Association of TNF-α-308G/A gene polymorphism with the risk of allergic rhinitis: a systematic review and meta-analysis

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Abstract

Purpose

Inconsistent reports of the association between tumor necrosis factor-alpha (TNF-α) 308G/A single nucleotide polymorphism (SNP) and allergic rhinitis (AR) prompted a meta-analysis to determine a relatively precise and reliable linkage between TNF-α-308G/A gene polymorphism and risk of AR.

Methods

PubMed, Web of Science, Excerpta Medica Database (EMBASE), China National Knowledge Infrastructure (CNKI), and Wanfang Database were used to search all published case-control studies on the relationship between TNF-α-308G/A polymorphism and susceptibility to AR. Data for each study were extracted using standardized forms, and summary odds ratios (ORs), with 95% confidence intervals (CIs) used to evaluate the intensity of the association by RevMan 5.4.1 software.

Results

7 studies (1383 AR cases and 1313 controls) were obtained for the meta-analysis. Comprehensive results showed that the polymorphism of TNF-α-308G/A gene was significantly associated with increased AR risk in the following two models: (1) AA vs. GG + GA: OR = 2.91, *P* = 0.003; (2) AA vs. GG: OR = 3.89, *P* = 0.0002. When participants were stratified by race, the TNF-α-308G/A polymorphism showed obviously increased AR risk in Asians under the following three models: (1) AA vs. GG + GA: OR = 3.08, *P* = 0.004; (2) AA vs. GG: OR = 4.38, *P* = 0.0002. In Europe, however, no obvious correlation was detected in any genetic models.

Conclusions

The results of our present analysis indicated that the TNF-α-308G/A gene polymorphism was associated with the susceptibility of AR, especially within the Asian population.

Introduction

Allergic rhinitis (AR), a kind of chronic inflammatory disease of the upper respiratory tract, is mainly mediated by IgE in the nasal mucosa [1], which causes allergic reactions when allergy-sensitive individuals are exposed to different environmental allergens. The common presenting symptoms of AR include nasal congestion, watery discharge, paroxysmal sneezing, and itchy nose. The incidence and prevalence rates of AR remain significantly high worldwide, accounting for > 50% of all types of allergic cases [2]. Asthma, as common comorbidity, has also increased dramatically, posing an extensive threat to public health and an increased socioeconomic burden worldwide [1, 3]. Moreover, an accumulated large body of studies has indicated that patients with AR are more likely to develop asthma than those without [4, 5]. Therefore, AR is a vital risk factor for asthma [6]. Although prior studies have significantly advanced the field of AR pathomechanisms, its exact etiology remains an open-ended question [7], resulting in high incidences and unsatisfying therapeutic outcomes. It is generally accepted that AR is caused by the interaction between multiple genes and environmental factors [8–10]. Gene polymorphism has attracted more and more attention from researchers [11, 12]. Searching for gene loci closely related to human complex diseases has become the focus and hotspot of current respiratory research. Polymorphism could as a key factor for AR, which can up-or down-regulate gene expression in a certain type of population or individual of AR, leading to differences in clinical manifestations of AR [13].

As early as 1997, Grossman first put forward the concept of “One Airway, One Disease”, emphasizing that upper and lower respiratory diseases are a whole viewpoint [14]. The relationship between the pathogenesis of asthma and gene polymorphism has been extensively studied. However, the study of polymorphism of AR is still insufficient. At the same time, given that AR may increase the risk of asthma, the causative genes of asthma patients may be considered as risk factors inducing AR. Tumor necrosis factor-alpha (TNF-α) is an inflammatory cytokine mainly produced by macrophages and monocytes [15, 16]. A recent meta-analysis supported that the TNF-α-308 promoter polymorphism was strongly associated with the risk of asthma [17]. Therefore, this study aimed to understand whether the polymorphism of the asthma gene was related to the susceptibility of AR. Many studies have evaluated the relationship between the polymorphism of TNF-α-308G/A gene and AR in different populations [9, 18, 19], but their results are inconsistent. In particular, the sample size of most studies was relatively small, resulting in the non-reproducibility of the results. In this study, we systematically searched the published literature on the case-control studies of TNF-α-308G/A polymorphism and AR susceptibility in domestic and foreign databases to compile a meta-analysis to determine whether polymorphism of TNF-α-308G/A gene increases the risk of AR.

Materials And Methods

The systematic review and meta-analysis were in line with the meta-analysis guide of priority report items of system review [20].

Literature search strategy

Searching PubMed, Web of Science, Excerpta Medica Database (EMBASE), China National Knowledge Infrastructure (CNKI), and Wanfang Database to identify available studies for human experimental research, the search strategy included the following keywords: “allergic rhinitis, AR, tumor necrosis factor, TNF, polymorphism, single nucleotide, genetic polymorphism, SNP, mutant and variant”, with the last search updated on December 7, 2021. The relevant pieces

of literature were primarily selected through title and abstract screening, then the full-text of the primary screening literature was read to obtain the final literature to be analyzed by the inclusion and exclusion criteria. To obtain a more comprehensive array of studies, the references of reviews and main articles were manually searched. In addition, each paper found in the literature retrieval was independently evaluated by two authors, and inconsistencies were resolved through discussion.

Inclusion and exclusion criteria

For the included studies, all the following criteria must be satisfied: (1) studies the correlation between TNF-α-308 polymorphism and the risk of AR have been published; (2) study design must be a case-control study on humans (AR cases and control groups); (3) the allele distribution or other genotype frequency, which was helpful to analyze the results, can be extracted from the studies for its odds ratios (ORs) and 95% confidence intervals (CIs). Studies that met one of the following criteria were excluded: (1) case reports, conference papers, dissertations, abstracts, and reviews; (2) overlapping data reported; (3) no genotype data reported.

Methodological quality assessment

To determine the research quality of eligible studies, the Newcastle-Ottawa Scale (NOS) was used for independent evaluation by two researchers (HY and LW). It evaluated the case-control study using three blocks and eight items, including the selection of study population, comparability, exposure evaluation. The semi-quantitative principle of NOS was adopted to assess the quality of literature, with a full score of 9 stars [21]. The differences between reviewers were resolved through discussion and negotiation until consensus was reached. If necessary, a third reviewer (JH) was consulted. When the NOS score is ≤ 5 stars, the research is regarded as “low and medium quality”, while the research with a NOS score ≥ 6 stars is considered as “high quality”.

Data extraction

For the data of the last 7 articles included in the literature, the two researchers (HY and LW) mentioned above independently extracted the data by reading the complete text, according to the inclusion and exclusion criteria established above, and then compared the results. The following information from each study was collected by using standardized data extraction lists: first author, publication time, the country, nationality of the research population, research design, the number of AR cases and control groups, allele, genotype frequency, and gene detection methods, and so on. If any inconsistent results appeared in the whole process, it was necessary to review this article by both researchers together, then discuss it with each other until reaching an agreement.

Statistical analysis

The goodness of fit of Hardy-Weinberg equilibrium (HWE) was assessed using the Chi-square test [22], which was calculated with controls for each included study. The ORs and 95%CIs of the TNF-α-308G/A gene polymorphism in the allelic model (A vs. G), dominant model (GA + AA vs. GG), recessive model (AA vs. GG + GA), co-dominant model (AA vs. GG), and over-dominant model (GG + AA vs. GA) were calculated for the AR cases and the control group. In addition, considering the heterogeneity in the study, subgroup analysis was conducted according to race. The heterogeneity of the included studies was evaluated by the Q-test and I^2 statistics [23]. If $P > 0.1$, $I^2 < 50\%$, this indicated that the heterogeneity was small, a fixed-effect model (FEM) was selected and vice versa using a random-effect model (REM) [24, 25]. The funnel plot was used to visually determine whether there was publishing deviation in the included literature; funnel plot symmetry may not exist publication bias, otherwise, there may be publication bias [26]. Finally, by removing individual studies one by one, the sensitivity was analyzed to verify the stability of the merged results [27]. All statistics were analyzed with RevMan (version 5.4.1), and p-value < 0.05 showed that the difference was statistically significant.

Results

Literature search

A total of 174 articles were initially identified from 5 electronic databases, and the specific screening process was presented in Fig. 1. According to the above retrieval strategy and based on the inclusion and exclusion criteria of the above-mentioned, 7 articles met the criteria and were selected for further analysis [9, 18, 19, 28–31]. As a result, the total sample size was 2696, including1383 AR cases and 1313 controls. Of the included studies, 3 were ethnically European [9, 18, 28], and 4 were Asian [19, 29–31]. The basic information, allele, and genotype frequency of the included literature were shown in Table 1. It should be noted that for the TNF-α-308G/A polymorphism, studies of Wei et al.[19]and Babic et al. [18] had no available HWE, while the study of Feng et al. [29] did not comply with HWE. According to the NOS, all the 7 studies obtained “high quality” (≥ 6 stars) for methodological quality assessment (Table 2).

Table 1
Main characteristics of included studies

First author	Year	Country	Ethnicity	Case genotype				Case allele		Control genotype				Control allele		Genotyping methods	HWE
				AA	GA	GG	Total	A	G	AA	GA	GG	Total	A	G		
Cardaba	2014	Spain	European	0	6	31	37	6	68	1	9	40	50	11	89	PCR	0.5683
Feng	2009	China	Asian	4	13	49	66	21	111	4	17	82	103	25	181	PCR-RFLP	0.0218
Minhas	2010	Pakistan	Asian	19	75	59	153	113	193	5	26	85	116	36	196	PCR-RFLP	0.1180
Nasiri	2013	Iran	Asian	4	34	60	98	42	154	0	39	98	137	39	235	PCR-SSP	0.0521
Song	2017	Danmark	European	3	60	495	558	66	1050	0	51	430	481	51	911	MassARRAY	0.2195
Wei	2013	China	Asian	-	-	-	414	89	739	-	-	-	293	65	531	MassARRAY	-
Babic	2016	Netherland	European	AA + AG = 10		47	57	-	-	AA + AG = 38		95	133	-	-	KASP SNP	-

HWE, Hardy–Weinberg equilibrium; NOS, Newcastle-Ottawa scale; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SSP, sequ specific-primers; KASP, kompetitive allele-specific; SNP, single nucleotide polymorphism.

Table 2
Methodological quality assessment using the Newcastle-Ottawa Scale

Item/Study	Selection				Comparability	Exposure		
	1*	2*	3*	4*	1**	1*	2*	3*
Cardaba	*	-	*	*	*	*	*	*
Feng	*	*	-	*	*	*	*	*
Minhas	*	-	-	*	*	*	*	*
Nasiri	*	*	*	*	*	*	*	*
Song	*	-	*	*	*	-	*	*
Wei	*	-	*	*	**	*	*	*
Babic	*	-	-	*	**	*	*	-

Selection: 1. Adequate definition of cases; 2. Representativeness of cases; 3. Selection of controls; 4. Definition of controls. Comparability: 1. Comparability of cases and controls based on the design or analysis. Exposure: 1. Ascertainment of exposure; 2. The same method of ascertainment for cases and controls; 3. Non-response rate.

Meta-analysis results and subgroup-analyses

RevMan (version5.4.1) was used for the combined analysis of the 7 included studies (Table 3). The pooled results suggested that the recessive model (AA vs. GG + GA: OR = 2.91, 95%CI = 1.44–5.88, I^2 = 0%, P = 0.003) and the co-dominant model (AA vs. GG: OR = 3.89, 95%CI = 1.92–7.89, I^2 = 9%, P = 0.0002) could markedly increase the risk of AR in the overall population (Fig. 2 and Fig. 3). Under the other three genetic models, there was no significant correlation between the TNF-α-308G/A polymorphism and AR susceptibility.

Table 3
Main results of the meta-analysis of the TNF-α-308G/A polymorphism and allergic rhinitis

Groups and Subgroup	Genetic model	n	OR	95%CI	I^2 (%)	*P*	Model
Total	A vs. G	6	1.40	0.92–2.12	78	0.12	REM
	GA + AA vs. GG	6	1.33	0.74–2.40	81	0.34	REM
	AA vs. GG + GA	5	2.91	1.44–5.88	0	0.003	FEM
	AA vs. GG	5	3.89	1.92–7.89	9	0.0002	FEM
	GG + AA vs. GA	5	0.91	0.78–1.05	83	0.19	REM
Asian	A vs. G	4	1.62	0.92–2.86	84	0.09	REM
	GA + AA vs. GG	3	1.50	0.97–2.33	0	0.07	FEM
	AA vs. GG + GA	3	3.08	1.43–6.64	0	0.004	FEM
	AA vs. GG	3	4.38	2.02–9.49	22	0.0002	FEM
	GG + AA vs. GA	3	0.55	0.28–1.06	71	0.08	REM
European	A vs. G	2	1.07	0.75–1.52	0	0.72	FEM
	GA + AA vs. GG	3	0.91	0.65–1.26	23	0.57	FEM
	AA vs. GG + GA	2	2.11	0.36–12.40	28	0.41	FEM
	AA vs. GG	2	2.09	0.36–12.27	30	0.41	FEM
	GG + AA vs. GA	2	1.00	0.69–1.45	0	1.00	FEM

OR, odds ratio; CI, confidence interval; FEM, fixed-effect model; REM, random-effect model.

However, the results of ethnic subgroup analysis showed that the recessive model (AA vs. GG + GA: OR = 3.08, 95%CI = 1.43–6.64, I^2 = 0%, p = 0.004) and the co-dominant model (AA vs. GG: OR = 4.38, 95%CI = 2.02–9.49, I^2 = 22%, p = 0.0002) were closely correlated with the risk of AR within the Asian population, and the TNF-α-308G/A polymorphism is a risk factor for AR, respectively as showed in Fig. 4 and Fig. 5. However, under all genetic models, there was no significant correlation between the TNF-α-308G/A polymorphism and AR susceptibility within the European population.

Sensitivity analysis and evaluation of heterogeneity

To evaluate the stability of the results of this study, a sensitivity analysis was performed. Additionally, a meta-analysis was conducted again after each study was sequentially excluded to reflect the influence of individual studies on the pooled OR.

There was a study by Feng et al. that did not comply with HWE [29]. However, after excluding the study from each genetic model, didn't significantly change the heterogeneity and results (OR, 95%CI, I^2, and *P*), indicating that the research results were relatively stable, so the article was included in the meta-analysis. In addition, since studies of Wei et al. [19] and Babic et al. [18] had no available HWE, the stability of the OR was tested with the exclusion of these two studies. However, the final results indicated the stability of the OR, so the two articles were included in the meta-analysis.

Furthermore, among the 7 included studies, the study of Minhas et al. [30]was found to be the main source of heterogeneity in the overall results through sensitivity analysis. In the comparison of allele model, dominant gene model and over-dominant gene model, before and after deletion of the study of Minhas et. al., the heterogeneity was basically eliminated (A vs. G: I^2 = 6%, p = 0.21, before deletion, I^2 = 78%, p = 0.12; GA + AA vs. GG: I^2 = 31%, p = 0.54, before deletion, I^2 = 81%, p = 0.34; GG + AA vs.GA: I^2 = 0%, p = 0.48, before deletion, I^2 = 83%, p = 0.19). The overall OR and 95%CI of the corresponding gene model also did not change significantly (A vs. G: OR = 1.14, 95%CI: 0.93–1.40, p = 0.21, before deletion, OR = 1.09, 95%CI: 0.84–1.41, p = 0.12; GA + AA vs. GG: OR = 1.09, 95%CI: 0.84–1.41, p = 0.54, before deletion, OR = 1.33, 95%CI: 0.74–2.40, p = 0.34; GG + AA vs. GA, OR = 0.98, 95%CI: 0.94–1.03, p = 0.47, before deletion, OR = 091, 95%CI: 0.78–1.05, p = 0.19). The above results indicated that our results for the overall ORs were not substantially affected. Thus, the research of Minhas et al. was included in this study. In terms of race as a subgroup analysis, the study of Minhas et al. was still the main source of heterogeneity. In the comparison of allele model, dominant gene model and over-dominant gene model, before and after deletion of the study of Minhas et al., the heterogeneity was also basically eliminated (A vs. G: I^2 = 41%, p = 0.19, before deletion, I^2 = 84%, p = 0.09; GG + AA vs.GA: I^2 = 0%, p = 0.26, before deletion, I^2 = 71%, p = 0.08). The overall ORs and 95% CIs of the corresponding genetic model also did not change significantly (A vs. G: OR = 1.18, 95%CI: 0.92–1.53, p = 0.19, before deletion, OR = 1.62, 95%CI: 0.92–2.86, p = 0.09; GG + AA vs. GA, OR = 0.77, 95%CI: 0.49–1.21, p = 0.26, before deletion, OR = 0.55, 95%CI: 0.28–1.06, p = 0.08). The above results indicated that our results were statistically stable. Therefore, the study of Minhas et al. was included in the meta-analysis.

Publication bias

The funnel plot was used to evaluate the publication bias of the included literature. A total of 7 articles were included in this study. In different models, it was found that the distribution of each study in the funnel diagram was basically symmetrical, suggesting that there was a slight possibility of publication bias. However, less than 10 articles were included, which can result in limited explanatory power [32].

Discussion

AR, a common chronic inflammatory disease of the nasal mucosa, because of its long course and easy repetition, has already affected the quality of life and health of human beings all over the world [33]. The potential pathogenesis of AR involves the interaction between genetic susceptibility and environmental exposure to different factors. Environmental factors, especially allergens, have been studied in depth. However, many recent case-control studies have found that certain SNP may be related to AR, indicating that SNP may have strong genetic susceptibility in the etiology and pathogenesis of AR [34, 35]. At the same time, many studies have found that AR was a risk factor for the occurrence and development of asthma, indicating an important relationship between AR and asthma [6], a meta-analysis including 50 case-control studies has found that the TNF-α-308G/A promoter polymorphism strongly correlated with asthma [17]. However, the results of TNF-α-308G/A polymorphism and AR susceptibility were inconsistent. Given the differences among these results, the overall effect of TNF-α-308G/A polymorphism on AR was not clear. Therefore, we conducted a meta-analysis of 7 studies including 1383 AR patients and 1313 controls to further analyze the possible association between the polymorphism of TNF-α-308G/A gene and AR susceptibility.

By applying the quality evaluation tool of NOS methodology, it was found that the NOS scores of all studies were ≥ six stars, which indicated a “high quality” of the included studies. The overall results showed that the difference between the recessive and co-dominant models was statistically significant. The analysis results of the allele model, dominant model, and over-dominant model showed significant heterogeneity, and the heterogeneity was eliminated after removing the study of Minhas et al. in the above three gene models. Therefore, the study of Minhas et al. was the major source of heterogeneity. Similarly, in the subgroup analysis, the difference between the recessive and co-dominant models was statistically significant. There was significant heterogeneity in the allele model and the over-dominant model. Therefore, we believed that the ethnic background could not be the primary source of heterogeneity in this meta-analysis. After removing the study of Minhas et al. from these three gene models, the heterogeneity was eliminated. Based on the above analysis results, the study of Minhas et al. was still the major source of heterogeneity. Compared with other included studies, further analysis of this study found that the ratio of males to females was quite different (7:3). We suspected that confounding factors related to male living habits, such as smoking, which may lead to heterogeneity [36]. The above results also showed that potential confounding factors such as gender of participants, characteristics of participants (occupation, smoking history), lifestyle, and environmental background might change the genetic tendency of diseases. As AR is a complicated atopic disease, including the complex interaction between genes and environmental factors, which could increase heterogeneity to some extent. However, there was not enough data to extract analysis from the study of Minhas et al. In addition, we observed that the heterogeneity of each gene model did not change significantly after excluding studies with inconsistent HWE or unavailable HWE, which indicated that the three studies might not be the source of heterogeneity. In terms of publication bias, the funnel graph was basically symmetrical. However, given the study included less than 10 articles, the explanatory power was limited. In a word, this meta-analysis supported the evidence that the TNF-α-308G/A gene polymorphism may lead to the AR susceptibility of the general population, especially in the Asian population. Alternatively, the sample size of Europeans and Asians in the meta-analysis was almost equal, so that may improve statistical power. However, whether these results can be applied to other regions will need further study.

Meta-analysis is usually used to improve statistical validity [37]. With a large number of different case-control studies, it can draw more accurate conclusions. Inevitably, there were some limitations in the present study, and the limitations listed below may cause some bias. First of all, in this meta-analysis, the relatively small number of AR cases and control groups in each study may lead to deviation of the results. Furthermore, 2/7 of the included studies had incomplete data, which limited the statistical effectiveness of subgroup analysis. Therefore, studies with large sample sizes and large enough subgroups would be helpful to verify our findings. Secondly, our analysis only included studies published in Chinese and English; therefore, and the literary language was Chinese and English. Therefore, publication bias could have appeared, although statistical tests did not show it. Third, there was heterogeneity in some genetic models. After the analysis of ethnic stratification, the heterogeneity had not been significantly reduced. However, different genotyping methods were used to collect samples, which may also affect the heterogeneity among studies. Most importantly, this study only statistically analyzed the individual gene loci of TNF-α, and the polymorphism of TNF-α-308G/A gene was only one of the phenotypes of AR. The interaction between sites and sites of the same gene, between genes and environment, and between genes has not been analyzed as to how it affects TNF-α and the pathogenesis of AR.

Conclusions

This study has greatly increased the sample size through a comprehensive evaluation of independent studies. There was no obvious publication deviation in this study, and the sensitivity analysis was good. The findings of our current analysis suggested that the polymorphism of TNF-α-308G/A gene may be related to the pathogenesis of AR, especially among Asian people. To further confirm the gene-disease relationship between TNF-α-308G/A polymorphism and susceptibility of AR, a more large-scale and high-quality research design under the background of other races are strongly encouraged. This will contribute to explaining the pathogenesis of AR from a genetic point of view and provide the corresponding theoretical basis for disease prevention and treatment.

Declarations

Statement of Ethics

This meta-analysis was conducted in accordance with the PRISMA guideline. Ethical approval and informed consent are not applicable to meta-analyses.

Consent for publication

All authors agree to publish this work.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Author contributions

Huajie Yuan and Hua Zhang produced the idea for this analysis and made the final version of this paper. Lingling Wang and Huajie Yuan did the literature search and evaluated the data, they both contributed equally to this work. Huaqiang Li performed the statistical analyses. Siyuan Liu and Limian Xiao critically revised this manuscript. Jiye Huang was involved in revising the data. Yan Wang and Yuping Yang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figures

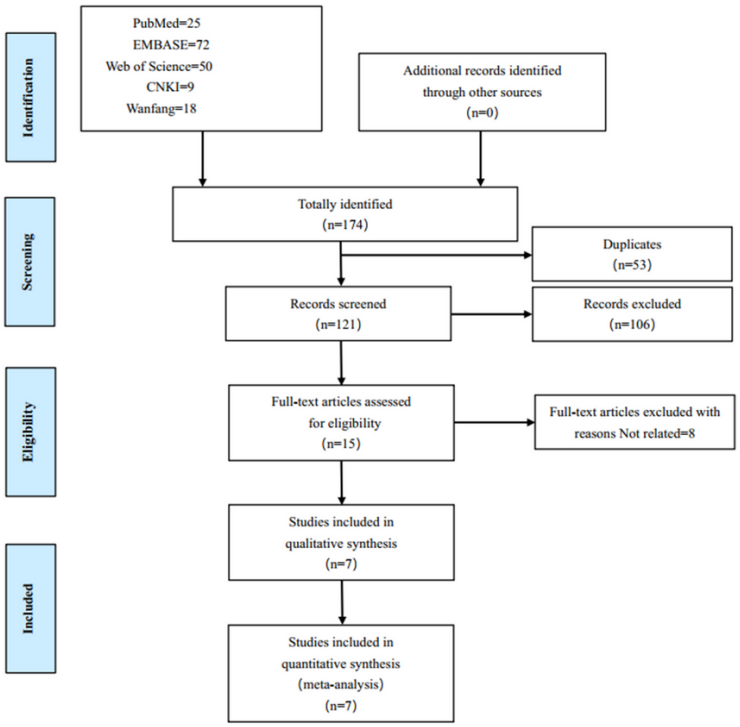

Figure 1

Literature retrieval and screening flow chart

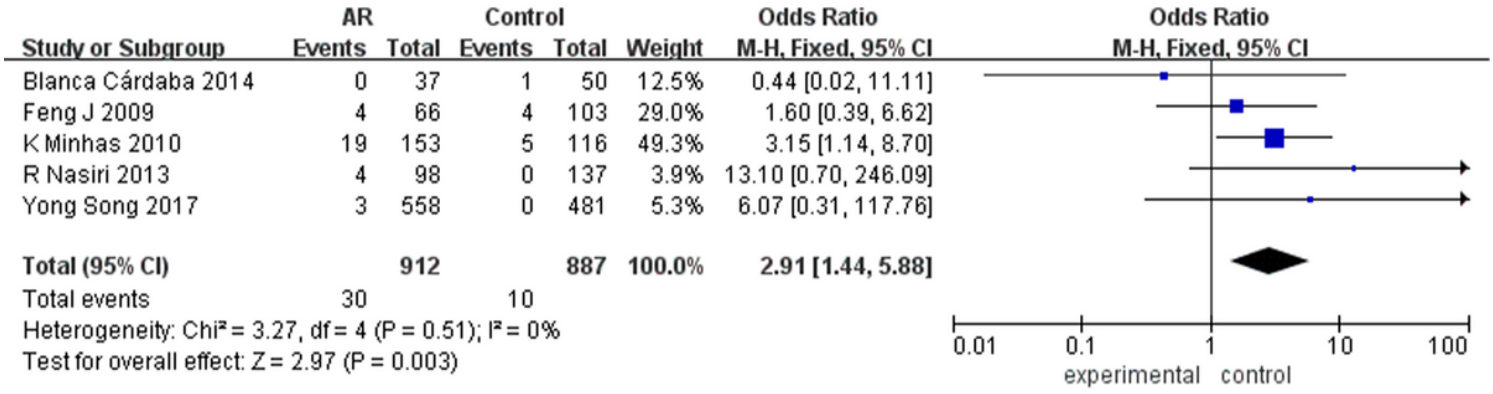

Figure 2

Overall meta-analysis of the association between the TNF-α-308G/A polymorphism and risk of allergic rhinitis for the recessive model (AA vs.GG + GA)

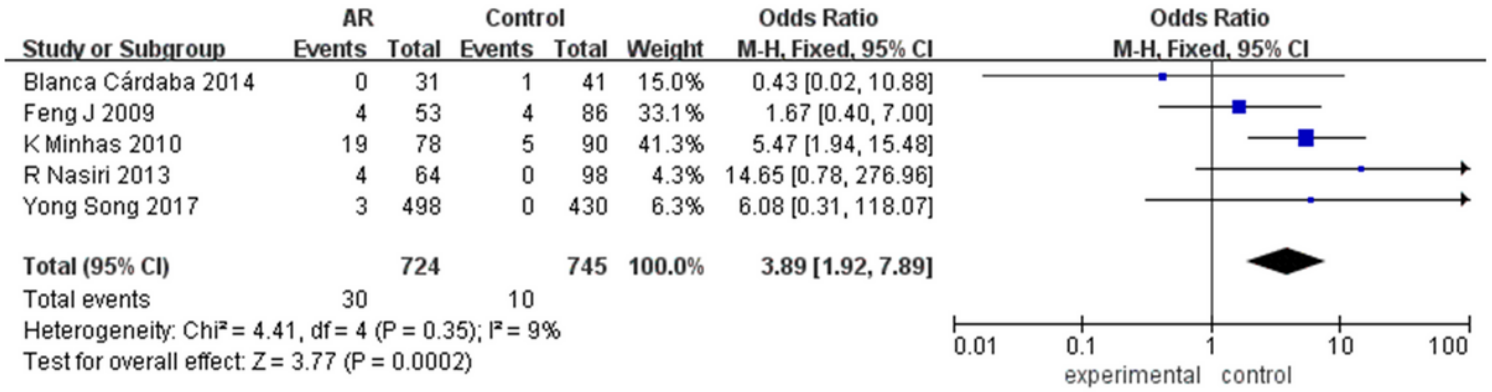

Figure 3

Overall meta-analysis of the association between the TNF-α-308G/A polymorphism and risk of allergic rhinitis for the co-dominant model (AA vs.GG)

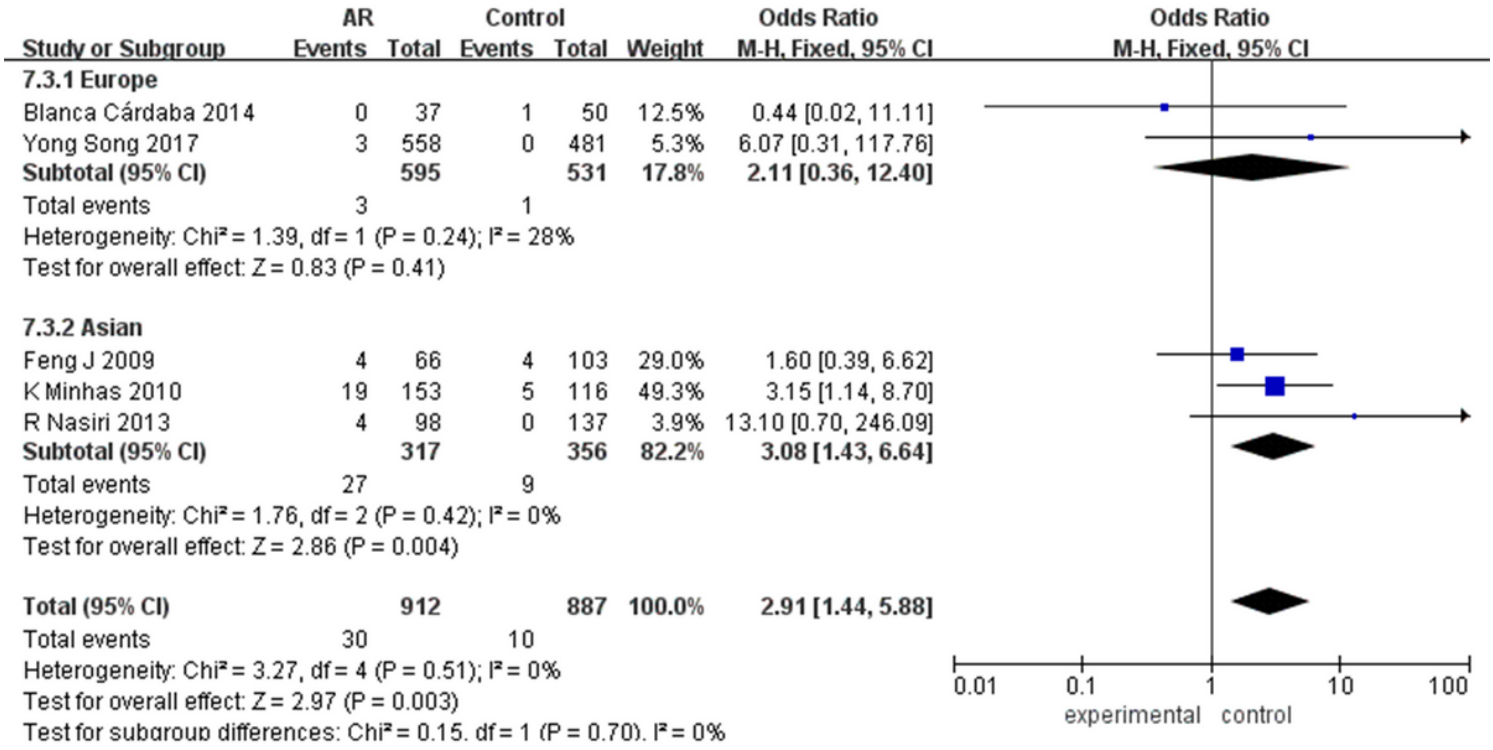

Figure 4

Ethnicity stratification analysis of the association between the TNF-α-308G/A polymorphism and risk of allergic rhinitis under the recessive model (AA vs.GG + GA)

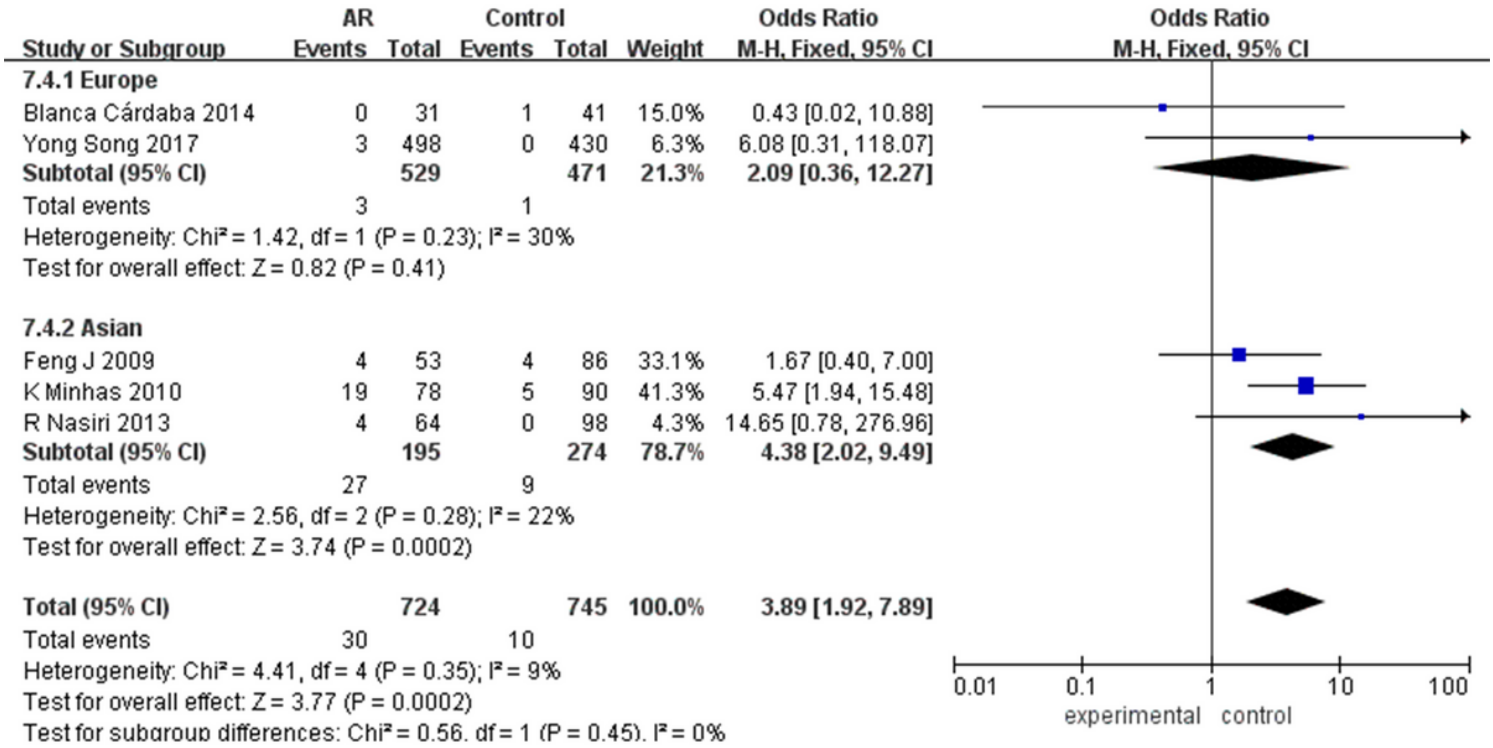

Figure 5

Ethnicity stratification analysis of the association between the TNF-α-308G/A polymorphism and risk of allergic rhinitis under the co-dominant model (AA vs.GG)