

Angiotensin-converting enzyme insertion/deletion polymorphism and susceptibility to allergic rhinitis in Chinese populations: a systematic review and meta-analysis

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Abstract In view of the controversies surrounding the angiotensin-converting enzyme (ACE)–allergic rhinitis (AR) association, a systematic review and meta-analysis of the ACE genetic association studies of AR was performed in Chinese populations. PubMed, Springer Link, OvidSP, Chinese biomedical database, Chinese national knowledge infrastructure, Chinese VIP and Wanfang databases were searched for related studies. A total of 4 studies including 415 AR patients and 309 controls were involved in this meta-analysis. Overall, significant association was found between ACE I/D polymorphism and AR risk when all studies in Chinese populations pooled into the meta-analysis (allele, OR 1.50, 95 % CI 1.19–1.90; homozygous, OR 2.59, 95 % CI 1.52–4.41, recessive, OR 2.05, 95 % CI 1.27–3.32). In the subgroup analysis by ethnicity, ACE I/D polymorphism was associated with significant elevated risks of AR in Chinese Han under homozygous and recessive models (homozygous, OR 4.36, 95 % CI 1.76–10.82, recessive, OR 2.51, 95 % CI 1.18–5.34). In conclusion, this meta-analysis provides the evidence that ACE I/D polymorphism may contribute to the AR development in Chinese populations and studies with large sample size and wider spectrum of population are warranted to verify this finding.

Keywords Meta-analysis · Angiotensin-converting enzyme · Polymorphism · Allergic rhinitis

Introduction

Allergic rhinitis (AR) is a complex immunoglobulin (Ig) E-mediated atopic disease, occurring in both children and adults. It is characterized by sneezing, rhinorrhea, nasal stuffiness and nasal itching, which may be involved in an imbalance in the Th1/Th2 immune response [1, 2]. Although not life threatening, AR symptoms are frequently bothersome, adversely affect work and quality of life of the affected individual and impose a significant burden on both the individual and society [3, 4]. Epidemiological studies have indicated that the prevalence of AR has increased progressively over the last three decades in the more developed ‘westernized’ societies and presently affects up to 40 % of the population worldwide [5], with 23–30 % of the population affected in Europe [6] and 12–30 % of individuals affected in the United States [7]. In China, a population-based study with 38,203 telephone interviews was conducted to assess self-reported AR in 11 major cities, which demonstrated that the prevalence of AR, after adjusting for age and gender, was highly variable and ranged from 8.7 % in Beijing to 24.1 % in Urumqi [8]. Especially for young children, Zhang et al.’s [9] investigation reported that the prevalence of epidemiologic AR was 48 % in preschool children in Beijing. It also shows a continuously increasing trend in morbidity of AR in China over recent years.

The development of AR entails a complex interaction between genetic predisposition and environmental exposure to different factors, of which the most important is the implicated allergen. Despite environmental exposures play important roles in the development of atopy, there is a strong inherited susceptibility in the etiology of AR. Variants in several genes have been identified as biologically plausible candidates for effects on AR, such as

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angiotensin-converting enzyme (ACE) [10]. The ACE exerts an anti-inflammatory effect by inactivating different proinflammatory peptides such as bradykinin and substance P, both of which are implicated in the pathogenesis of atopic neurogenic inflammation. ACE gene contains a polymorphism based on the presence [insertion (I)] or absence [deletion (D)] of a non-sense DNA fragment, which may influence the strength of immunological response and has been reported to be associated with atopic diseases including AR.

Some publications [11–16] have reported the role of ACE gene polymorphism in AR risk, but provided controversial or inconclusive results. To lessen the impact of different genetic background, we performed this meta-analysis to assess the relationship of ACE gene polymorphism with the risk of AR in Chinese populations.

Materials and methods

Materials

We systematically searched PubMed, Springer Link, OvidSP, Chinese biomedical database (CBM), Chinese national knowledge infrastructure (CNKI), Chinese VIP and Wanfang databases for studies published before 12 December 2013, without language restriction. We also reviewed the reference lists of the relevant articles and performed searching based on Google scholar and Baidu scholar to identify additional studies. The search strategy involved exploring ‘ACE’ or ‘angiotensin-converting enzyme’ combined with ‘allergic rhinitis’ or ‘hayfever’ or ‘pollinosis’. The PubMed search was run using the terms: [ACE (All Fields) OR “angiotensin-converting enzyme” (All Fields)] AND (“Allergic Rhinitis” (All Fields) OR “hayfever” (All Fields) OR “pollinosis” (All Fields)].

Inclusion/exclusion criteria

Studies included in our meta-analysis have to meet the following criteria: (1) the study clearly assessed the association between ACE I/D polymorphism and AR risk; (2) the diagnosis of allergic rhinitis was clearly described in the study; (3) the criteria of atopy included clinical signs, a positive family history, and abnormal serum total immunoglobulin E (IgE) or at least 1 allergen-specific IgE measurement >0.35 kU/L; (4) the normal healthy controls had no diagnosis of atopic diseases such as asthma or AR; (5) all participants were Chinese. Studies were excluded when they were: (1) studies without normal healthy controls; (2) not offering the number of cases and controls and other essential information; (3) reviews, letters, meeting proceedings, or repeated literature.

Data extraction

Data were independently extracted by two reviewers using a standardized data extraction form. Discrepancies were resolved by discussion and if consensus was not achieved then the decision was made by the third reviewer. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. We extracted standardized data sets from studies of ACE polymorphism and AR. The following information was sought from each publication: authors, journal and year of publication, geographical location, ethnicity, age, total number of AR patients and controls, genotype frequencies of ACE I/D and *p* value of Hardy–Weinberg equilibrium tested in controls. The categorization of ethnicity comprised Han and other ethnic Chinese. The categorization of age included adults and children.

Quality assessment of included studies

The quality of papers was also independently assessed by two reviewers based on the evaluating checklist edited by M Avis [17]. The checklist consists of 24 items, which relate to the objectives and design, sample, controls, evidence and validity of conclusions. Each item is awarded two points (major weakness = 0, minor weakness = 1, no problem or not applicable = 2), and the total scores ranged from 0 to 48. Any discrepancies between the two reviewers were resolved by discussion and consultation with a third reviewer.

Statistical analysis

Statistical analysis was conducted using STATA statistical package (version 10, STATA, College Station, TX, USA). The distributions of genotypes in controls were tested by Hardy–Weinberg equilibrium using the Chi-square test. The association of polymorphism of ACE and AR risk was estimated by odds ratio (OR) with 95 % confidence intervals (CI). We calculated pooled ORs and 95 % CIs for all studies combined. The heterogeneity was tested by the *Q*-statistics with *p* values <0.1. If there was heterogeneity, the random effect model would be used. Otherwise, a fixed-effect model was applied to obtain the summary OR and their 95 % CI. Before the analysis, we formed a prior hypothesis that if heterogeneity existed in the studies, subgroup analyses were performed by geographical location, age stratification and ethnic groups. In addition, sensitivity analysis was conducted to verify stability of the meta-analysis using both the models (the fixed-effect model and random effect model).

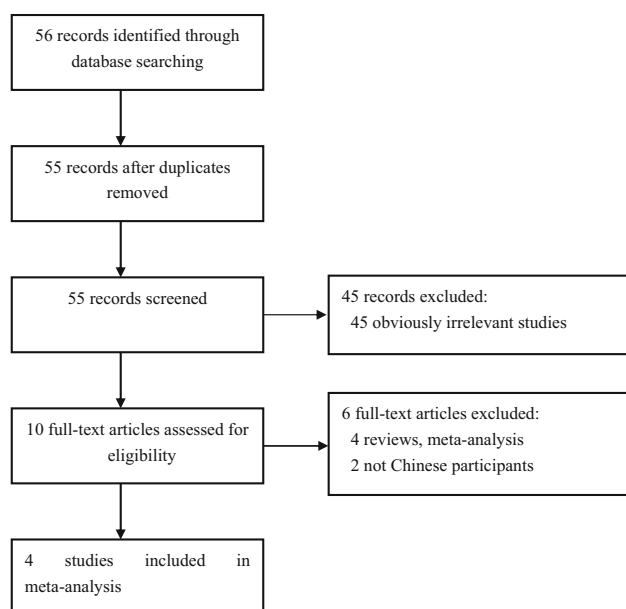


Fig. 1 Flow diagram of the literature search

Results

The characteristics of included studies

The election process is summarized by the flow diagram in Fig. 1. In summary, a total of 56 records were identified after searching the PubMed, Springer Link, OvidSP, CBM, CNKI, VIP and Wanfang databases. Forty-six papers including duplicates (one) or unrelated articles (forty-five) were excluded during screening. Then, ten potentially relevant papers on ACE I/D polymorphism and susceptibility to AR were assessed for eligibility. After careful examination of these full-text articles, six were excluded for the following reasons: four were reviews or meta-analyses [19–22], two reported for other populations [15, 16]. As a result, four eligible studies [11–14] with a total sample size of 415 AR patients and 309 controls were included in the meta-analysis. Two studies [13, 14] were performed in Taiwan China, and two studies [11, 12] were conducted in Mainland China. Two studies [13, 14] involved children and two [11, 12] recruited adults. Two studies [12, 13] reported the same race (Chinese Han) and two studies [11, 14] did not mention the ethnicity. The characteristics of the included studies are summarized in Table 1.

Overall analysis

The main results of this meta-analysis under five distinct genetic models are shown in Table 2. In overall analysis (Fig. 2), the results showed that ACE I/D polymorphism had a statistically significant association with increased AR

risk in Chinese populations under three models (allele, OR 1.50, 95 % CI 1.19–1.90; homozygous, OR 2.59, 95 % CI 1.52–4.41; recessive, OR 2.05, 95 % CI 1.27–3.32), but not in heterozygous and dominant models (heterozygous, OR 1.36, 95 % CI 0.98–1.88; dominant, OR 1.69, 95 % CI 0.96–2.97).

Subgroup and sensitivity analyses

Pre-specified subgroup analyses were performed on different age categories, different geographical location as well as ethnicity (Table 2). In the subgroup analysis by geographical location and age stratification, significantly increased risk was only found in Chinese Mainland and adults under recessive model (OR 1.93, 95 % CI 1.08–3.45). In the subgroup analysis by ethnicity, ACE I/D polymorphism was associated with significant elevated risks of AR in Chinese Han under homozygous and recessive models (homozygous, OR 4.36, 95 % CI 1.76–10.82; recessive, OR 2.51, 95 % CI 1.18–5.34). Sensitive analysis indicated that all the results were not materially altered in overall analysis under all genetic models (ORs for fixed-effect model can be seen in Table 2; ORs for random effect model: allele, OR 1.58, 95 % CI 1.03–2.41; homozygous, OR 2.67, 95 % CI 1.09–6.53; heterozygous, OR 1.45, 95 % CI 0.90–2.32; dominant, OR 1.69, CI 0.96–2.97; recessive, OR 2.00, 95 % CI 1.17–3.44). Hence, the conclusion of this meta-analysis is relatively stable and credible for the overall analysis.

Discussion

To date, a series of studies have focused on the relation between ACE I/D polymorphism and AR risk [11–16]. Nevertheless, the results were inconclusive and inconsistent. Several papers have reported that a statistically significant correlation was found between ACE I/D SNP and AR risk [12, 14, 15]. Conversely, the results from other studies suggested that the ACE I/D SNP was not associated with AR risk [11, 13, 16]. Therefore, we conducted this meta-analysis by critically reviewing 4 individual studies on ACE gene polymorphism with AR risk in Chinese populations only, to lessen the impact of different genetic background. In the meta-analysis, we found that the variant genotypes of the ACE I/D polymorphism were significantly associated with AR risk. Our results were consistent with a previously published meta-analysis [18], which showed an increased risk of AR associated with ACE I/D genotype in overall analysis (allele, OR 1.46, 95 % CI 1.14–1.86; homozygous, OR 2.17, 95 % CI 1.29–3.67; heterozygous, OR 1.42, 95 % CI 1.11–1.81; dominant, OR 1.54, 95 % CI 1.22–1.94; recessive, OR 1.64, 95 % CI 1.22–2.21).

Table 1 Characteristics of included studies

First author	Year	Geographical location	Ethnicity	Age	Total number		Cases			Controls					HWE of controls	Quality score		
					Cases	Controls	II	ID	DD	I	D	II	ID	DD			I	D
Wang [11]	2005	Guangzhou	Not stated	Adults	69	101	27	29	13	83	55	44	41	16	129	73	0.226	40
Lu [12]	2006	Tianjin	Han	Adults	60	40	6	23	31	35	85	17	13	10	47	33	0.037	42
Ku [13]	2006	Taiwan	Han	Children	75	66	36	35	4	107	43	36	27	3	99	33	0.460	43
Lue [14]	2006	Taiwan	Not stated	Children	211	102	100	88	23	288	134	56	42	4	154	50	0.255	44

D deletion, I insertion, HWE Hardy–Weinberg equilibrium

D deletion, *I* insertion, *HWE* Hardy–Weinberg equilibrium

Table 2 Main results of pooled odds ratios (ORs) in this meta-analysis

Study groups	<i>n</i>	D versus I		DD versus II		ID versus II		ID + DD versus II		DD versus II + ID	
		OR (95 % CI)	<i>p_h</i>	OR (95 % CI)	<i>p_h</i>	OR (95 % CI)	<i>p_h</i>	OR (95 % CI)	<i>p_h</i>	OR (95 % CI)	<i>p_h</i>
Total	4	1.50 (1.19–1.90)	0.023	2.59 (1.52–4.41)	0.064	1.36 (0.98–1.88)	0.138	1.69 (0.96–2.97)	0.035	2.05 (1.27–3.32)	0.322
Geographical location											
Mainland	2	1.98 (0.68–5.71)	0.004	3.27 (0.51–20.86)	0.011	2.23 (0.53–9.33)	0.031	2.68 (0.50–14.29)	0.006	1.93 (1.08–3.45)	0.116
Taiwan	2	1.35 (0.99–1.84)	0.603	2.40 (0.97–5.93)	0.366	1.21 (0.81–1.81)	0.816	1.33 (0.91–1.96)	0.926	2.30 (0.96–5.47)	0.331
Age stratification											
Adults		1.98 (0.68–5.71)	0.004	3.27 (0.51–20.86)	0.011	2.23 (0.53–9.33)	0.031	2.68 (0.50–14.29)	0.006	1.93 (1.08–3.45)	0.116
Children		1.35 (0.99–1.84)	0.603	2.40 (0.97–5.93)	0.366	1.21 (0.81–1.81)	0.816	1.33 (0.91–1.96)	0.926	2.30 (0.96–5.47)	0.331
Ethnicity											
Han	2	2.02 (0.72–5.68)	0.009	4.36 (1.76–10.82)	0.059	2.35 (0.63–8.75)	0.048	2.79 (0.56–13.78)	0.010	2.51 (1.18–5.34)	0.269
Not stated	2	1.32 (0.99–1.76)	0.499	1.96 (1.01–3.82)	0.215	1.17 (0.78–1.74)	0.967	1.29 (0.89–1.89)	0.768	1.79 (0.96–3.34)	0.195

CI confidence interval, *p_h* *p* value of *Q*-test for heterogeneity test

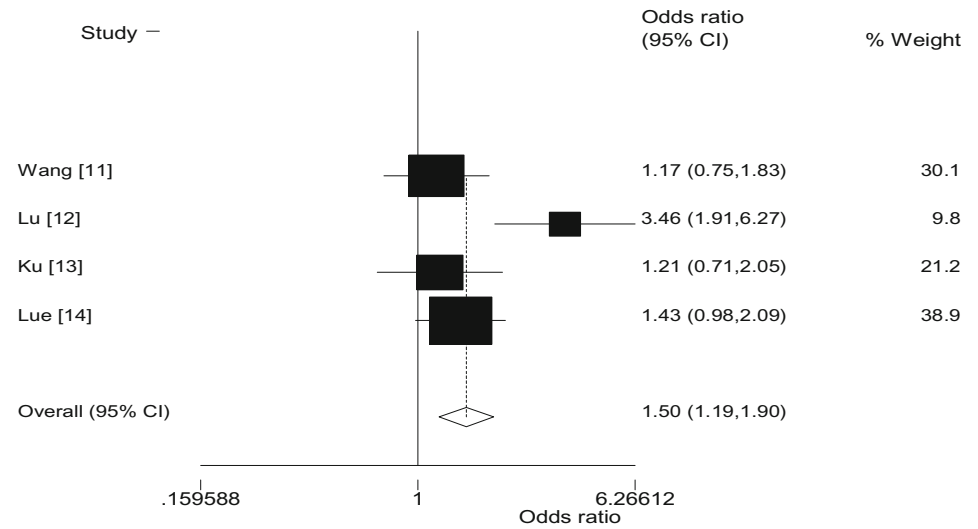
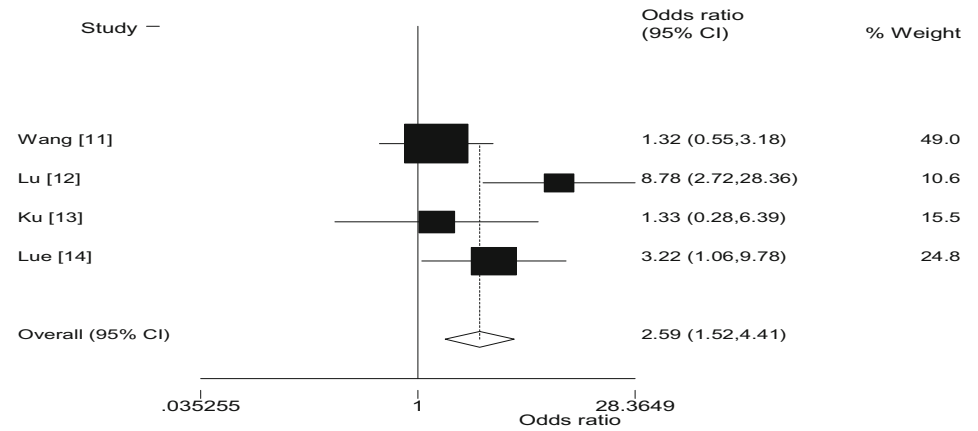
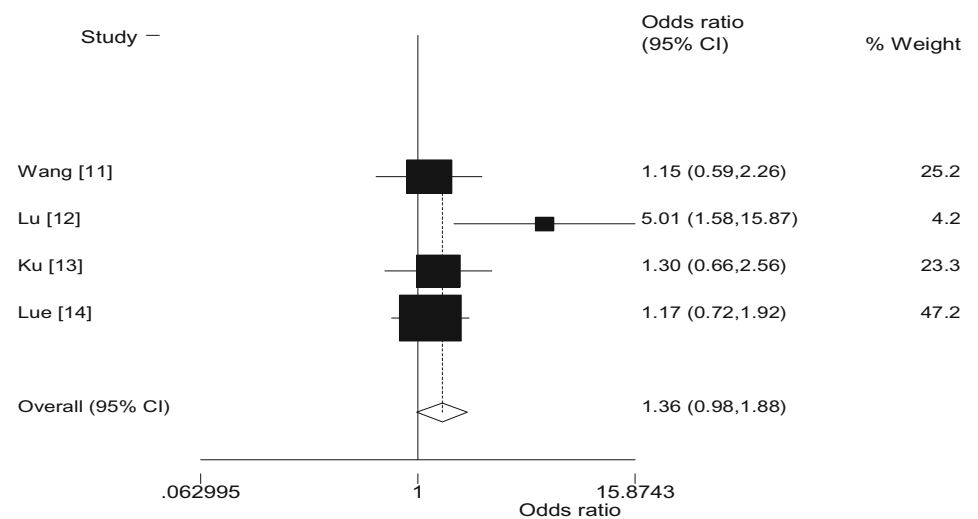
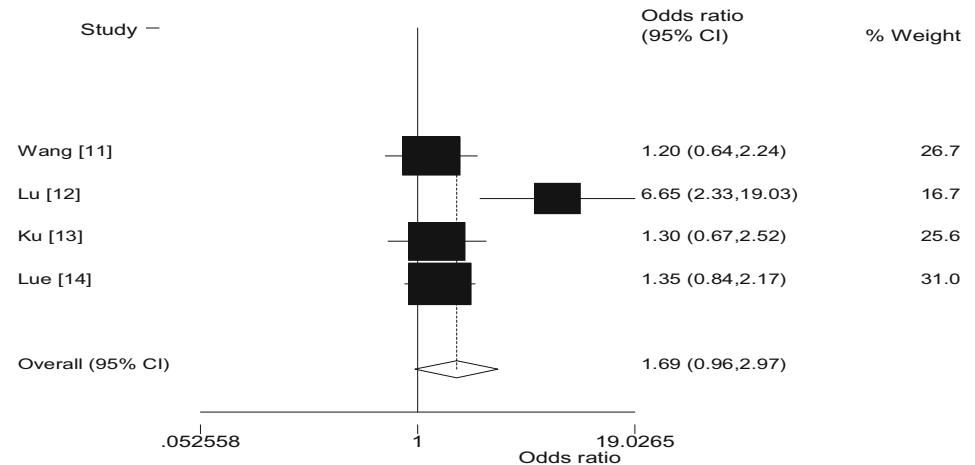
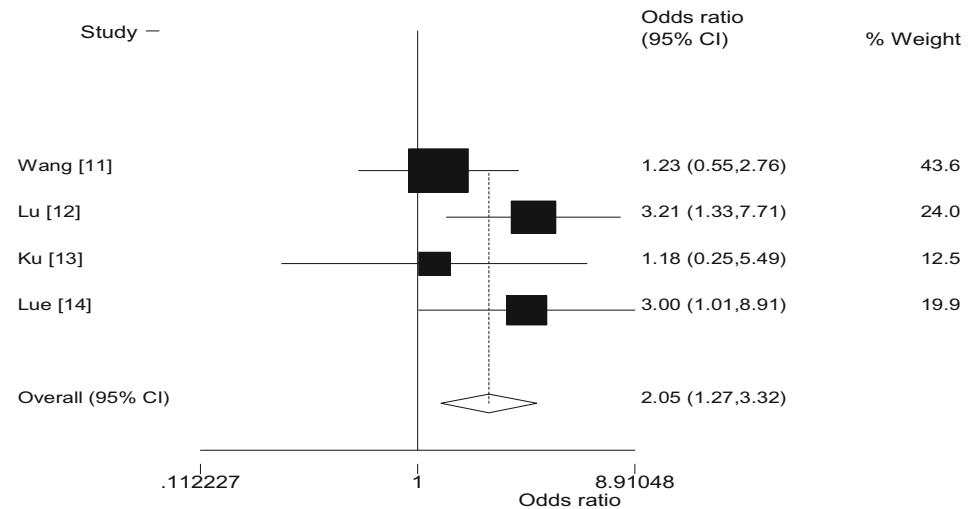
Fig. 2 Forest plots for the overall association between ACE I/D polymorphism and AR risk**D versus I****DD versus II****ID versus II**

Fig. 2 continued

ID +DD versus II



DD versus II+ID



However, this meta-analysis [18] did not calculate pooled ORs in Chinese populations.

When we performed the subgroup analyses by age, significant association with susceptibility for the development of AR was only found in adults under recessive model. It was inconsistent with the previous meta-analysis which suggested that ACE I/D polymorphism was associated with significant elevated risks of AR in adults under all genetic models (allele, OR 1.55, 95 % CI 1.07–2.24; homozygous, OR 2.19, 95 % CI 1.10–4.34; heterozygous, OR 1.55, 95 % CI 1.14–2.11; dominant, OR 1.67, 95 % CI 1.25–2.23; recessive, OR 1.55, 95 % CI 1.13–2.14) [18]. This is because AR is a complex atopic disorder and is affected by many factors including both genetic and environmental factors, and different genetic backgrounds including age or ethnicity may lead to different outcomes [19, 20] and other undiscovered genes involved in AR development might mask the influence of the D or I allele. Moreover, some

potentially suspected factors such as smoking status, alcohol consumption, occupational and lifestyle might influence the development of AR. Our research also showed that significantly increased AR risk in ACE D genotype carriers was found in Chinese Mainland, in Han and other ethnic Chinese. These results support our overall analysis, suggesting that ACE gene polymorphism might be associated with risk of AR in Chinese populations.

Our meta-analysis has several strengths. First, we obeyed the inclusion and exclusion criteria strictly to reduce selection bias. Second, our inclusion of non-English language reports was important in minimizing a major potential threat to the validity of any meta-analysis—publication bias and the related threat of a language bias. At last, the sensitivity analysis had been performed to confirm the reliability and stability of this meta-analysis. Therefore, the 4 studies would appear to be comparable in all respects relevant to our meta-analysis.

Some limitations of this meta-analysis should be discussed. First was the small sample size, only two studies in subgroup analysis, which increased the limitation of statistical power. Hence, studies with larger sample sizes and with sufficient large subgroups would be warranted to verify our findings. Secondly, due to the limitations of funnel plotting, which requires a range of studies, we did not evaluate publication bias in this meta-analysis. Another potential limitation was that our results were based on unadjusted estimates. More precise analyses can be conducted if individual data were available, which would allow for the adjustment by other covariates including sex, age, location, race and other factors. Finally, we applied a more liberal definition of AR, because most of the literature on AR employ less strict criteria, though allergic rhinitis and its impact on asthma (ARIA) 2010 guidelines suggested that a diagnosis of AR should be made based on symptoms and an objective marker of allergen sensitization (positive skin prick test or allergen-specific IgE) [22].

In summary, this meta-analysis supports that ACE I/D gene polymorphism most likely contributes to individual susceptibility to AR in Chinese populations. As studies among other ethnic populations are currently limited, it is of great essentiality to conduct large sample studies with wider spectrum of subjects to investigate the relationship between ACE polymorphism and AR risk, which would greatly help summarize the results from published papers.

Conflict of interest We declare that we have no conflict of interest.

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