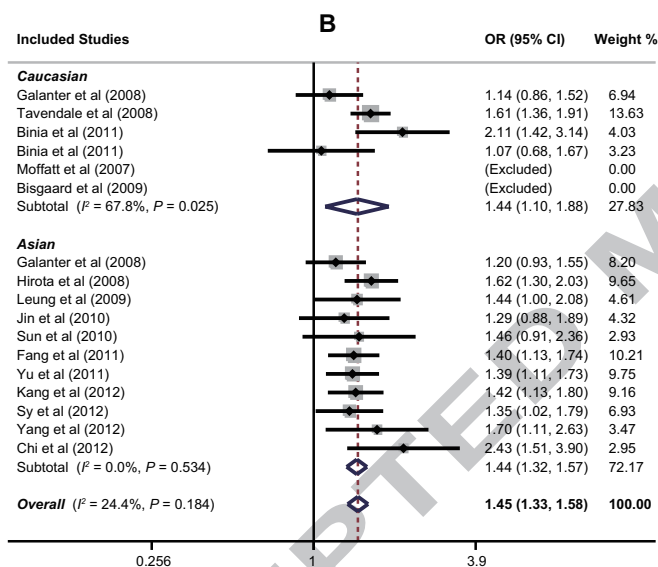
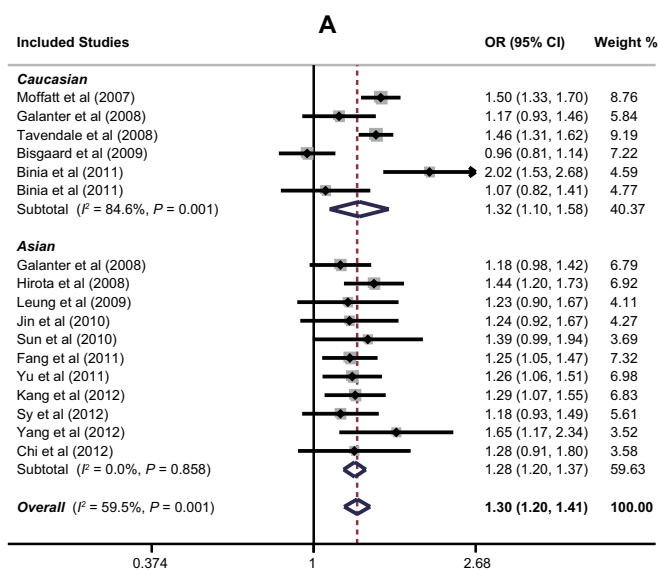
Fig. 4. Forest plot of ORs for the association between the rs7216389 SNP and asthma risk in subgroup analysis by ethnicity (A: T allele vs. C allele; B: TT vs. TC + CC; C: TT vs. CC).

Fig. 5. Forest plot of ORs for the association between rs7216389 SNP and asthma risk in subgroup analysis by age-of-onset (A: T allele vs. C allele; B: TT vs. TC + CC; C: TT vs. TC).









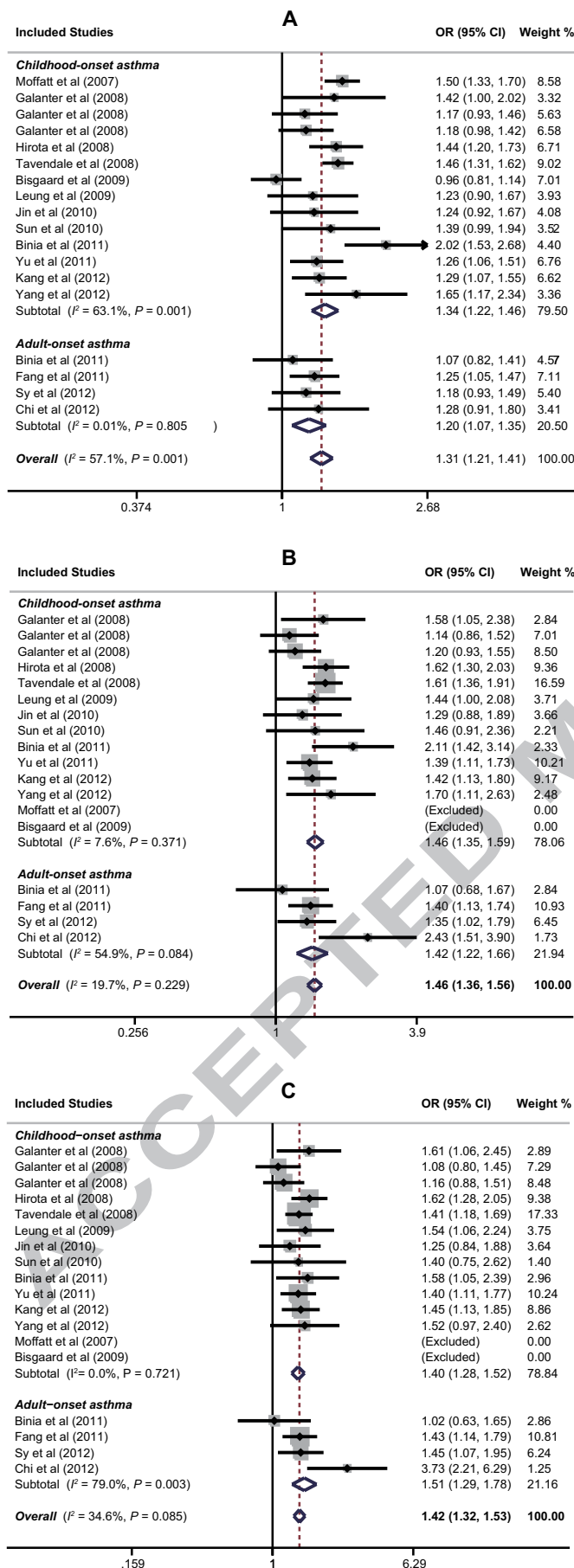


Table 1

Main characteristics and methodological quality of all eligible studies in this meta-analysis

Included studies	Country	Ethnicity	Asthma patients		Healthy controls		Study subjects	Study design	Detection method	MAF (Case/Control)	P value of HWE	NOS star
			Number	Age	Number	Age						
2007 Moffatt et al	UK	Caucasian	994	mean 10.95	1,243	mean 9.62	Childhood-onset asthma	Case-control	RT-PCR	0.620/0.520	0.977	8
2008 Galanter et al	USA	African	259	range 12-14	169	range 12-14	Childhood-onset asthma	Case-control	AS-PCR	0.838/0.784	0.392	8
		Caucasian	289	range 11-19	566	NR.	Childhood-onset asthma	Family	AS-PCR	0.732/0.701	0.804	
		Asian	363	range 10-15	736	NR.	Childhood-onset asthma	Family	AS-PCR	0.668/0.631	0.214	
2008 Hirota et al	Japan	Asian	545	mean 9.50	738	mean 49.0	Childhood-onset asthma	Case-control	TaqMan	0.782/0.713	0.378	8
2008 Tavendale et al	UK	Caucasian	1,279	mean 10.4	1,541	mean 7.50	Childhood-onset asthma	Case-control	TaqMan	0.559/0.464	0.425	8
2009 Bisgaard et al	Denmark	Caucasian	316	NR.	1,500	NR.	Childhood-onset asthma	Family	TaqMan	0.530/0.540	0.976	8
2009 Leung et al	China	Asian	315	mean 11.1	192	mean 11.8	Childhood-onset asthma	Case-control	PCR-RFLP	0.803/0.768	0.010	8
2010 Jin et al	China	Asian	220	mean 5.80	208	mean 7.15	Childhood-onset asthma	Case-control	TaqMan	0.741/0.697	0.529	6
2010 Sun et al	China	Asian	178	mean 12.5	129	mean 13.4	Childhood-onset asthma	Case-control	PCR-RFLP	0.601/0.520	0.001	7
2011 Binia et al	UK	Caucasian	114	NR.	1,429	NR.	Childhood-onset asthma	Case-control	TaqMan	0.645/0.473	0.383	6
			112	NR.	1,429	NR.	Adult-onset asthma	Case-control	TaqMan	0.491/0.473	0.383	
2011 Fang et al	China	Asian	710	mean 28.7	656	mean 29.1	Adult-onset asthma	Case-control	PCR-RFLP	0.737/0.692	0.174	8
2011 Yu et al	Korea	Asian	786	mean 8.98	522	mean 9.69	Childhood-onset asthma	Case-control	PCR-RFLP	0.774/0.730	0.259	8
2012 Kang et al	Korea	Asian	775	mean 8.98	451	mean 9.63	Childhood-onset asthma	Case-control	TaqMan	0.763/0.714	0.628	8
2012 Sy et al	China	Asian	345	mean 44.2	464	mean 42.5	Adult-onset asthma	Case-control	TaqMan	0.778/0.749	0.123	8
2012 Yang et al	China	Asian	152	mean 5.90	190	mean 6.00	Childhood-onset asthma	Case-control	MassARRAY	0.780/0.682	0.562	8
2012 Chi et al	China	Asian	152	mean 39.8	140	mean 41.9	Adult-onset asthma	Case-control	PCR-RFLP	0.684/0.629	0.008	7

NR, not reported; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; RT-PCR, reverse transcription-PCR; AS-PCR, allele-specific-PCR; MAF, minor allele frequency; NOS, the Newcastle-Ottawa scale

Table 2Summary ORs of the association between *ORMDL3* rs7216389 (C>T) and risk for asthma

Genetic models	Study subjects	NO. of studies (Case/Control)	OR (95% CI)	P-value	Test of heterogeneity		
					I ² (%)	P-value	Model
T allele vs. C allele	<i>Overall</i>	18 (7,904/10,874)	1.31 (1.21-1.41)	<0.001	57.1	0.001	Random
	Caucasians	6 (3,104/6,297)	1.32 (1.10-1.58)	0.003	84.6	0.001	Random
	Asians	11 (4,541/4,426)	1.28 (1.20-1.37)	<0.001	0.0	0.858	Random
	Childhood-onset asthma	14 (6,585/9,614)	1.34 (1.22-1.46)	<0.001	63.1	0.001	Random
	Adult-onset asthma	4 (1,319/2,689)	1.20 (1.07-1.35)	0.002	0.0	0.805	Random
TT + TC vs. CC	<i>Overall</i>	16 (6,594/9,560)	1.39 (1.25-1.55)	<0.001	60.8	0.001	Random
	Caucasians	4 (1,794/3,536)	1.72 (1.19-2.49)	0.004	67.5	0.026	Random
	Asians	11 (4,541/4,426)	1.11 (0.90-1.37)	0.320	39.7	0.084	Random
	Childhood-onset asthma	12 (5,275/6,871)	1.54 (1.37-1.74)	<0.001	44.9	0.073	Fixed
	Adult-onset asthma	4 (1,319/2,689)	0.91 (0.71-1.16)	0.450	57.8	0.069	Fixed
TT vs. TC + CC	<i>Overall</i>	16 (6,594/9,560)	1.46 (1.36-1.56)	<0.001	19.7	0.229	Fixed
	Caucasians	4 (1,794/3,536)	1.44 (1.10-1.88)	0.008	67.8	0.025	Random
	Asians	11 (4,541/4,426)	1.44 (1.32-1.57)	<0.001	0.0	0.534	Random
	Childhood-onset asthma	12 (5,275/6,871)	1.46 (1.35-1.59)	<0.001	7.6	0.371	Fixed
	Adult-onset asthma	4 (1,319/2,689)	1.42 (1.22-1.66)	<0.001	54.9	0.084	Fixed
TT vs. CC	<i>Overall</i>	16 (6,594/9,560)	1.48 (1.21-1.81)	<0.001	56.4	0.003	Random
	Caucasians	4 (1,794/3,536)	2.03 (1.27-3.24)	0.003	74.4	0.008	Random
	Asians	11 (4,541/4,426)	1.32 (1.12-1.56)	0.001	1.9	0.424	Random
	Childhood-onset asthma	12 (5,275/6,871)	1.68 (1.35-2.09)	<0.001	49.8	0.025	Random
	Adult-onset asthma	4 (1,319/2,689)	1.07 (0.82-1.41)	0.596	0.0	0.562	Random
TT vs. TC	<i>Overall</i>	16 (6,594/9,560)	1.42 (1.32-1.53)	<0.001	34.6	0.085	Fixed

Caucasians	4 (1,794/3,536)	1.68 (1.21-2.30)	<0.001	97.9	0.001	Random
Asians	11 (4,541/4,426)	1.28 (1.17-1.40)	<0.001	87.7	0.001	
Childhood-onset asthma	12 (5,275/6,871)	1.39 (1.28-1.52)	<0.001	0.0	0.721	Random
Adult-onset asthma	4 (1,319/2,689)	1.52 (1.29-1.78)	<0.001	79.0	0.003	

OR, odd ratio; CI, confidence interval.