



Association of the *TNF- α* +489 G/A polymorphism with chronic obstructive pulmonary disease risk in Asians: meta-analysis

K. Cui, X.Y. Ge and H.L. Ma

Department of Epidemiology and Biostatistics, School of Public Health,
Liaoning Medical University, Jinzhou Liaoning, China

Corresponding author: H.L. Ma
E-mail: mahonglinly@163.com

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ABSTRACT. The association between the *TNF- α* +489 G/A polymorphism and chronic obstructive pulmonary disease (COPD) remains controversial because of small group size and varied design among different studies. In the present study, a meta-analysis was conducted to assess the association between the +489 G/A polymorphism and COPD risk. A comprehensive search was conducted to identify articles that have reported an association between the *TNF- α* +489 G/A polymorphism and COPD risk. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated under both dominant (AA+GA vs GG genotypes) and allele (A vs G) models. Heterogeneity was assessed, as well as publication bias. Nine articles with ten eligible studies were included in this analysis. Significant association between the +489 G/A polymorphism and COPD was identified in Asians under the allele model (OR = 1.582, 95%CI = 1.035-2.419). However, no significant difference was found in the Caucasian groups. Strong evidence for between-study heterogeneity was identified under both models, and no publication bias was detected. Our results indicated a potential role of the A allele of the *TNF- α* +489 G/A polymorphism

in increasing COPD risk in Asians, but not in Caucasians. Additional studies will be necessary to verify this conclusion.

Key words: Chronic obstructive pulmonary disease; Meta-analysis; Tumor necrosis factor-alpha; Polymorphism

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic systemic inflammatory disease characterized by progressive airflow obstruction, and is a major cause of morbidity and mortality world-wide (Zhan et al., 2011; Jose Soler-Cataluna et al., 2014). Smoking is the most important risk factor for COPD, but only 10-15% of smokers develop COPD (Manino et al., 2002; Corhay et al., 2012). There also appears to be a familial clustering of COPD (Zhan, et al., 2011), together suggesting that the susceptibility to COPD might be influenced by genetic factors.

An increasing number of studies have found elevated tumor necrosis factor (TNF)- α in the sputum, bronchoalveolar lavage fluid, and bronchial biopsies from patients with COPD (Mueller et al., 1996; Yanbaeva et al., 2006; Du et al., 2014), implying a key role of this cytokine in the progression of COPD. Since 1992, several genomic polymorphisms of *TNF- α* have been identified, such as -238 G/A, -308 G/A, -376 G/A, -863 C/A, +489 G/A, -857T/C, and -1031T/C (Brogger et al., 2006; Trajkov et al., 2009; Cordoba-Lanus et al., 2011). Many studies have assessed the association between COPD risk and *TNF- α* polymorphisms; however, the -308 G/A variant is the best studied among all the polymorphisms (Zhang et al., 2011; Ezzeldin et al., 2012). The +489 G/A polymorphism is located in the first intron of the *TNF- α* gene, and its role in increasing the susceptibility of certain pathologic conditions has been identified, including prostate cancer, systemic lupus erythematosus, and rheumatoid arthritis (van Krugten et al., 1999; Lin et al., 2009). However, the association between the +489 G/A polymorphism and COPD is still controversial, owing to the small sample sizes and varied design among different studies. A recently published meta-analysis was conducted to assess the effect of the +489 G/A polymorphism on COPD risk (Smolonska et al., 2009), but few studies were included that had recruited Asians. Although the authors suggested that the +489 G/A polymorphism was not associated with COPD in Caucasians, additional evidence was still needed to elucidate its role in Asians. In the present study, we conducted a comprehensive literature search and meta-analysis to assess the effect of the *TNF- α* +489 G/A polymorphism on COPD risk in both Asians and Caucasians.

MATERIAL AND METHODS

Search strategy

Relevant available articles published in English or Chinese were searched from six databases, including PubMed, ISI Web of Science, China Biology Medical Literature database (CBM), China National Knowledge Infrastructure (CNKI), Database of Chinese Scientific and Technical Periodicals (VIP), and Wanfang Data. The combinations of the following medical subject headings (MeSH) terms and key words were used: “TNF”, “tumor necrosis factor”,

“polymorphism”, “SNP” (which stands for single nucleotide polymorphism), “COPD”, and “chronic obstructive pulmonary disease”. An upper date limit of Jul 28, 2014 was applied, and a lower date limit was not specified. Additional studies that were not captured in the key word search were identified by manually reviewing the bibliographies of relevant articles as well as relevant review articles.

Inclusion criteria

Two investigators independently reviewed all studies identified to determine whether an individual study was eligible for this meta-analysis. The inclusion criteria applied in the present study was as follows: 1) case-control study published as an original study to evaluate the association between the *TNF- α* +489 G/A SNP and risk of COPD; 2) numbers of individuals with each genotype were reported in the study, or data provided from which numbers could be calculated; and 3) patients and controls were unrelated and drawn from the same temporally and geographically defined underlying population. Disagreements about the eligibility of an article between the two investigators were resolved by consensus with a third reviewer.

Data extraction and quality assessment

Extracted data included the following: name of the first author, publication year, country/territory, ethnicity of the study population, source of control subjects, mean age, male sex percentage in patients and controls, smoking status, genotyping methods, definition of COPD, matching methods, number of patients and controls, and genotype and allele distributions.

The quality of each study was assessed independently by two investigators using the Newcastle-Ottawa quality assessment scale (Wells et al., 2000). The quality of case-control studies were evaluated for three major components, including selection of patients and controls, comparability of patients and controls, and ascertainment of exposure.

Statistical analysis

Deviation from Hardy-Weinberg equilibrium (HWE) for *TNF- α* +489 G/A genotype distribution in the control group was analyzed using Fisher’s exact test. A pooled measure was calculated with the inverse variance-weighted mean of the logarithm of odds ratio (OR) with 95% confidence interval (CI) to assess the association between *TNF- α* +489 polymorphism and COPD under two models, the dominant model (AA+GA versus GG genotypes) and the allele model (A versus G). The I^2 statistic was used to assess heterogeneity among studies, which described the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance. $I^2 > 50\%$ was considered to represent significant statistical heterogeneity, and the DerSimonian and Laird random effect model (DerSimonian and Kacker, 2007) was adopted as the pooling method; for $I^2 < 50\%$, the Mantel and Haenszel fixed effect model (Higgins and Thompson, 2002) was used. Pooled measures in subgroups stratified by ethnicity (categorized as Asians and Caucasians) and published language (categorized as English and Chinese) were also meta-analyzed. Meta-regression with restricted maximum likelihood estimation was adopted to assess the potentially important co-variables exerting substantial impact on between-study heterogeneity. One-way sensitivity analyses, namely the sequential deletion of a single study followed by re-analysis, were conducted to describe how

robust the pooled estimators were to removal of individual studies (Tobias, 1999). An individual study was suspected of excessive influence if the point estimate of its omitted analysis lay outside the 95%CI of the pooled measures (Zhan, et al., 2011; Zhou et al., 2012). Publication bias was estimated with the asymmetry linear regression of Egger's test (Egger et al., 1997), and displayed as a funnel plot. All statistical analyses were performed with the STATA version 9.2 software (Stata Corporation, College Station, TX, USA). All reported probabilities were two-tailed, with $P < 0.05$ considered to be statistically significant.

RESULTS

Characteristics of studies

Nine published articles (Küçükaycan et al., 2002; Hegab et al., 2005; Du et al., 2008; Gingo et al., 2008; Hsieh et al., 2008; Song et al., 2008; Gao, 2010; Matokanovic et al., 2012; Yao et al., 2012), with a total of 1184 patients with COPD and 1439 controls, were included in this analysis. Among all the articles, four were published in Chinese (Du et al., 2008; Song et al., 2008; Gao, 2010; Yao et al., 2012) with the others in English (Küçükaycan et al., 2002; Hegab et al., 2005; Gingo et al., 2008; Hsieh et al., 2008; Matokanovic et al., 2012). One article (Hegab et al., 2005) recruited two different ethnic populations, Japanese and Egyptian. Therefore, there were 10 eligible studies in the present meta-analysis. Two studies (Du et al., 2008; Hsieh et al., 2008) recruited two different control groups. In one study (Küçükaycan et al., 2002), the genotype distributions in the control group were not consistent with that expected under HWE. General characteristics, the +489 G/A allele and genotype distributions, and quality assessment of the studies are shown in Tables 1 and 2.

Quantitative synthesis

As shown in Figure 1, the overall OR for the dominant model was 1.393 (95%CI = 0.974-1.992, $P = 0.069$, $I^2 = 64.6\%$). There was a marginally non-significant difference in the Asian subgroup (OR = 1.588, 95%CI = 0.993-2.540, $P = 0.053$, $I^2 = 60.8\%$), but a conspicuously non-significant difference in the Caucasian subgroup (OR = 1.166, 95%CI = 0.679-2.003, $P = 0.578$, $I^2 = 65.8\%$). Pooled measures for the allele model are shown in Figure 2. The overall OR and that in the Asian subgroup were 1.387 (95%CI = 1.011-1.902, $P = 0.042$, $I^2 = 63.1\%$) and 1.582 (95%CI = 1.035-2.419, $P = 0.034$, $I^2 = 61.3\%$), respectively. However, there was no significant difference in the Caucasian subgroup (OR = 1.146, 95%CI = 0.758-1.732, $P = 0.519$, $I^2 = 52.5\%$). Subgroup analyses in the Asian subgroup were also performed according to the published language, and the results are shown in Table 3.

Sources of heterogeneity

Because strong evidence of heterogeneity was demonstrated among individual studies, a univariate regression was conducted to explore the potential co-variables exerting substantial impact on between-study heterogeneity under both inheritance models. The co-variables were as follows: publication year, gender (ratio of males in percent in patients to that in controls), age (ratio of mean age in patients to that in controls), sample size, genotyping method (categorized as polymerase chain reaction-restriction fragment length polymorphism

Table 1. General characteristics of studies included in the meta-analysis.

1st author	Year of publication	Country/territory	Ethnicity	COPD definition	Source of controls	Matching method	Genotyping method	Mean age (patients/controls)	Male % (patients/controls)
Du	2008	China	Asian	CMA criteria of 2002	Hospital population Healthy population (school-aged children)	Age, gender, smoking NA	PCR-RFLP PCR-RFLP	73.4/72.5 -/18.2	43.6/51.5 -/43.6
Song	2008	China	Asian	CMA criteria of 2002	Healthy population (check-up)	NA	PCR-RFLP	72.2/41.5	68.2/70.0
Yao	2012	China	Asian	CMA criteria of 2007	Healthy population (check-up)	Age, gender	PCR-RFLP	64.2/62.8	68.3/68.3
Gao	2010	China	Asian	CMA criteria of 2007	Healthy population (check-up)	NA	PCR-RFLP	64.4/62.8	68.3/61.3
Gingo	2008	USA	Caucasian	GOLD criteria	Healthy population	NA	PCR-SSP	65.6/58.7	52.0/70.3
Küçükaycan	2002	Netherlands	Caucasian	American Thoracic Society criteria	Healthy population	NA	PCR-DBA	66.0/44.0	65.0/57.0
Hegab	2005	Japan	Asian	GOLD criteria	Healthy population	Age, smoking	PCR-RFLP	66.9/67.8	96.6/98.4
Hsieh	2008	Egypt Taiwan	Caucasian Asian	GOLD criteria GOLD criteria	Healthy population Patients at risk for COPD	Age, smoking Age, gender	PCR-RFLP PCR-RFLP	62.5/59.0 68.7/64.0	100/100 80/89.1
Matkanovic	2012	Croatia	Caucasian	GOLD criteria	Hospital population Healthy population	Age, gender NA	PCR-RFLP PCR-RFLP	-/65.0 70.0/51.5	-/89.6 79.2/72.6

COPD = chronic obstructive pulmonary disease; CMA = Chinese Medicine Association; DBA = dot blot analysis; GOLD = Global Initiative for Chronic Obstructive Lung Disease; NA = not applicable; PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism; SSP = sequence-specific priming.

(PCR-RFLP) and non-PCR-RFLP, matched (categorized as yes and no), and definition of COPD (categorized as global initiative for chronic obstructive lung disease criteria (GOLD) and non-GOLD (Vestbo et al., 2012). However, as shown in Table 4, no co-variables had a significant impact on between-study heterogeneity.

Table 2. Distributions of the +489 G/A genotypes and alleles of the studies included in the present meta-analysis.

1st author	Smoking status		Genotypes (AA/GA/GG)		Alleles (A/G)		HWE	Quality score
	Patient	Control	Patient (N)	Control (N)	Patient (N)	Control (N)		
Du	Mixed	Mixed	2/11/42	0/7/40	15/95	7/87	Y	8
		N	-/-/-	0/5/50	-/-	5/105	Y	-
Song	Mixed	Mixed	2/22/61	1/18/51	26/144	20/120	Y	6
Yao	Mixed	Mixed	4/50/126	2/46/312	58/302	50/670	Y	8
Gao	Mixed	Mixed	2/16/42	1/8/53	20/100	10/114	Y	6
Gingo	NA	Y	1/28/264	0/7/116	30/556	7/239	Y	7
Küçükaycan	Mixed	Mixed	1/38/118	6/45/264	40/274	57/573	N	5
Hegab	Y	Y	5/26/57	2/19/40	36/140	23/99	Y	8
	Y	Y	2/19/85	1/13/58	23/189	15/129	Y	-
Hsieh	Mixed	Mixed	0/7/23	0/15/49	7/53	15/113	Y	8
		Mixed	-/-/-	1/35/79	-/-	37/193	Y	8
Matokanović	Mixed	Mixed	5/38/87	3/39/53	48/212	45/145	Y	5

HWE = Hardy-Weinberg equilibrium; N = numbers; Mixed = smoker and non-smoker; NA = not applicable; Y = yes; N = no.

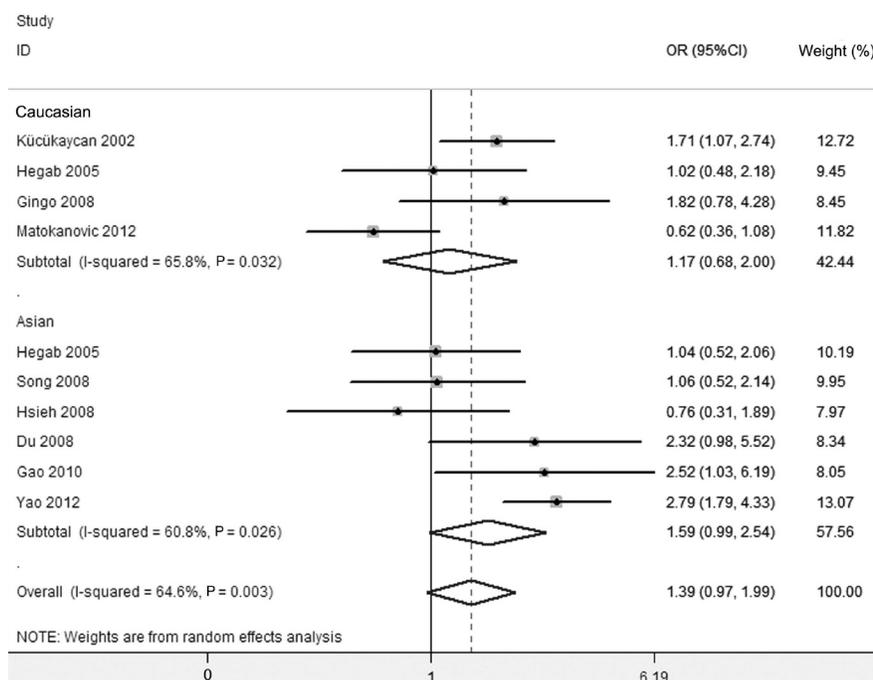


Figure 1. Forest plot of the association between COPD risk and the TNF- α +489 G/A polymorphism under the dominant inheritance model in the overall subject population and in subgroups, using a random-effects model. Each box represents the odds ratio (OR) point estimate, and its area is proportional to the weight of the study. The diamond and broken line represent the overall estimate, with the 95% confidence interval (CI) represented by its width. The unbroken vertical line is set at the null value (OR = 1.0).

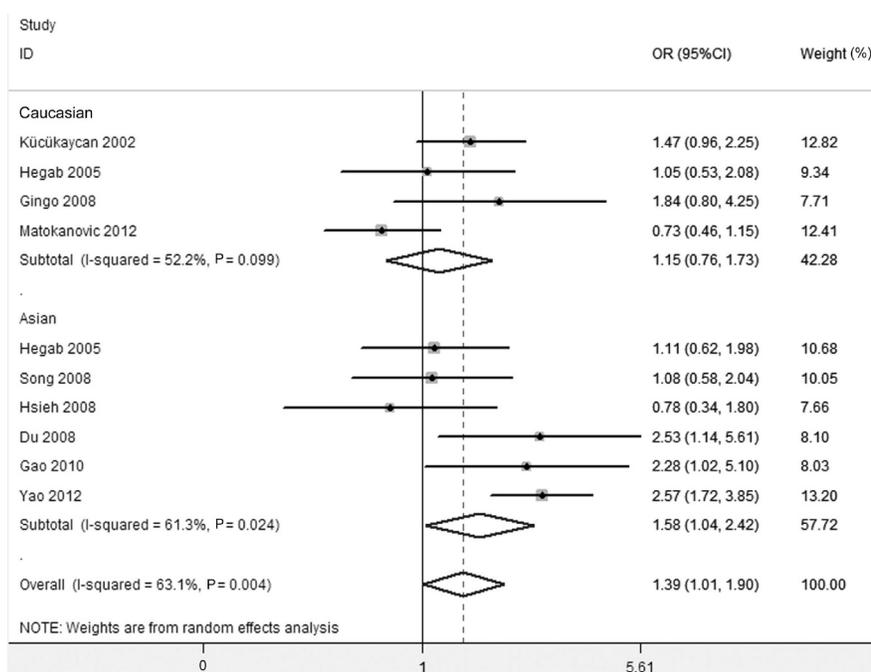


Figure 2. Forest plot of the association between COPD risk and the *TNF- α* +489 G/A polymorphism under an allele inheritance model in the overall study population and in subgroups, using a random effects model. COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

Table 3. Pooled measures in subgroups stratified by publication language.

Inheritance model	Publication language	No. of studies	Pooled ORs, (95%CI)	I ²
Dominant model	English	2	0.927 (0.537-1.602)	0%
	Chinese	4	2.080 (1.307-3.310)	43.9%
Allele model	English	2	0.987 (0.611-1.594)	0%
	Chinese	4	2.018 (1.319-3.087)	45%

OR = odds ratio; CI = confidence interval.

Table 4. P values for co-variables under two models under meta-regression.

Inheritance model	Co-variables	P
Dominant model	Publication year	0.308
	Gender	0.845
	Age	0.293
	Sample size	0.346
	Genotyping method	0.247
	Matched	0.255
	Definition of COPD	0.074
	Allele model	Publication year
Allele model	Gender	0.849
	Age	0.368
	Sample size	0.308
	Genotyping method	0.232
	Matched	0.224
	Definition of COPD	0.080

COPD = chronic obstructive pulmonary disease.

Sensitivity analyses and publication bias

When each study was sequentially deleted from the analysis in either inheritance model, the corresponding results were not materially altered (data not shown). As shown in Figures 3 and 4, the Egger's test and funnel plot did not suggest evidence of publication bias for either inheritance model ($P = 0.520$, $P = 0.827$, respectively).

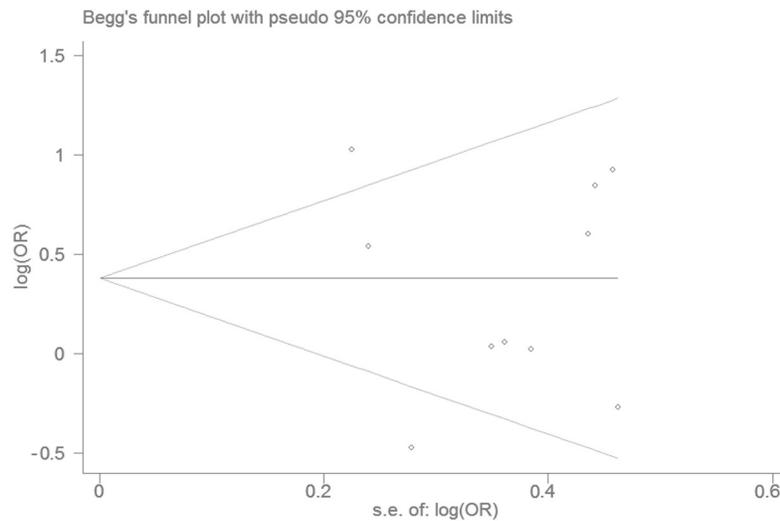


Figure 3. Funnel plot of the association between the *TNF- α* +489 G/A polymorphism and COPD risk under the dominant inheritance model. The X-axis consists of the natural logarithm of ORs, and the Y-axis represents the standard error of the natural logarithm of ORs. COPD = chronic obstructive pulmonary disease; OR = odds ratio.

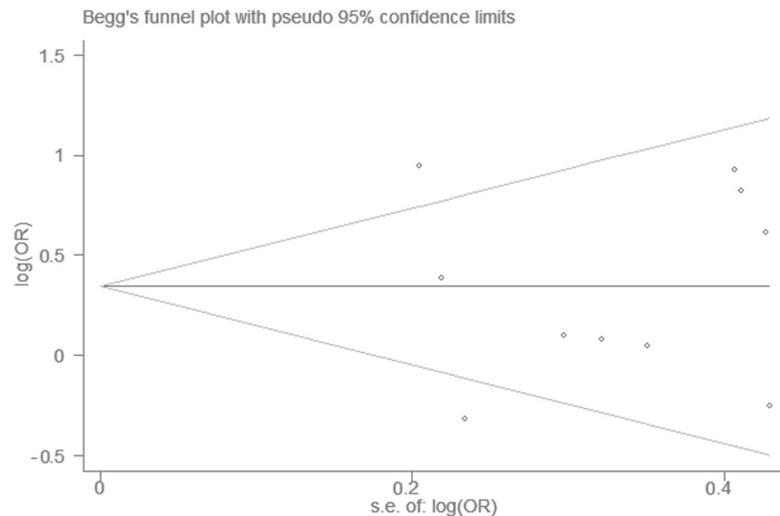


Figure 4. Funnel plot of the association between the *TNF- α* +489 G/A polymorphism and COPD risk under the allele inheritance model. The X-axis consists of the natural logarithm of ORs, and the Y-axis represents the standard error of the natural logarithm of ORs. COPD = chronic obstructive pulmonary disease; OR = odds ratio.

DISCUSSION

The *TNF- α* +489 G/A polymorphism, located in the first intron of the *TNF- α* gene, was identified in 1996 (D'Alfonso and Richiardi, 1996). Considering that the polymorphism would not interfere with the TNF protein sequence, Kaijzel et al. (2001) examined the allele-specific pre-mRNA expression of TNF. However, no difference was detected in the *TNF- α* pre-mRNA yield upon *in vitro* and physiological stimulation conditions between the A and G alleles in healthy individuals or patients with rheumatoid arthritis (Kaijzel et al., 2001), suggesting that this polymorphism had no impact on the production of TNF- α . Despite these observations, the polymorphism was found to be associated with several pathologic conditions. Lin et al. (2009) indicated that the A allele of the *TNF- α* +489 G/A polymorphism increased the risk of systemic lupus erythematosus in the Taiwanese population. Oh et al. (2000) demonstrated an association between the *TNF- α* +489 G/A polymorphism and prostate cancer. van Krugten et al. (1999) discovered that this polymorphism was associated with susceptibility to and disease severity of rheumatoid arthritis, and indicated that the association might be explained by linkage disequilibrium with alleles within or nearby the *TNF* locus. There were also studies on the association between this polymorphism and COPD. In Küçükaycan's study, the +489 G/A polymorphism was found to be related with COPD, especially in the patients without radiological emphysema (Küçükaycan, et al., 2002), and this conclusion was supported by several additional studies (Du et al., 2008; Gao, 2010; Yao et al., 2012). Nevertheless, in some other studies, no similar conclusion was reached. An indeterminate number of characteristics that varied among studies could be the cause of the controversy, e.g. design quality, ethnic population, sample size, etc. Smolonska et al. (2009) performed a meta-analysis to reveal the role of 20 candidate polymorphisms on COPD, including the *TNF- α* +489 G/A polymorphism. In that study, the author included six studies, with only two from Asian ethnic populations, and assessed the effect of the polymorphism under a dominant model. The author suggested that the polymorphism was unlikely to be associated with COPD susceptibility in whites, and that larger studies were needed to elucidate its role in Asians. Thus, in this study, we searched in both Chinese and English databases and conducted a meta-analysis to assess the association between the *TNF- α* +489 G/A polymorphism and COPD risk in both populations. We also performed analyses under dominant and allele models. There were nine articles published with ten eligible studies included in our analysis, among which five were consistent with Smolonska's study, and four were from Chinese databases. Chappell's study was included in Smolonska's study but not in ours, because the number of individuals with each genotype, which we used to calculate ORs, were not reported (Chappell et al., 2007).

According to the results of the present study, we found that the *TNF- α* +489 G/A polymorphism was associated with COPD under the allele model. Since ethnic difference is a common factor that influences human diseases, subgroup analyses stratified by ethnicity were performed. The results suggested a potential role of the A allele of the *TNF- α* +489 G/A polymorphism in increasing COPD risk in Asians. Because most of the Chinese studies reported positive conclusions, we performed subgroup analyses in the Asian subgroup, stratified by the language of publication. The results showed that the pooled measures of the studies published in Chinese were positive. However, the other studies by Asians that were published in English reported negative results. This analysis suggested that the association between the +489 G/A polymorphism and COPD risk in Asians might be caused by the positive conclusions reached by the Chinese studies. Furthermore, in the present study, no evidence of association was

found under either model in Caucasians, which implied that it seemed unlikely that the polymorphism was associated with COPD risk in Caucasians. This conclusion was similar with that of Smolonska's study.

Munafo and Flint (2004) indicated that between-study heterogeneity was common in meta-analysis for genetic association studies. Our study also showed significant heterogeneity under both models. Besides using the Newcastle-Ottawa quality assessment scale to assess the quality of each eligible study to reduce the heterogeneity, we also adopted meta-regression to explore the potential source thereof. However, none of the co-variables had a significant impact on between-study heterogeneity. COPD has a complex etiology, and genetic and environment variables as well as their interaction might be considered as contributors to the un-conformity. In this respect, the lack of relevant study-level co-variables in the reported articles precluded our assessment of the source of this heterogeneity.

The sensitivity analysis investigated how robust the pooled estimators were to removal of individual studies, in which the meta-analysis was reestimated omitting each study in turn, and an individual study was suspected of excessive influence if the point estimate of its omitted analysis lay outside the 95%CI of the combined analysis (Tobias, 1999, Singh et al., 2008, Liu et al., 2013). In this meta-analysis, no individual study was found to have influence on the pooled effect. A known threat to the validity of meta-analysis was publication bias, which occurs when studies with statistically significant results are more likely to be published than those with non-significant results (Ahmed et al., 2012). In the present study, no publication bias was observed in either inheritance model, indicating that the results of this meta-analysis were reliable.

In conclusion, this meta-analysis demonstrated a potential role of the A allele of the TNF- α +489 G/A polymorphism in increasing COPD risk in Asians, but not in Caucasians. Considering the influence of the positive results of the Chinese studies and the significant heterogeneity among studies, further studies are needed to confirm this conclusion.

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