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Original Article

Association between *ORMDL3* polymorphism and susceptibility to asthma: a meta-analysis

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Abstract: The aim of this study was to determine whether orosomucoid1- like 3 *(ORMDL3)* single nucleotide polymorphisms *rs7216389*, *rs11650680*, *rs12603332* are associated with susceptibility to asthma. We performed a meta-analysis by searching PubMed, EMBASE, Elsevier and Wanfang Databases. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the strength of associations. We examined the association between the three SNPs and asthma risk in four genetic models (TT + TC vs. CC, TC vs. CC, TT vs. CC, TT vs. TC + CC). Thirteen published case-control studies involving 6462 cases and 7357 controls were included. Our meta-analysis indicated that *rs7216389* was significantly associated with increased asthma risk in overall population. Subgroup analysis by age indicated significant association between the *rs7216389* and asthma in children. Moreover, *ORMDL3 rs11650680* was significantly associated with decreased asthma risk in dominant model (TT + TC vs. CC), and *rs12603332* was significantly associated with decreased asthma risk in 3 models (TT + TC vs. CC, TC vs. CC and TT vs. CC). To Conclude, *ORMDL3 rs7216389* polymorphism is associated with susceptibility to asthma. Children with variant T allele (TT or TC) and adults with TT homozygote in *rs7216389* are at high risks to suffer from asthma. However, people with T allele in *rs11650680* or *rs12603332* are protected from asthma.

Keywords: Childhood asthma, single nucleotide polymorphism, ORM gene family

Introduction

Asthma is a crucial public health problem worldwide [1]. The occurrence of asthma is determined by the interaction between host genetic susceptibility and environment [2]. It has been reported that genetic variants regulating *ORMDL3* expression are associated with susceptibility to childhood asthma [3]. The *ORMDL3* gene is located at chromosome 17q21 and belongs to the novel *ORM* gene family, which plays an important role in maintaining sphingolipid homeostasis in yeast [4]. *ORMDL3*, with a full length of 6560 bps, including three exons, encodes a protein of 153 amino acids with four putative transmembrane domains that are anchored at the endoplasmic reticulum [5, 6]. This gene was found to be expressed in many human tissues, especially in liver and peripheral blood lymphocytes [3]. The polymorphisms within the 17q21 locus regulate *ORMDL3* gene expression, and further regulate interleukin 17 secretion in cord blood [7]. *ORMDL3* was recently found to alter endoplasmic reticulum mediated Ca^{2+} homeostasis and facilitate the unfolded-protein response, which was considered as an endogenous inducer of inflammation [8].

The *ORMDL3* transcription was closely related to the *rs7216389* which was considered as the marker most strongly associated with childhood asthma in combined genome-wide association analysis [3]. Several studies have investigated the association between *rs7216389* and asthma susceptibility. However, the conclusions of these studies have been conflicting. Although a meta-analysis showed that the T allele of the *rs7216389* was associated with increased risk of childhood asthma [9], it remains unclear whether *rs7216389* is associated with asthma in the whole population. Therefore, we performed a meta-analysis on the association between *rs7216389* and other two *SNPs* (*rs11650680* and *rs12603332*) in *ORMDL3* and asthma risk.

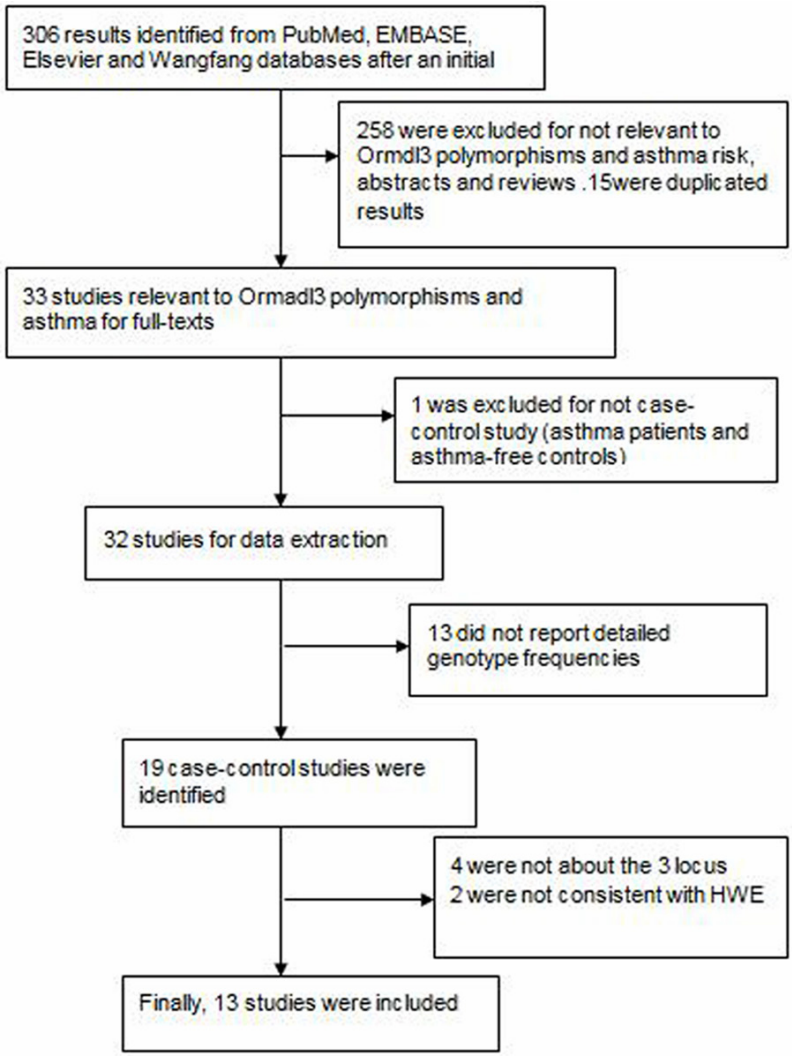

Figure 1. Flow diagram of the selection for the present meta-analysis.

Method

Publication search

We conducted a comprehensive search in PubMed, EMBASE, Elsevier and Wanfang Databases, covering all articles published up to October, 2014. The following terms were used: "asthma" or "asthmatic" or "wheeze" in combination with "polymorphism" or "variant" or "mutation" and in combination with "*ORMDL3*" or "*orosomucoid 1-like 3*" or "*GSDML*". All of the related articles and reviews were examined for additional references. There was no language restriction.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if (1) they evaluated the association between the *rs7216389* or *rs11650680* or *rs12603332 SNPs* and asthma risk; (2) they used a case-control design based on unrelated individuals; (3) they provided sufficient genotype distributions data in both asthma cases and controls for estimating an odds ratio (OR) with 95% confidence interval (CI). Studies were excluded if any of the following conditions existed: (1) only reviews, editorial articles, case reports and abstracts were available without sufficient data; (2) reports in which genotype distributions in the control population were not in accord with Hardy-Weinberg equilibrium (HWE); (3) the design was based on family or sibling pairs. For overlapping studies, only the one with the largest sample size was included.

Data extraction

Two investigators independently extracted the data and reached a consensus on all items. If there was disagreement, a third investigator was asked to assess the data. The following information was extracted from each publication if available: first author's name, year of publication, country of the study population, age, genotype number in cases and controls, genotyping method.

Statistical analysis

For each case-control study, the HWE of control group was evaluated using Chi-square test and $P<0.05$ was considered representative of a departure from HWE. ORs with 95% CIs were used to assess the strength of the association between the *ORMDL3* polymorphism and asthma risk under all of the comparisons (TT + TC vs. CC, TC vs. CC, TT vs. CC, TT vs. TC + CC). The significance of the pooled OR was determined by the Z-test and $P<0.05$ was considered as

Table 1. Included studies information and gene frequency distribution

	Year	Country	Case age	Control age	Case No.	Control No.	Genotype method	Case			Control			HWE (*p*)
								TT (%)	TC (%)	CC (%)	TT (%)	TC (%)	CC (%)	
Article (*rs7216389*)														
Binia A	2011	UK	48.95	*	385	1429	sequenced	116 (30)	200 (52)	69 (18)	328 (23)	696 (49)	405 (28)	0.38
Brauner EV	2011	Denmark	1.5	1.5	1112	734	PCR	290 (26)	555 (50)	267 (24)	165 (22)	365 (50)	204 (28)	0.92
Fang Q	2011	China	28.7	29.1	696	637	PCR-RFLP	384 (55)	258 (37)	54 (8)	298 (47)	286(45)	53 (8)	0.17
Hitrota T	2008	Japan	9.5	49	545	738	sequenced	338 (62)	176 (32)	31 (6)	370 (50)	312(42)	56 (8)	0.38
Leung TF	2008	China	11.1	11.8	315	192	PCR	203 (64)	100 (32)	12 (4)	107 (56)	81 (42)	4 (2)	0.10
Tavendale R	2008	UK	10.4	7.5	1279	1541	sequenced	401 (31)	627 (49)	251 (20)	340 (22)	751(49)	450(29)	0.42
Yang FF	2012	China	5.872	6.038	152	190	PCR	92 (61)	53 (35)	7 (4)	90 (47)	79 (42)	21(11)	0.56
Yu J	2011	Korea	9.69	8.98	786	522	PCR-RFLP	474 (60)	268 (34)	44 (6)	273 (52)	216(41)	33 (7)	0.26
Ding YP	2012	China	53.6	50.3	120	150	PCR-RFLP	71 (59)	41 (34)	8 (7)	80 (53)	58 (39)	12 (8)	0.74
Jin Z	2010	China	5.8	7.15	220	208	PCR	123 (56)	80 (36)	17 (8)	103 (50)	84 (40)	21 (10)	0.53
Huang HZ	2011	China	42	41	80	84	PCR	30 (38)	36 (45)	14 (17)	18 (21)	40 (48)	26 (31)	0.72
Article (*rs11650680*)														
Leung TF	2008	China	11.1	11.8	315	192	PCR	11 (4)	108 (34)	196 (62)	16 (9)	66 (35)	108 (56)	0.2
Yang FF	2012	China	5.872	6.038	152	190	PCR	7 (4)	57 (38)	88 (58)	9 (5)	66 (35)	115 (60)	0.92
Yu X	2014	China	6.68	6.45	435	601	PCR	14 (3)	96 (22)	325 (75)	21 (3)	180 (30)	400 (67)	0.89
Article (*rs12603332*)														
Fang Q	2011	China	28.7	29.1	710	656	PCR-RFLP	57 (8)	268 (38)	385 (54)	54 (8)	300 (46)	302 (46)	0.09
Yang FF	2012	China	5.872	6.038	152	190	PCR	7 (5)	55 (36)	90 (59)	10 (5)	79 (42)	101(53)	0.28
Yu X	2014	China	6.68	6.45	435	601	PCR	39 (9)	165 (38)	231 (53)	80 (13)	252 (42)	269 (45)	0.089
Hrdickova B	2011	Czech	30.7	38.1	337	331	sequenced	67 (20)	168 (50)	102 (30)	72 (22)	171(51)	88 (27)	0.52

*Represents data not given.

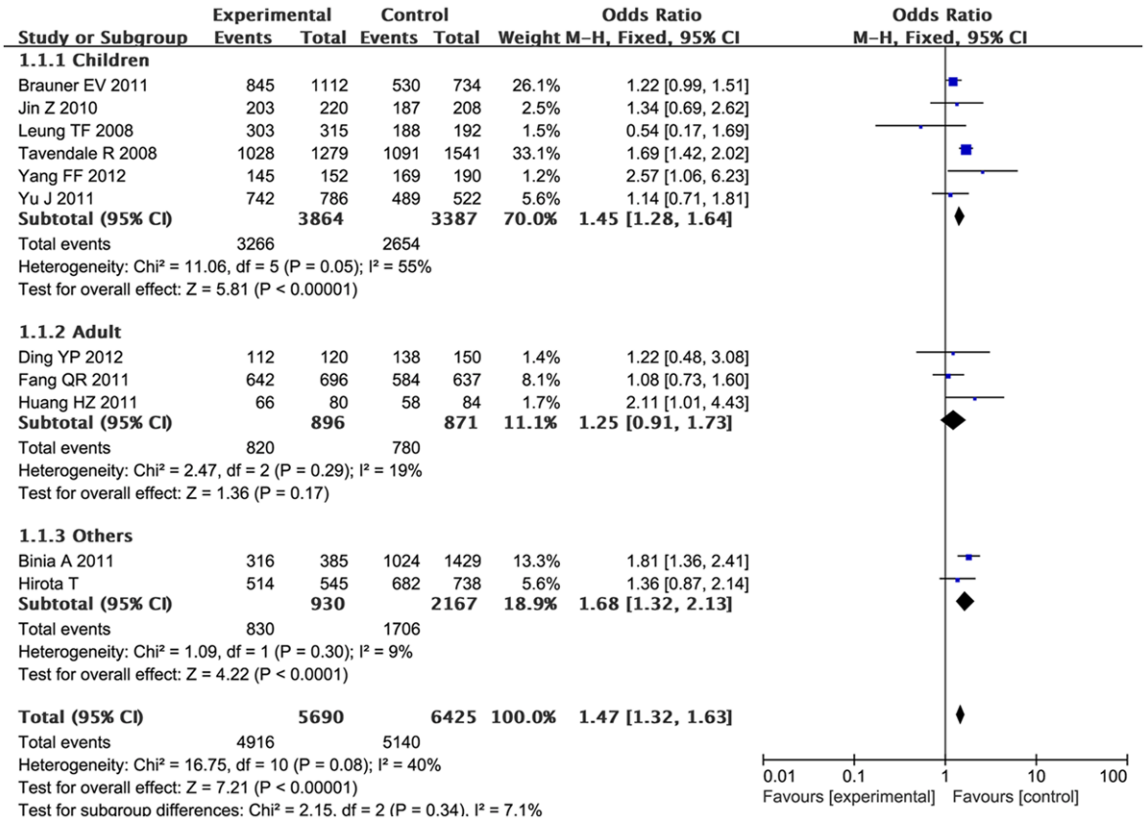

Figure 2. Meta-analysis with a fixed-effects model for the association between asthma risk and the *rs7216389* polymorphism (TT + TC vs. CC).

statistically significant. Heterogeneity was assessed using the chi-square based *Q* and I^2 test and it was considered statistically significant at I^2>50%. When the I^2<50%, the pooled OR was calculated by the fixed-effects model, otherwise a random-effects model was used. All of the analyses were performed using RevMan 5.2 and STATA 11.0 software. In addition, possible publication bias was investigated with the Begg's funnel plot and Egger's linear regression test [10, 11].

Results

Study selection and characteristics

The process of study selection was shown in **Figure 1**. A total of 306 articles were retrieved initially. After reading the titles and full texts, 15 studies were chosen for further evaluation. Two case-control studies were excluded for not being consistent with HWE [12, 13]. Finally, a total of 13 articles were included in this meta-analysis [14-26]. For *rs7216389,* 3 case-control studies were performed in adults, 6 studies were performed in children, 1 study included both adults and children and 1 study did not mention the age. We put them into 3 subgroups: adults, children and others (mixed or unknown). The characteristics and genotype frequencies and HWE examination results of each study included in this meta-analysis are listed in **Table 1**.

Quantitative synthesis

rs7216389: A total of 5690 cases and 6425 controls from 11 case-control studies were included for rs7216389 data synthesis. As shown in **Figure 2**, we analyzed the heterogeneity of TT + TC vs. CC for all 11 studies. The value of Chi^2 was 16.75 with 10 degrees of freedom and P=0.08, I^2=40% in a fix-effects model. The OR was 1.47 (95% CI=1.32-1.63) in overall population and the Z value for overall effect was 7.21 (P<0.00001). Our results suggest that the TT homozygote and TC heterozygote carriers have a significantly increased risk to asthma when compared with those individuals with the CC homozygote. The forest plots of other genetic comparisons were shown in **Figures 6-8** and the summary of the results were as follows: TT vs.

Table 2. Summary of different comparative result

	n	Case/control	TT vs. CC OR (95% CI)	*P*	TC vs. CC OR (95% CI)	*P*	TT vs. TC + CC OR (95% CI)	*P*
Rs7216389								
total	11	5690/6425	1.71 (1.52, 1.93)	<0.00001	1.30 (1.16, 1.45)	<0.00001	1.46 (1.35, 1.58)	<0.00001
children	6	3864/3387	1.70 (1.47, 1.97)	<0.00001	1.30 (1.13, 1.48)	<0.0001	1.44 (1.30, 1.59)	<0.00001
adult	3	896/871	1.47 (1.04, 2.07)	0.03	1.02 (0.73, 1.44)	0.89	1.43 (1.18, 1.73)	0.0002
other	2	930/2167	1.92 (1.47, 2.51)	<0.00001	1.47 (1.14, 1.89)	0.003	1.54 (1.31, 1.83)	<0.00001
Rs11650680								
total	3	902/981	0.66 (0.42, 1.06)	0.08	0.84 (0.61, 1.16)	0.29	0.70 (0.44, 1.11)	0.13
Rs12603332								
total	4	1634/1778	0.72 (0.57, 0.92)	0.007	0.75 (0.65, 0.87)	0.0001	0.83 (0.67, 1.03)	0.009

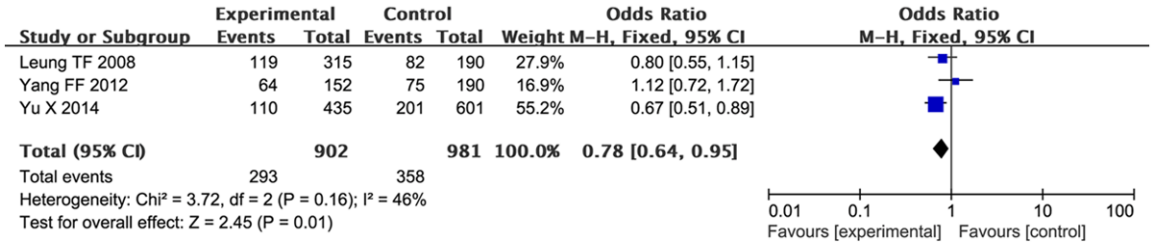

Figure 3. Meta-analysis with a fixed-effects model for the association between asthma risk and the *rs11650680* polymorphism (TT + TC vs. CC).

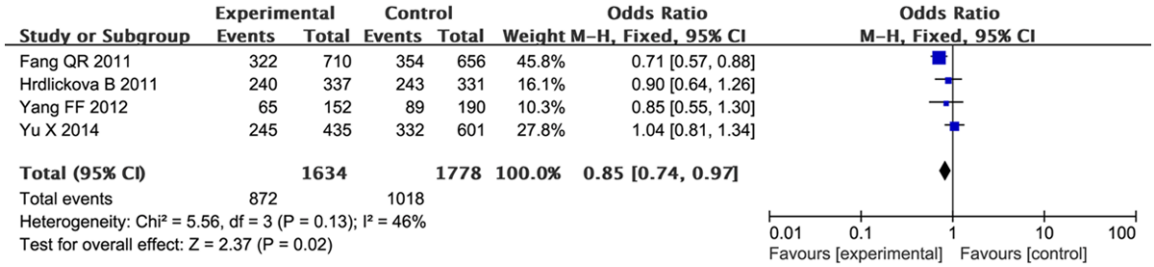

Figure 4. Meta-analysis with a fixed-effects model for the association between asthma risk and the *rs12603332* polymorphism (TT + TC vs. CC).

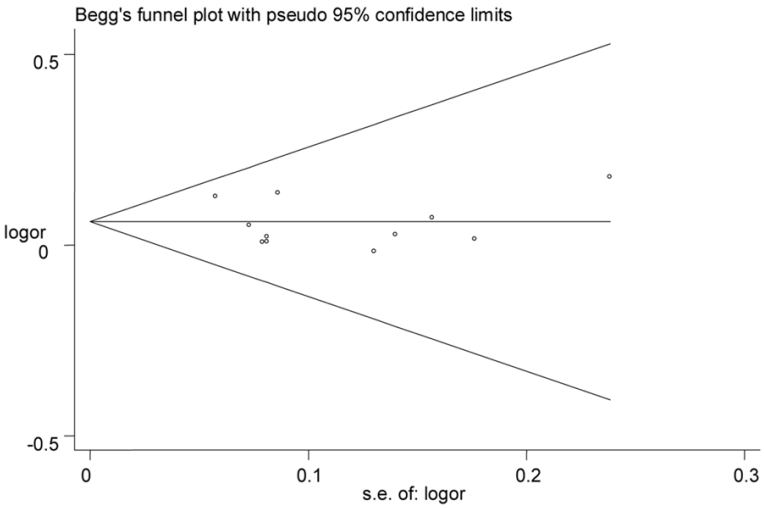

Figure 5. Begg's funnel plot for evaluation of publication bias in the selection of studies on the association between asthma risk and the *rs7216389* (TT + TC vs. CC).

CC (OR=1.71, 95% CI=1.52-1.93, P<0.00001); TC vs. CC (OR=1.30, 95% CI=1.16-1.45, P<0.00001); TT vs. TC + CC (OR=1.46, 95% CI=1.35-1.58, P<0.00001) (**Table 2**).

rs11650680 and rs12603332: A total of 902 cases and 981 controls from 3 case-control studies were included for rs11650680 data synthesis. As shown in **Figure 3**, the results of TT + TC vs. CC (OR=0.78, 95% CI=0.64-0.95, P=0.01) indicate that the TT homozygote and TC heterozygote carriers had a significantly decreased risk to asthma when compared with those individuals with the CC homozygote.

A total of 1634 cases and 1778 controls from 4 case-control studies were included for *rs12603332* data synthesis. The results of TT + TC vs. CC (OR=0.85, 95% CI=0.74-0.97, P=0.02) indicate that the TT homozygote and TC heterozygote carriers have a significantly decreased risk to asthma when compared with those individuals with the CC homozygote (**Figure 4**). Consistent with this, the results of TT vs. CC (OR=0.72, 95% CI=0.57-0.92, P=0.007) and TC vs. CC (OR=0.75, 95% CI=0.65-0.87, P=0.0001) also indicate decreased asthma risk in these models.

Subgroup analyses

Subgroup analysis by age for *rs7216389* was performed in the dominant model (TT + TC vs.

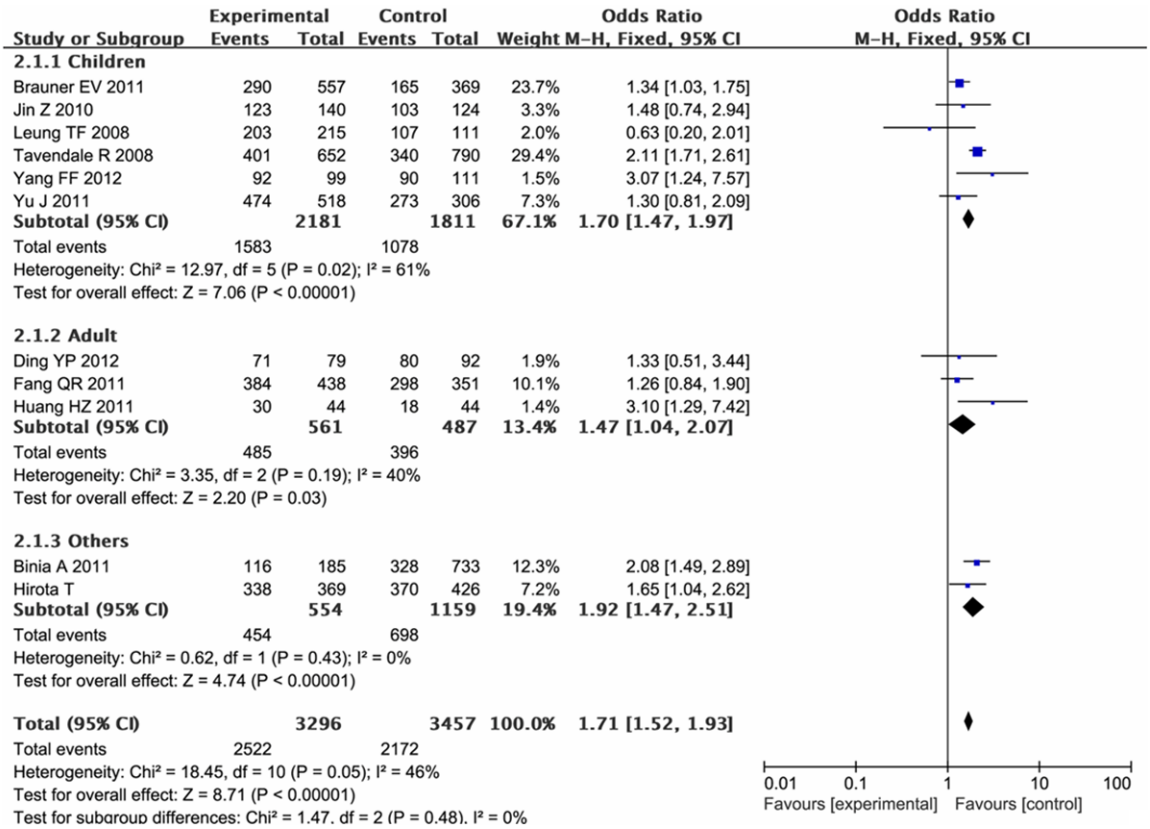

Figure 6. Meta-analysis with a fixed-effects model for the association between asthma risk and the *rs7216389* polymorphism (TT vs. CC).

CC). There was no significant associations between asthma risk and rs7216389 in adults (OR=1.25, 95% CI=0.91-1.73, P=0.17), whereas there was significant association in children (OR=1.45, 95% CI=1.28-1.64, P<0.00001) (**Figure 2**). Although the test of the heterogeneity showed I^2>50% in the children group, the result of additional analysis by the random-effects was coincident with the fix-effects model (OR=1.37, 95% CI=1.07-1.76, P=0.01). The forest plots of other genetic comparisons were presented in **Figures 6-8** and the final results were presented in **Table 2**. For adults: TT vs. CC (OR=1.47, 95% CI=1.04-2.07, P=0.03); TC vs. CC (OR=1.02, 95% CI=0.73-1.44, P=0.89); TT vs. TC + CC (OR=1.43, 95% CI=1.18-1.73, P=0.0002). For children: TT vs. CC (OR=1.70, 95% CI=1.47-1.97, P<0.00001); TC vs. CC (OR=1.30, 95% CI=1.13-1.48, P=0.0001); TT vs. TC + CC (OR=1.44, 95% CI=1.30-1.59, P<0.00001).

Publication bias

Publication bias was assessed using Begg's funnel plots and Egger's test. The shapes of the Begg's funnel plots didn't reveal obvious asymmetry in the TT + TC vs. CC model for the all three SNPs (*rs7216389, rs11650680, rs12603332*) (**Figure 5** for *rs7216389*). Egger's test was conducted to provide statistical evidence of funnel plot asymmetry, and the results did not suggest any publication bias (P=0.64 for rs7216389; P=0.078 for rs11650680; P=0.812 for rs12603332). These data indicated that there was no significant evidence of publication bias.

Sensitivity analysis

Sensitivity analysis was performed by sequentially excluding a single study each time to identify the potential influence of the individual data set to the pooled ORs. Statistically similar results were obtained after sequentially excluding each study, suggesting the stability of our meta-analysis.

Discussion

It is well known that asthma is a complex chronic inflammatory disease, and both environmen-

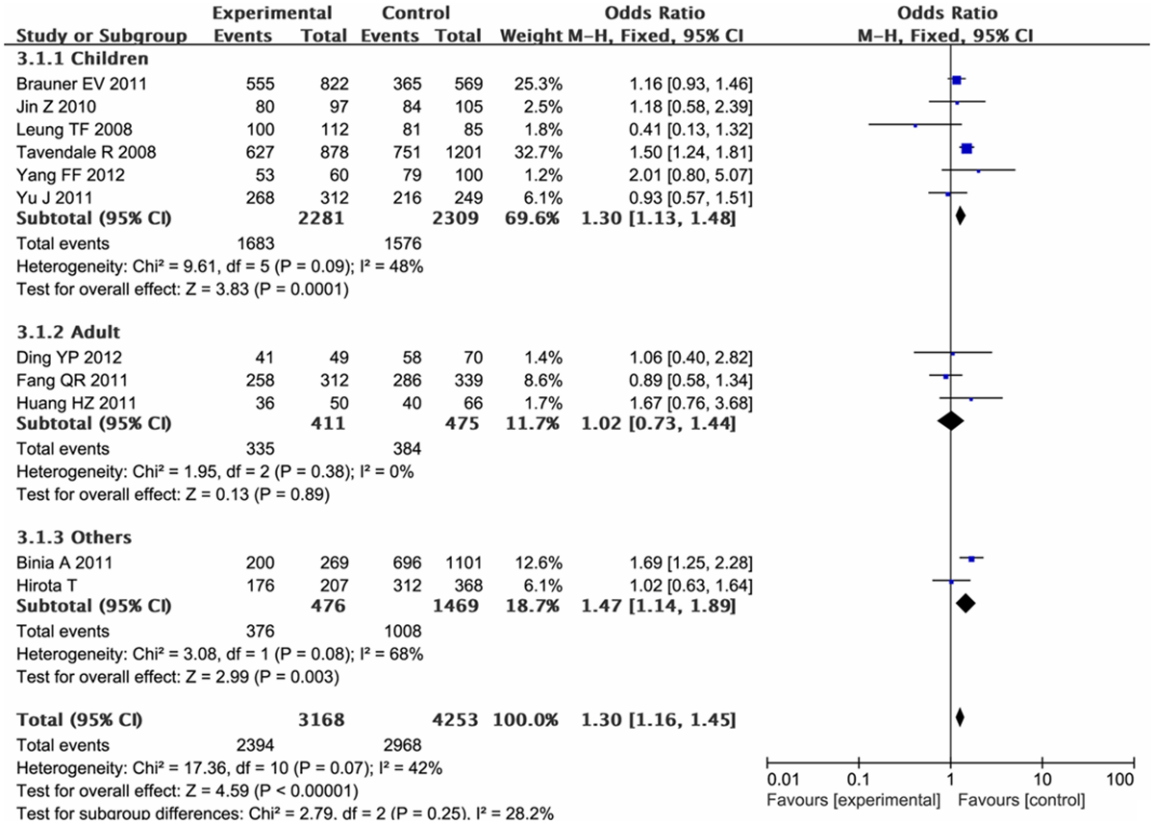

Figure 7. Meta-analysis with a fixed-effects model for the association between asthma risk and the *rs7216389* polymorphism (TC vs. CC).

tal and genetic factors are involved in the pathogenesis of the disease [27]. Now that host genetic susceptibility may play a crucial role in this process [28], many studies have focused on identifying specific genes involved in asthma. It was reported that transfection of ORMDL3 in lung epithelial cells induced SERCA2b which has been implicated in airway remodeling in asthma [29]. Another study reported IL4/IL13 up-regulation of ORMDL3 expression depends on STAT6 which binds to the ORMDL3 gene promoter directly [30].

Rs7216389 located within GSDML was strongly associated with the transcription of ORMDL3 [3]. So far, numerous studies have focused on the association between asthma and the SNP *rs7216389* in ORMDL3, whereas the results of these studies were conflicting. Therefore, we performed this meta-analysis on the association between asthma risk and SNPs *rs7216389*, *rs11650680*, *rs12603332*. Our meta-analysis indicated that *rs7216389* is significantly associated with susceptibility to asthma. In the overall population analysis, we found all the four models (TT vs. CC, TC vs. CC, TT + TC vs. CC, TT vs. TC + CC), namely the T carriers (homozygote and heterozygote), were at significantly higher risk for asthma. In subgroup analysis by age, *rs7216389* was significantly associated with susceptibility to asthma in children. However, there was a significant association between asthma and *rs7216389* only in two models (TT vs. CC and TT vs. TC + CC) in adults. Moreover, *ORMDL3 rs11650680* was significantly associated with decreased asthma risk in the dominant model (TT + TC vs. CC), and *rs12603332* was significantly associated with decreased asthma risk in 3 models (TT + TC vs. CC, TC vs. CC and TT vs. CC).

Heterogeneity and publication bias may affect the reliability of results in a meta-analysis. In the present meta-analysis, no significant heterogeneity was found in the comparisons in the all four models. This indicates the homogeneity of included case-control studies. Publication bias was estimated by Begg's funnel plots and

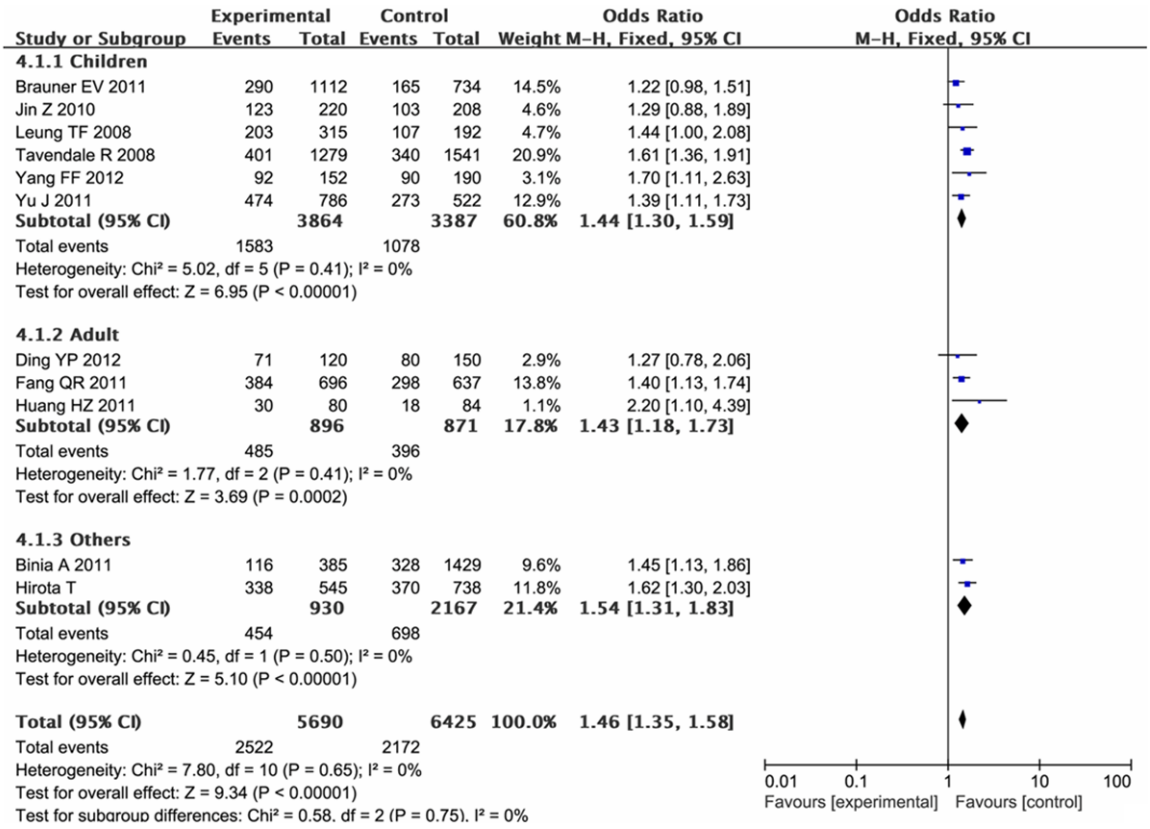

Figure 8. Meta-analysis with a fixed-effects model for the association between asthma risk and the *rs7216389* polymorphism (TT vs. TC + CC).

Egger's test. We did not detect a significant publication bias, suggesting our results are reliable.

The present study had some limitations. First, because the sample size of the included studies was relatively small, the results could be influenced by random error. Second, although our Begg's funnel plots and Egger's test showed no evidence of publication bias, it is still possible that selection bias may exist.

In summary, this meta-analysis demonstrated that the *rs7216389* polymorphism is associated with susceptibility to asthma. Children with allele T (TC or TT) and adults with TT homozygote in *rs7216389* are at high risk for asthma. However, people who have T variant in *rs11650680* or *rs12603332* may be protected from asthma.

Disclosure of conflict of interest

None.

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