

Association between TNF- α –308 G/A polymorphism and COPD susceptibility: a meta-analysis update

Lu Zhang¹
Hao Gu²
Yihang Gu²
Xiaoning Zeng²

¹Clinical Research Centre,

²Department of Respiratory & Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, People's Republic of China

Background and objective: The association between TNF- α –308 G/A polymorphism and COPD remains controversial due to insufficiently strict study designs and small group sizes among different studies. In the present study, a meta-analysis update which followed a stricter procedure was performed to obtain a clearer understanding of this association.

Methods: A comprehensive database search was conducted to identify the case-control studies published up to July 2015 which reported an association between the TNF- α –308 G/A polymorphism and COPD risk. Data were extracted to calculate pooled odds ratios with 95% confidence intervals under the most appropriate genetic and allelic models. Sensitivity was analyzed, and heterogeneity as well as publication bias was assessed.

Results: Thirty-eight eligible studies, comprising 3,951 COPD cases and 5,110 controls, were included in this study, among which 22 studies comprising 2,067 COPD cases and 2,167 controls were performed in Asians, and 16 studies comprising 1,884 COPD cases and 2,943 controls were in non-Asians. The overall result showed that TNF- α –308 G/A polymorphisms were significantly associated with increased COPD risk in both the codominant genetic and allelic models. Individuals with the GA or AA genotype were more susceptible to COPD development than those with the GG genotype. In addition, individuals with the AA genotype were more susceptible to developing COPD than those with the GA genotype. The subgroup analysis stratified by ethnicity supported the results in Asians but not in non-Asians. However, no association was found between TNF- α –308 G/A polymorphisms and COPD susceptibility either in Asians or in non-Asians in the meta-analysis conducted with restriction to former/current smokers.

Conclusion: The present meta-analysis suggested that the TNF- α –308 G/A polymorphism was associated with an increased risk of COPD among Asians but not in non-Asians. Furthermore, individuals with the AA genotype of TNF- α –308 were more susceptible to developing COPD.

Keywords: cytokine, genotype, ethnicity, COPD, smokers

Introduction

COPD is characterized by the progressive development of airflow limitation that is not fully reversible.¹ COPD has been estimated to become the third leading cause of death in the world by 2020.² According to statistics, COPD is ranked as the third and fourth leading cause of death in rural and urban areas of the People's Republic of China, respectively.³ Cigarette smoking is considered to be a major environmental factor contributing to the development of COPD. However, only 25%–40% of cigarette smokers develop COPD,⁴ indicating that other components may be involved in COPD development.^{5–7}

Correspondence: Xiaoning Zeng
Department of Respiratory & Critical Care Medicine, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, Jiangsu, People's Republic of China
Tel +86 25 6813 6804
Fax +86 25 8367 3567
Email zeng_xiao_ning@hotmail.com

Accumulated evidence indicates that genetic factors influence COPD susceptibility. A number of studies have demonstrated that TNF- α is relevant to the pathogenesis of COPD, including involvement in neutrophil release from the bone marrow and neutrophil activation.⁸ Increased levels of TNF- α have been found in the sputum,⁹ bronchoalveolar lavage fluid, bronchial biopsies, and circulation¹⁰ of COPD patients. Genetic polymorphism analyses have identified several single-nucleotide polymorphisms in the TNF- α gene associated with COPD risk, including -238 G/A, -308 G/A, -376 G/A, -863 C/A, -857 T/C, -1031 T/C, and +489 G/A.^{11–14} Among these, the -308 G/A polymorphism is the best studied; however, a consistent association has not yet been found.¹⁵ Studies in Asians^{16,17} and non-Asians¹⁸ have demonstrated that the TNF- α -308 G/A polymorphism is associated with an increased risk of COPD. However, other studies in both Asians^{19,20} and non-Asians^{21–25} have showed opposite results.

A limited number of meta-analyses have been performed to further clarify the association between the TNF- α -308 polymorphisms and COPD risk;^{26–29} however, a firm conclusion has not been achieved because of several limitations in the previous meta-analyses including 1) failure to check the Hardy–Weinberg equilibrium (HWE), 2) lack of quality assessment, 3) inappropriate genetic model, and 4) a limited number of included studies. All these factors have led to considerable argument regarding the studies' paradoxical conclusions. Additionally, only studies published up to 2010 were included in the most recent meta-analysis.²⁹ In the present study, we conducted a meta-analysis update with studies published up to July 2015. Additionally, we followed a stricter procedure: 1) only studies in accordance with HWE were included, 2) all included studies had a quality score no less than 5 because studies with quality scores ≤ 4 are considered as low-quality studies,³⁰ and 3) the most appropriate genetic model was employed. Thus, our report presented more detailed information which will not only help obtain a clearer understanding of the association between TNF- α -308 polymorphisms and COPD but also help pave the way for individualized treatment of COPD patients.

Materials and methods

The current meta-analysis was conducted according to the guidelines presented in the review by Sagoo et al.³¹

Search strategy for publication

A comprehensive search was conducted using the terms “TNF”, “tumor necrosis factor”, “polymorphism”, and

“COPD” in several electronic databases (PubMed, EMBASE, ISI Web of Science, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, Database of Chinese Scientific and Technical Periodicals, China Biology Medicine disc database, and WANFANG databases) to identify studies that examined the association of TNF- α -308 (rs1800629) G/A polymorphisms with COPD published up to July 2015. Additional studies were identified by manually reviewing the bibliographies of relevant articles as well as relevant review articles. The search was performed without restriction regarding race, ethnicity, or geographic area. Only published studies with full text in English or Chinese were included. Concerning duplicate populations included in several publications, only the most recent or complete study was included in this meta-analysis.

Eligibility criteria

Eligible studies were required to meet the following inclusion criteria: 1) evaluation of the TNF- α -308 polymorphism and COPD risk, 2) employment of a case–control design, 3) inclusion of adult subjects within the case group or control group, 4) disclosure of the number of individual genotypes with COPD in cases and controls, and 5) congruency of the distribution of genotypes among controls with HWE. Studies were excluded if 1) they contained overlapping data with another study, 2) the number of wild-type genotypes or alleles was not stated, and 3) they reviewed only editorials, reviews, and abstracts. All articles were reviewed to determine eligibility by two independent investigators. A consensus with a third reviewer was needed if there was any disagreement between the two investigators.

Data extraction

Data were checked and extracted from each study by two independent investigators. Data inconsistencies or discrepancies were resolved by consensus of all investigators before being standardized into a unified dataset. The following information was extracted from each study: first author's name, publication year, country/territory, numbers of cases and controls, ethnicity of the study population, source of control subjects, smoking status in cases and controls, and genotype and allele distribution.

Quality assessment

The Newcastle–Ottawa quality assessment scale³² was applied to assess the quality of each study by two investigators. The quality was evaluated with three major components: 1) selection of cases and controls, 2) comparability of cases

and controls, and 3) ascertainment of exposure. Any disagreement was resolved by a third investigator. Only studies with a quality score ≥ 5 were included in the current study.

Statistical analysis

Statistical analysis was performed according to standard procedures.³⁰ Pooled odds ratios (ORs) were calculated with the Mantel-Haenszel (M-H) mean of the logarithm with a 95% confidence interval (CI). First, an allele comparison was conducted to determine the allele risk. Second, OR1, OR2, and OR3 were explored for the genotypes (GG vs AA [OR1], GG vs GA [OR2], and GA vs AA [OR3]) to identify the most appropriate genetic model. When $OR1 = OR3 \neq 1$ and $OR2 = 1$, a recessive model was suggested. When $OR1 = OR2 \neq 1$ and $OR3 = 1$, then a dominant model was suggested. When $OR1 > OR2 > 1$ and $OR1 > OR3 > 1$ (or $OR1 < OR2 < 1$ and $OR1 < OR3 < 1$), then a codominant model was suggested.³³ Lastly, the most appropriate genetic model was used to pool the results.

Heterogeneity was assessed by using the chi-square-based Cochran Q -test, which was considered significant if $P < 0.10$, and the I^2 statistic. If $I^2 > 50\%$, the random-effect model was adopted as the pooling method; otherwise, the fixed-effect model was used. To explore the source of the heterogeneity, subgroup analyses were performed with respect to ethnicity and smoking status.

A sensitivity analysis was conducted to assess the stability of the results. One study at a time was excluded to evaluate how robust the pooled estimator was. Publication bias was estimated by using Egger's test.

All statistical analyses were performed with STATA version 11.0. A P -value < 0.05 was considered statistically significant.

Results

Study characteristics

The flow diagram in Figure 1 summarizes the selection process carried out for this meta-analysis. A total of 38 eligible

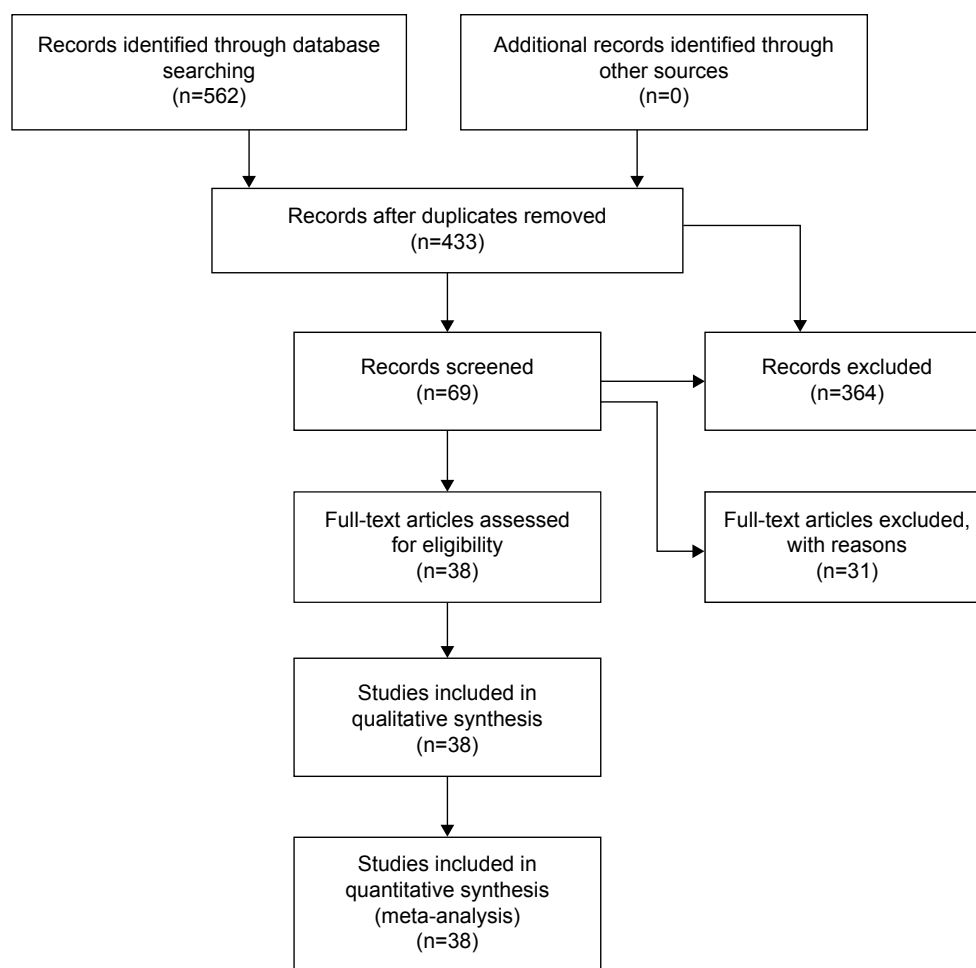


Figure 1 Study flow chart of identification, inclusion, and exclusion.

articles were included in the current meta-analysis, comprising 3,951 COPD cases and 5,110 controls.^{11–13,16,18,19,22,24,34–63} Twenty articles were published in English and 18 in Chinese. There were 16 studies performed in non-Asians which comprised 1,884 COPD cases and 2,943 controls and 22 studies in Asians which comprised 2,067 COPD cases and 2,167 controls. Fifteen studies contained sufficient information for subgroup analysis by smoking status. All of the cases were confirmed by the diagnostic criteria of COPD.^{64–68} The genotype distributions of the TNF- α –308 polymorphism were in accordance with HWE in the controls of all the studies. Based on the quality assessment scale for case–control studies, two studies scored 5 points, 22 studies scored 6 points, eleven studies scored 7 points, and the other three scored 8 points. The characteristics of these studies are shown in Table 1. The detailed genotype, allele information, and HWE results are listed in Table 2.

Meta-analysis results

A summary of the meta-analysis results concerning association between TNF- α –308 polymorphism and COPD risk is provided in Table 3. The A allele was associated with an increased COPD risk in the overall population (OR =1.56, 95% CI 1.29–1.89, $P=0.000$ for heterogeneity, $I^2=70.8\%$) (Figure 2). The estimated OR1, OR2, and OR3 were 1.776 ($P=0.000$), 1.513 ($P=0.211$), and 1.216 ($P=0.000$), respectively, suggesting a codominant model as the most appropriate genetic model. Then, the pooled ORs were calculated under the codominant genetic model. OR was 1.78 for GG vs AA and 1.51 for GG vs GA (Figures 3 and 4), demonstrating a significant association between TNF- α –308 polymorphism and COPD in the overall population. Individuals with AA genotype were more susceptible to develop COPD than those with GA genotype. To identify the origin of heterogeneity, a subgroup analysis stratified by ethnicity was conducted. As shown in Figures 2–4, a stronger correlation of the polymorphism with COPD risk was found in Asians under the genetic model (OR =3.25 for GG vs AA and OR =2.22 for GG vs GA), and similar results were observed in the allelic model. Interestingly, the AA genotype carriers had a higher risk of developing COPD than GA carriers in Asian patients. Conversely, no association was found in non-Asians in the genetic model (OR =1.05 for GG vs AA and OR =1.00 for GG vs GA). Notably, heterogeneity was significantly decreased when stratified analysis was performed by ethnicity status in both models, indicating the ethnicity contributed partly to heterogeneity, and similar results were found in the allelic model.

Specific environmental factors, such as smoking, may contribute to the distribution of genetic polymorphisms.⁶⁹ Moreover, there was a difference in the TNF- α –308 polymorphism between smoking and nonsmoking COPD patients.⁴⁵ To minimize the effect of cigarette smoking on the association between the TNF- α –308 G/A polymorphism and COPD risk, a second meta-analysis was conducted with studies in which the COPD cases and the controls were current/former smokers. Interestingly, no significant association was found between the TNF- α –308 polymorphism and COPD risk either in Asian smokers or in non-Asian smokers. The statistics in non-Asians included OR =1.32 for GG vs AA and OR =1.07 for GG vs GA. The statistics in Asians included OR =1.66 for GG vs AA and OR =1.24 for GG vs GA (Figures 5 and 6). Our study indicated that the A allele was not a risk factor for the development of COPD in smoking populations.

Sensitivity analysis

Sensitivity analysis was performed by sequentially excluding each study to assess the stability of the results in this meta-analysis. The corresponding pooled ORs were not materially altered in the overall meta-analysis (Figure 7). In the meta-analysis with restriction to smokers, two studies^{18,47} were found to be the source of heterogeneity in Asian smokers (Figure 8). After excluding these two studies from the analysis, the pooled OR did not vary significantly, indicating that the results were relatively reliable (data not shown).

Publication bias

As shown in Figure 9, Egger's test was performed to assess the publication bias of the literature. No publication bias was detected ($P=0.726$).

Discussion

In the present meta-analysis update, we conducted a comprehensive database search for potential articles published up to July 2015 to evaluate the association between TNF- α –308 polymorphism and COPD risk, and several of the articles were not included in the previous meta-analysis. To our knowledge, this is the first report to analyze the association between TNF- α –308 polymorphism and COPD risk under the codominant genetic model. Thus, more detailed information can be achieved under this genetic model. Finally, a total of 38 studies with 3,951 patients and 5,110 controls were included in the meta-analysis. The results showed a significant association between the TNF- α –308 polymorphism and COPD susceptibility in the overall population. Individuals with the

Table 1 Characteristics of the included studies

| Study | Year | Country/territory | Ethnicity | Source of control | Genotyping method | Quality score |
|-----------------------------------|------|----------------------------|------------|---|-------------------|---------------|
| Huang et al ¹⁶ | 1997 | Taiwan | Asian | Healthy controls | PCR-RFLP | 6 |
| Higham et al ²² | 2000 | UK | Non-Asians | Population controls Smoking controls | PCR-RFLP | 8 |
| Ishii et al ³⁴ | 2000 | Japan | Asian | Smoking controls | PCR-RFLP | 7 |
| Keatings et al ³⁵ | 2000 | Ireland | Non-Asians | Smoking controls | PCR-RFLP | 6 |
| Shi et al ³⁶ | 2000 | People's Republic of China | Asian | Healthy controls Smoking controls | PCR-RFLP | 6 |
| Kucukaycan et al ³⁷ | 2002 | the Netherlands | Non-Asians | Population controls | PCR-DBA | 6 |
| Ferrarotti et al ³⁸ | 2003 | Italy | Non-Asians | Smoking controls | PCR-RFLP | 6 |
| He et al ³⁹ | 2003 | People's Republic of China | Asian | Population controls | PCR-RFLP | 7 |
| Ma et al ⁴⁰ | 2004 | People's Republic of China | Asian | Patient controls | PCR-SSP | 6 |
| Broekhuizen et al ⁴¹ | 2005 | the Netherlands | Non-Asians | Population controls | PCR-ARMS | 6 |
| Chierakul et al ¹⁹ | 2005 | Thailand | Asian | Population controls Smoking controls | PCR-SSP | 6 |
| Hegab et al ⁴² | 2005 | Egypt | Non-Asians | Population controls with matched age and smoking history | PCR-RFLP | 6 |
| Ma et al ⁴³ | 2005 | People's Republic of China | Asian | Population controls | PCR-RFLP | 6 |
| Jiang et al ⁴⁴ | 2005 | People's Republic of China | Asian | Patient controls | PCR-RFLP | 8 |
| Seifart et al ²⁴ | 2005 | Germany | Non-Asians | Population controls Smoking controls | PCR-RFLP | 6 |
| Brogger et al ¹¹ | 2006 | Norway | Non-Asians | Population controls | Real-time PCR | 7 |
| Li et al ⁴⁵ | 2006 | People's Republic of China | Asian | Population controls | PCR-RFLP | 7 |
| Jiang and Li ⁴⁶ | 2006 | People's Republic of China | Asian | Hospital outpatients/check-ups | PCR-RFLP | 5 |
| Papatheodorou et al ¹² | 2007 | Greece | Non-Asians | Population controls Smoking controls | PCR-RFLP | 6 |
| Shi et al ⁴⁷ | 2007 | People's Republic of China | Asian | Smoking controls | PCR-RFLP | 7 |
| Zhang et al ⁴⁸ | 2007 | People's Republic of China | Asian | Population controls | PCR-RFLP | 7 |
| Du et al ⁴⁹ | 2008 | People's Republic of China | Asian | Population controls | PCR-RFLP | 7 |
| Gingo et al ¹⁸ | 2008 | USA | Non-Asians | Smoking controls | PCR-RFLP | 7 |
| Gong et al ⁵⁰ | 2008 | People's Republic of China | Asian | Smoking controls Nonsmoking controls | PCR-RFLP | 8 |
| Hsieh et al ⁵¹ | 2008 | Taiwan | Asian | Patient controls | PCR-RFLP | 6 |
| Li et al ⁵² | 2008 | People's Republic of China | Asian | Population controls | PCR-RFLP | 5 |
| Tang et al ⁵³ | 2008 | People's Republic of China | Asian | Population controls | PCR-RFLP | 6 |
| Zhang and Xiong ⁵⁴ | 2008 | People's Republic of China | Asian | Population controls | PCR-RFLP | 7 |
| Stankovic et al ⁵⁵ | 2009 | Serbia | Non-Asians | Patient controls | PCR-RFLP | 6 |
| Trajkov et al ¹³ | 2009 | Macedonia | Non-Asians | Population controls | PCR-SSP | 6 |
| Chen et al ⁵⁶ | 2010 | People's Republic of China | Asian | Smoking controls | PCR-RFLP | 6 |
| Yao et al ⁵⁷ | 2012 | People's Republic of China | Asian | Smoking controls Nonsmoking controls | PCR-RFLP | 7 |
| Shukla et al ⁵⁸ | 2012 | India | Non-Asians | Population controls | PCR-RFLP | 6 |
| Wang and Ling ⁵⁹ | 2013 | People's Republic of China | Asian | Hospital check-ups | PCR-sequencing | 7 |
| Yang et al ⁶⁰ | 2014 | People's Republic of China | Asian | Population controls | PCR-RFLP | 6 |
| Ozdogan et al ⁶¹ | 2014 | Turkey | Non-Asians | Smoking controls | Real-time PCR | 6 |
| Chiang et al ⁶² | 2014 | Taiwan | Asian | Smoking controls Nonsmoking controls | PCR-RFLP | 6 |
| Wu et al ⁶³ | 2014 | People's Republic of China | Asian | Hospital check-ups | PCR-sequencing | 6 |

Note: Quality score was calculated based on the criteria mentioned in Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol.* 2010;25(9):603–605.

Abbreviations: PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; DBA, dot blot analysis; SSP, sequence-specific primers; ARMS, amplification-refractory mutation system.

A allele (GA or AA) were more susceptible to developing COPD than those with the GG genotype. Additionally, we further clarified that individuals with the AA genotype had a higher risk of developing COPD than those with the GA genotype (77.6% vs 51.3%). The previous meta-analysis

investigating the current question employed a dominant genetic model, and did not provide detailed information about the AA and GA genotypes separately. Here, for the first time, our report indicated that carriers of the AA genotype of TNF- α -308 were the most vulnerable to COPD development.

Table 2 Genotype distribution of the TNF- α –308 G/A polymorphism in case and control

| Study | COPD | | | | | | Control | | | | | | HWE (P-value) | G | A |
|-----------------------------------|-------------------|-----|----|----|----------|-----|---------|-------------------|-----|----|----|----------|------------------|-----|-----|
| | Smoking status | GG | GA | AA | Subtotal | G | A | Smoking status | GG | GA | AA | Subtotal | | | |
| Huang et al ¹⁶ | Yes | 27 | 14 | 1 | 42 | 68 | 16 | Yes | 40 | 2 | 0 | 42 | 0.874 | 82 | 2 |
| Higham et al ²² | Yes | 62 | 22 | 2 | 86 | 146 | 26 | Mixed | 181 | 74 | 7 | 262 | 0.863 | 436 | 88 |
| | | | | | | | | Yes | 45 | 17 | 1 | 63 | 0.670 | 107 | 19 |
| Ishii et al ³⁴ | Yes | 52 | 1 | 0 | 53 | 105 | 1 | Yes | 64 | 1 | 0 | 65 | 0.950 | 129 | 1 |
| Keatings et al ³⁵ | Yes | 62 | 38 | 6 | 106 | 162 | 50 | Yes | 59 | 37 | 3 | 99 | 0.324 | 155 | 43 |
| Shi et al ³⁶ | Unknown | 30 | 23 | 7 | 60 | 83 | 37 | Unknown | 32 | 11 | 1 | 44 | 0.962 | 75 | 13 |
| Kucukaycan et al ³⁷ | Mixed | 113 | 49 | 1 | 163 | 275 | 51 | Unknown | 237 | 91 | 7 | 335 | 0.612 | 565 | 105 |
| Ferrarotti et al ³⁸ | Yes | 54 | 9 | 0 | 63 | 117 | 9 | Yes | 72 | 14 | 0 | 86 | 0.411 | 158 | 14 |
| He et al ³⁹ | Mixed | 90 | 10 | 1 | 101 | 190 | 12 | Mixed | 90 | 6 | 0 | 96 | 0.752 | 186 | 6 |
| Ma et al ⁴⁰ | Unknown | 72 | 27 | 5 | 104 | 171 | 37 | Unknown | 39 | 5 | 0 | 44 | 0.689 | 83 | 5 |
| Broekhuizen et al ⁴¹ | Unknown | 64 | 29 | 6 | 99 | 157 | 41 | Unknown | 158 | 64 | 12 | 234 | 0.264 | 380 | 88 |
| Chierakul et al ¹⁹ | Yes | 48 | 9 | 0 | 57 | 105 | 9 | Mixed | 162 | 21 | 0 | 183 | 0.509 | 345 | 21 |
| | | | | | | | | Yes | 57 | 10 | 0 | 67 | 0.410 | 124 | 10 |
| Hegab et al ⁴² | Yes | 91 | 14 | 1 | 106 | 196 | 16 | Yes | 57 | 14 | 1 | 72 | 0.895 | 128 | 16 |
| Ma et al ⁴³ | Unknown | 35 | 14 | 1 | 50 | 84 | 16 | Unknown | 27 | 3 | 0 | 30 | 0.773 | 57 | 3 |
| Jiang et al ⁴⁴ | Mixed | 90 | 10 | 1 | 101 | 190 | 12 | Mixed | 90 | 6 | 0 | 96 | 0.752 | 186 | 6 |
| | | | | | | | | Yes | 38 | 3 | 0 | 41 | 0.808 | 79 | 3 |
| Seifart et al ²⁴ | Yes | 64 | 28 | 3 | 95 | 156 | 34 | Mixed | 171 | 67 | 4 | 242 | 0.374 | 409 | 75 |
| | | | | | | | | Yes | 74 | 25 | 5 | 104 | 0.150 | 173 | 35 |
| Brogger et al ¹¹ | Mixed | 154 | 74 | 12 | 240 | 382 | 98 | Mixed | 159 | 73 | 12 | 244 | 0.343 | 391 | 97 |
| Li et al ⁴⁵ | Mixed | 56 | 26 | 2 | 84 | 138 | 30 | Mixed | 76 | 14 | 0 | 90 | 0.424 | 166 | 14 |
| Jiang and Li ⁴⁶ | Mixed | 55 | 46 | 4 | 105 | 156 | 54 | Mixed | 50 | 10 | 0 | 60 | 0.481 | 110 | 10 |
| Papatheodorou et al ¹² | Yes | 101 | 14 | 1 | 116 | 216 | 16 | Mixed | 257 | 47 | 5 | 309 | 0.051 | 561 | 57 |
| | | | | | | | | Yes | 88 | 18 | 1 | 107 | 0.940 | 194 | 20 |
| Shi et al ⁴⁷ | Yes | 46 | 31 | 11 | 88 | 123 | 53 | Yes | 69 | 24 | 3 | 96 | 0.959 | 162 | 30 |
| Zhang et al ⁴⁸ | Mixed | 48 | 17 | 1 | 66 | 113 | 19 | Mixed | 45 | 6 | 0 | 51 | 0.655 | 96 | 6 |
| | | | | | | | | Yes | 17 | 2 | 0 | 19 | 0.808 | 36 | 2 |
| Du et al ⁴⁹ | Mixed | 90 | 34 | 4 | 128 | 214 | 42 | Mixed | 94 | 18 | 0 | 112 | 0.355 | 206 | 18 |
| Gingo et al ¹⁸ | Yes | 220 | 67 | 11 | 298 | 507 | 89 | Yes | 105 | 18 | 2 | 125 | 0.250 | 228 | 22 |
| Gong et al ⁵⁰ | Yes | 55 | 4 | 0 | 59 | 114 | 4 | Mixed | 76 | 8 | 0 | 84 | 0.167 | 160 | 8 |
| | | | | | | | | Yes | 36 | 5 | 0 | 41 | 0.678 | 77 | 5 |
| Hsieh et al ⁵¹ | Mixed | 23 | 6 | 1 | 30 | 52 | 8 | Mixed | 96 | 18 | 1 | 115 | 0.878 | 210 | 20 |
| | | | | | | | | Yes | 35 | 8 | 0 | 43 | 0.501 | 78 | 8 |
| Li et al ⁵² | Mixed | 98 | 46 | 4 | 148 | 242 | 54 | Mixed | 124 | 22 | 0 | 146 | 0.324 | 270 | 22 |
| Tang et al ⁵³ | No | 43 | 19 | 0 | 62 | 105 | 19 | No | 96 | 12 | 0 | 108 | 0.541 | 204 | 12 |
| Zhang and Xiong ⁵⁴ | Unknown | 23 | 18 | 9 | 50 | 64 | 36 | Unknown | 33 | 16 | 1 | 50 | 0.552 | 82 | 18 |
| Stankovic et al ⁵⁵ | Mixed | 79 | 17 | 1 | 97 | 175 | 19 | Mixed | 71 | 28 | 3 | 102 | 0.905 | 170 | 34 |
| Trajkov et al ¹³ | Mixed | 45 | 14 | 1 | 60 | 104 | 16 | Unknown | 231 | 66 | 4 | 301 | 0.769 | 528 | 74 |
| Chen et al ⁵⁶ | Yes | 117 | 28 | 0 | 145 | 262 | 28 | Yes | 109 | 27 | 3 | 139 | 0.398 | 245 | 33 |
| Yao et al ⁵⁷ | Mixed | 128 | 48 | 4 | 180 | 304 | 56 | Mixed | 302 | 57 | 1 | 360 | 0.321 | 661 | 59 |
| Shukla et al ⁵⁸ | Mixed | 178 | 30 | 0 | 208 | 386 | 30 | Mixed | 159 | 41 | 4 | 204 | 0.483 | 359 | 49 |
| Wang and Ling ⁵⁹ | Unknown | 58 | 18 | 4 | 80 | 134 | 26 | Unknown | 72 | 7 | 1 | 80 | 0.116 | 151 | 9 |
| Yang et al ⁶⁰ | Mixed | 73 | 25 | 3 | 101 | 171 | 31 | Mixed | 71 | 9 | 0 | 80 | 0.594 | 151 | 9 |
| Ozdogan et al ⁶¹ | Yes | 44 | 16 | 0 | 60 | 104 | 16 | Yes | 24 | 6 | 0 | 30 | 0.543 | 48 | 12 |
| Chiang et al ⁶² | Unknown | 99 | 11 | 0 | 110 | 209 | 11 | Mixed | 140 | 4 | 0 | 144 | 0.866 | 284 | 4 |
| Wu et al ⁶³ | Mixed | 109 | 32 | 9 | 150 | 250 | 50 | Mixed | 131 | 17 | 2 | 150 | 0.113 | 279 | 21 |

Note: Mixed smoking status refers to a mixed population of smokers and non-smokers.

Abbreviation: HWE, Hardy-Weinberg equilibrium.

To identify the origin of heterogeneity, a subgroup analysis stratified by ethnicity was conducted. In our study, significant associations were shown in Asians but not in non-Asians, which is consistent with the previous meta-analysis.^{28,29} Our data reconfirmed that the TNF- α –308 G/A polymorphism

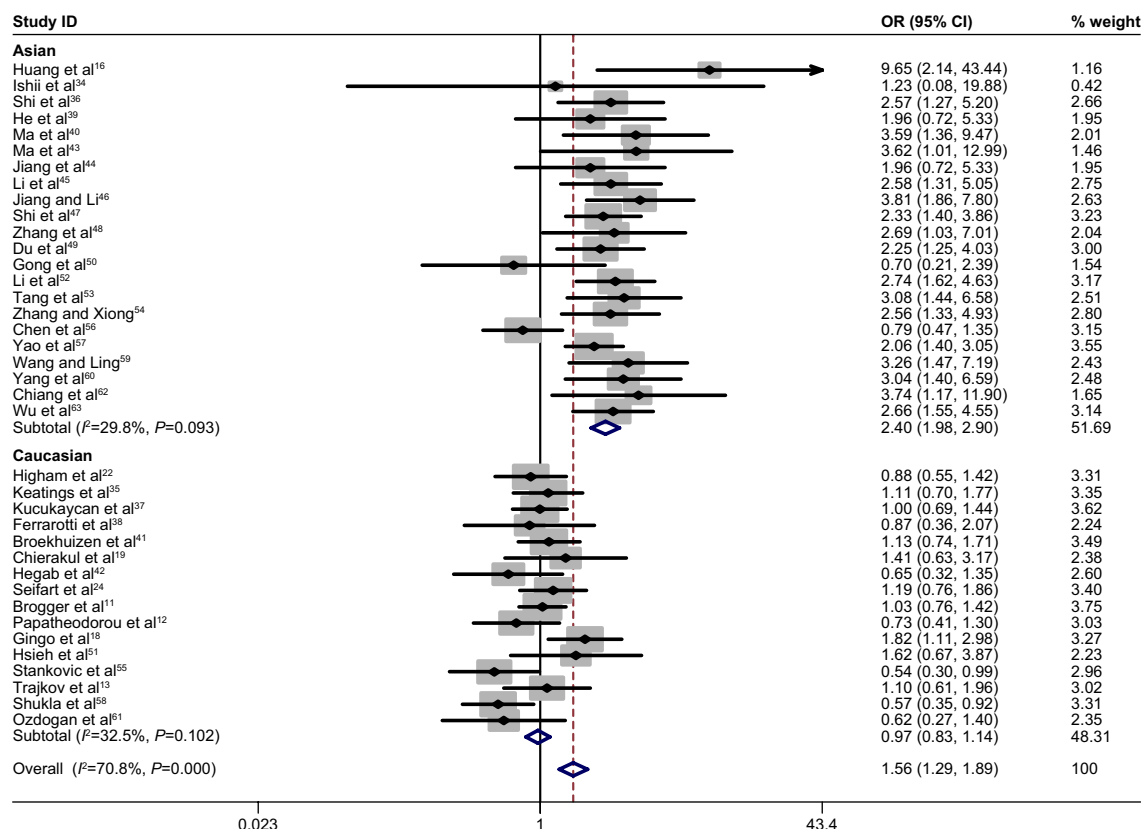
was associated with COPD risk even under a stricter study design and procedure. Furthermore, our study further identified a stronger correlation between the TNF- α –308 G/A polymorphism and COPD risk in Asians with the AA genotype compared with those with the GA genotype. Notably,

Table 3 Summary ORs for relationship between the TNF- α -308 polymorphism and COPD risk

| Polymorphism | Study | Number of studies | Hypothesis tests | | | Heterogeneity tests | | |
|-----------------------|------------|-------------------|------------------|-------|---------|---------------------|--------------------|---------|
| | | | OR (95% CI) | Z | P-value | Model | I ² (%) | P-value |
| G vs A | Overall | 38 | 1.56 (1.29–1.89) | 4.55 | 0.000 | R | 70.8 | 0.000 |
| GG vs AA (OR1) | Overall | 38 | 1.78 (1.34–2.36) | 3.98 | 0.000 | F | 0.0 | 0.645 |
| GG vs GA (OR2) | Overall | 38 | 1.51 (1.26–1.81) | 4.52 | 0.000 | R | 56.4 | 0.000 |
| GA vs AA (OR3) | Overall | 38 | 1.22 (0.90–1.65) | 1.24 | 0.211 | F | 0.0 | 0.988 |
| Codominant model | | | | | | | | |
| GG vs AA | Overall | 38 | 1.78 (1.34–2.36) | 3.98 | 0.000 | F | 0.0 | 0.645 |
| GG vs GA | Overall | 38 | 1.51 (1.26–1.81) | 4.52 | 0.000 | R | 56.4 | 0.000 |
| G vs A | Overall | 38 | 1.56 (1.29–1.89) | 4.55 | 0.000 | R | 70.8 | 0.000 |
| GG vs AA | Asian | 22 | 3.25 (2.08–5.08) | 5.19 | 0.000 | F | 0.0 | 0.899 |
| GG vs GA | Asian | 22 | 2.22 (1.85–2.66) | 9.43 | 0.000 | F | 10.3 | 0.323 |
| G vs A | Asian | 22 | 2.40 (1.98–2.90) | 11.49 | 0.000 | F | 29.8 | 0.093 |
| GG vs AA | Non-Asians | 16 | 1.05 (0.71–1.55) | 0.23 | 0.818 | F | 0.0 | 0.834 |
| GG vs GA | Non-Asians | 16 | 1.00 (0.86–1.16) | 0.01 | 0.995 | F | 0.0 | 0.504 |
| G vs A | Non-Asians | 16 | 0.97 (0.83–1.14) | 0.27 | 0.785 | F | 32.5 | 0.102 |
| GG vs AA ^a | Overall | 15 | 1.45 (0.88–2.40) | 1.45 | 0.146 | F | 0.0 | 0.812 |
| GG vs GA ^a | Overall | 15 | 1.12 (0.91–1.37) | 1.08 | 0.279 | F | 0.0 | 0.567 |
| G vs A ^a | Overall | 15 | 1.13 (0.95–1.35) | 1.39 | 0.164 | F | 34.9 | 0.089 |
| GG vs AA ^a | Asian | 6 | 1.66 (0.75–3.68) | 1.26 | 0.208 | F | 24.3 | 0.252 |
| GG vs GA ^a | Asian | 6 | 1.24 (0.85–1.82) | 1.10 | 0.270 | F | 24.3 | 0.433 |
| G vs A ^a | Asian | 6 | 1.26 (0.69–2.30) | 0.75 | 0.455 | R | 52.2 | 0.063 |
| GG vs AA ^a | Non-Asians | 9 | 1.32 (0.69–2.53) | 0.85 | 0.396 | F | 0.0 | 0.961 |
| GG vs GA ^a | Non-Asians | 9 | 1.07 (0.84–1.37) | 0.59 | 0.558 | F | 0.0 | 0.511 |
| G vs A ^a | Non-Asians | 9 | 1.06 (0.86–1.30) | 0.51 | 0.608 | F | 15.8 | 0.301 |

Notes: ^aOnly cases and controls with smoking history. Results are in response to a chi-square-based Cochran Q-test to test for heterogeneity.

Abbreviations: OR, odds ratio; CI, confidence interval; R, random model; F, fixed model.

**Figure 2** Forest plot for the association between TNF- α -308 polymorphism and COPD in all subjects using allelic model (G vs A).

Note: Weights are from random effects analysis.

Abbreviations: OR, odds ratio; CI, confidence interval.

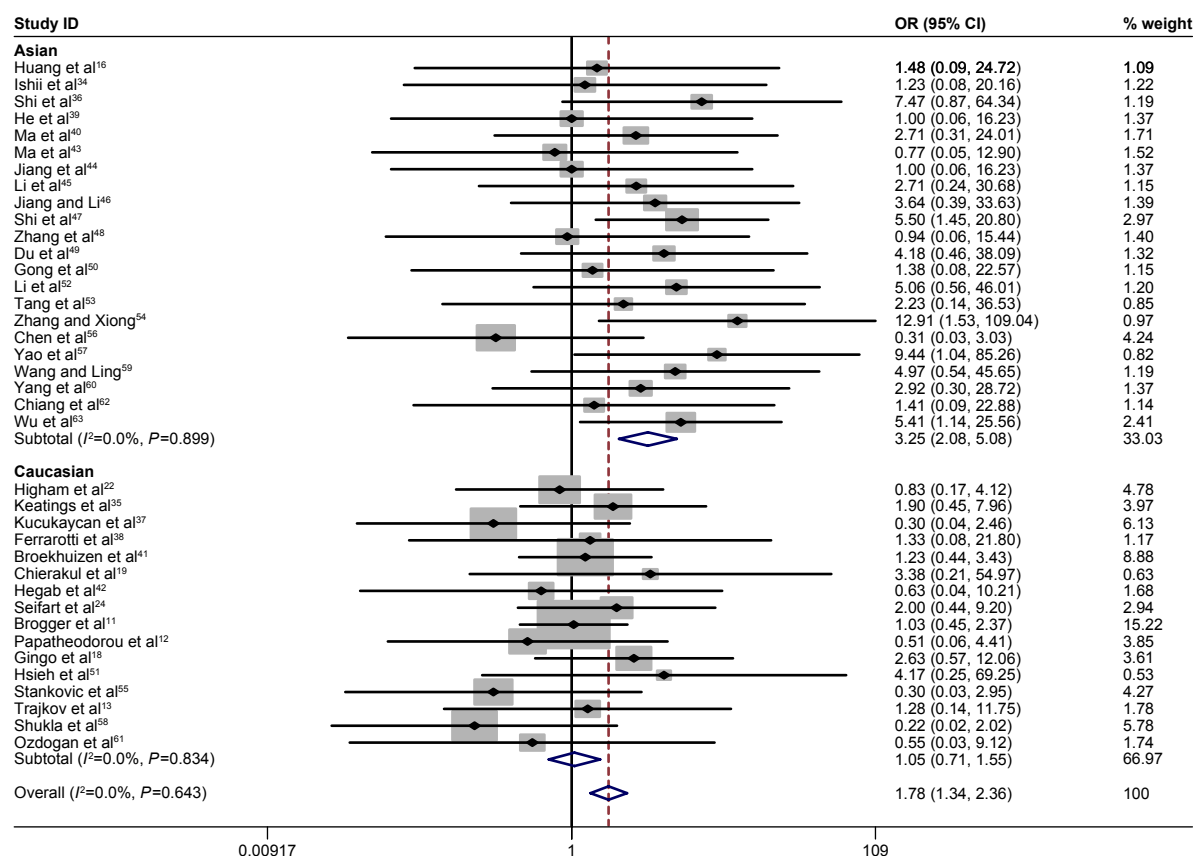


Figure 3 Forest plot for the association between TNF- α -308 polymorphism and COPD in all subjects using codominant genetic model (G/G vs A/A genotype).
Abbreviations: OR, odds ratio; CI, confidence interval.

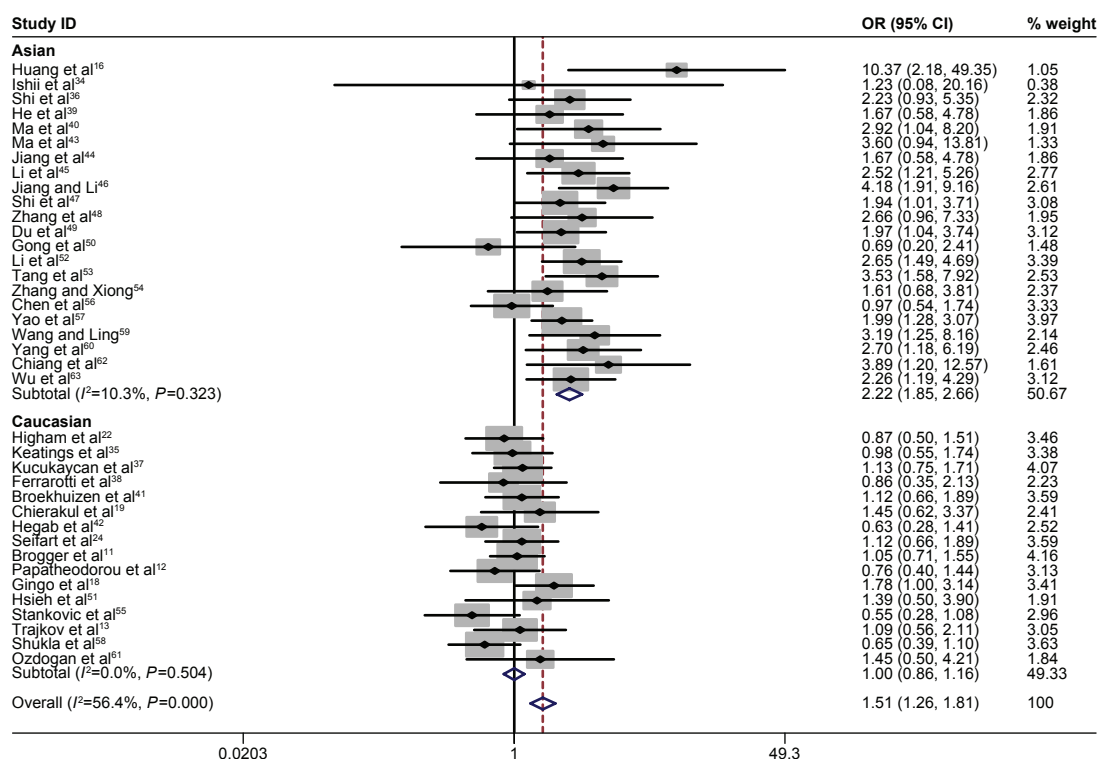


Figure 4 Forest plot for the association between TNF- α -308 polymorphism and COPD in all subjects using codominant genetic model (G/G vs G/A genotype).

Note: Weights are from random effects analysis.

Abbreviations: OR, odds ratio; CI, confidence interval.

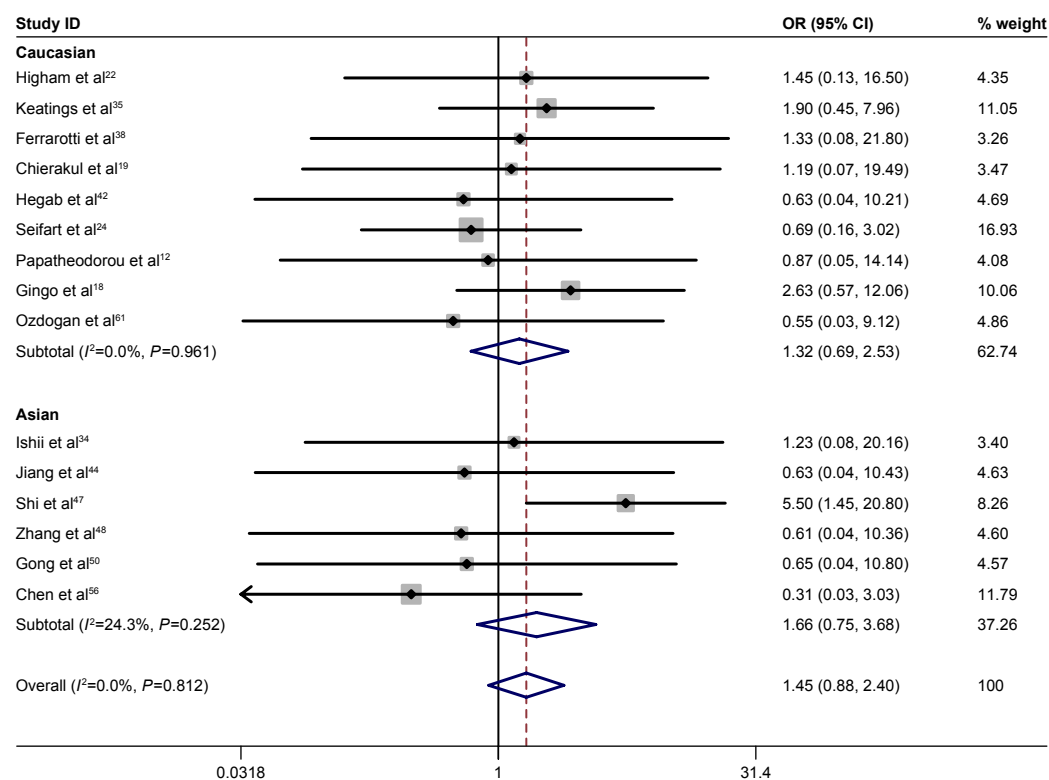


Figure 5 Forest plot for the association between TNF- α -308 polymorphism and COPD in smoking subjects using codominant genetic model (G/G vs A/A genotype).
Abbreviations: OR, odds ratio; CI, confidence interval.

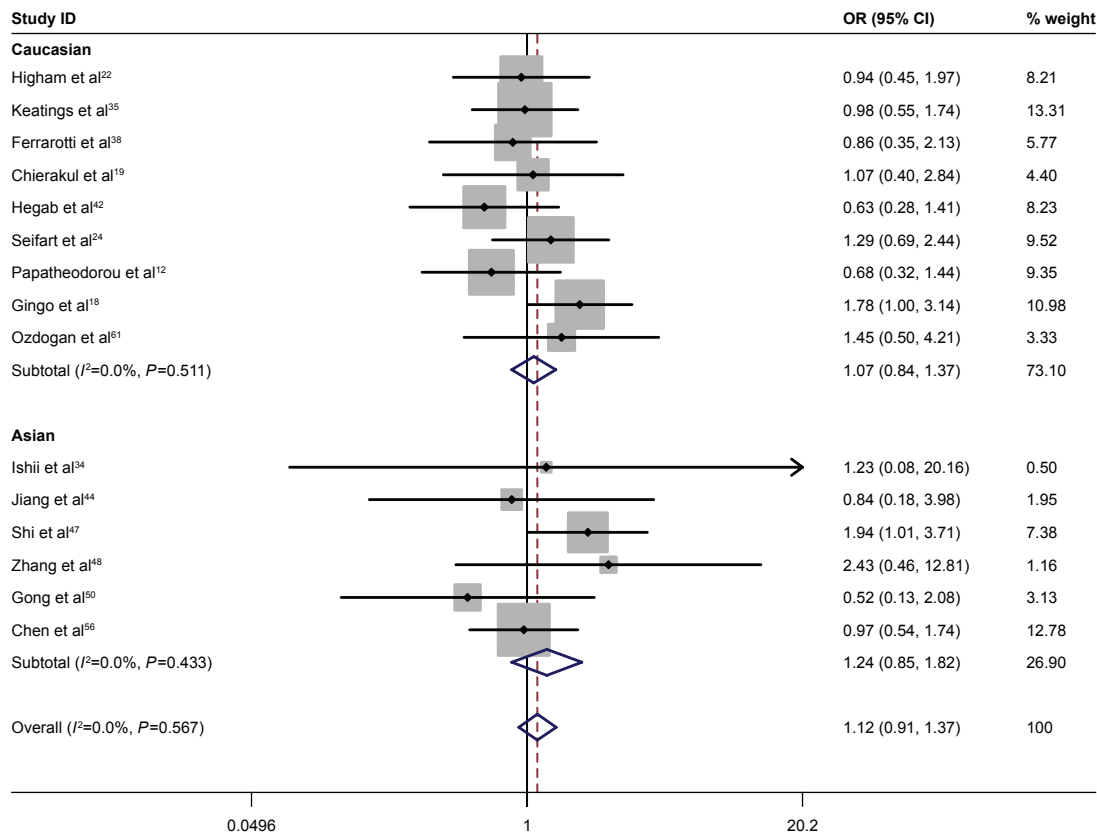


Figure 6 Forest plot for the association between TNF- α -308 polymorphism and COPD in smoking subjects using codominant genetic model (G/G vs G/A genotype).
Abbreviations: OR, odds ratio; CI, confidence interval.

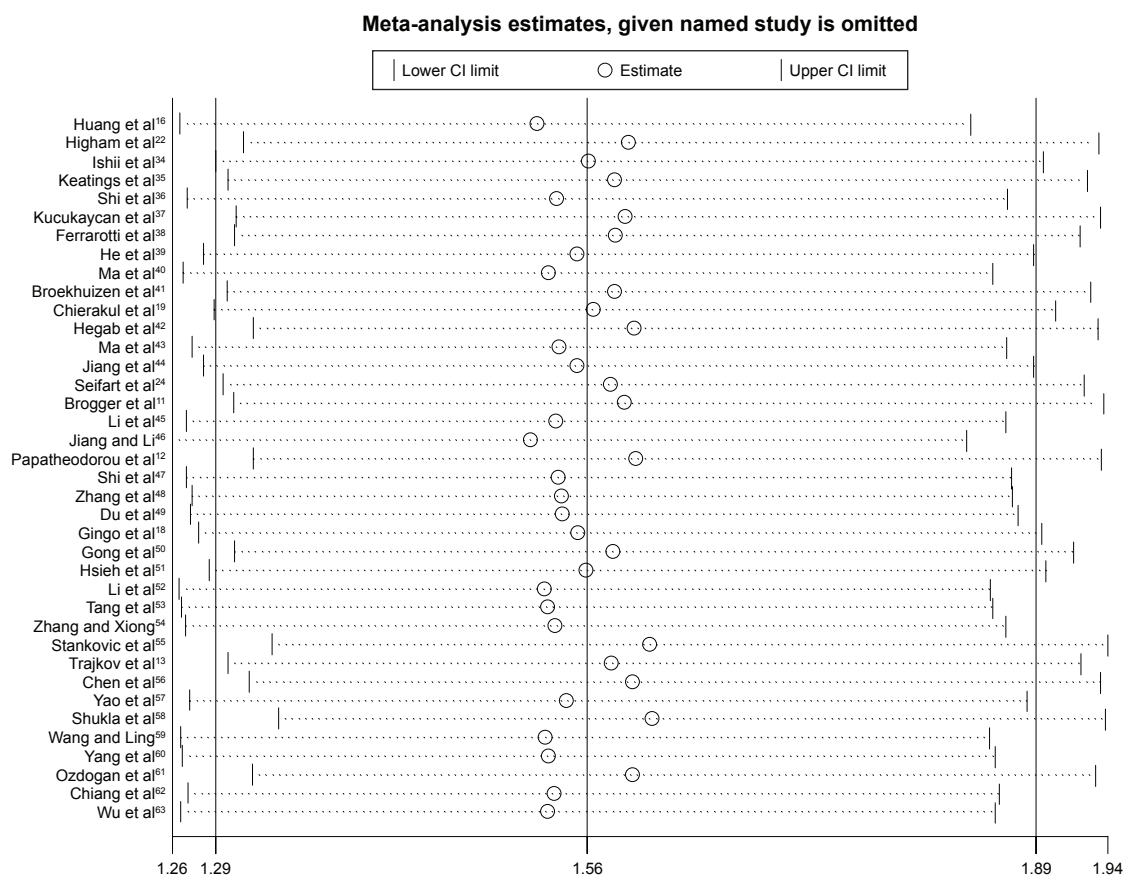


Figure 7 Sensitivity analysis for TNF- α -308 polymorphism with COPD in all subjects.

Abbreviation: CI, confidence interval.

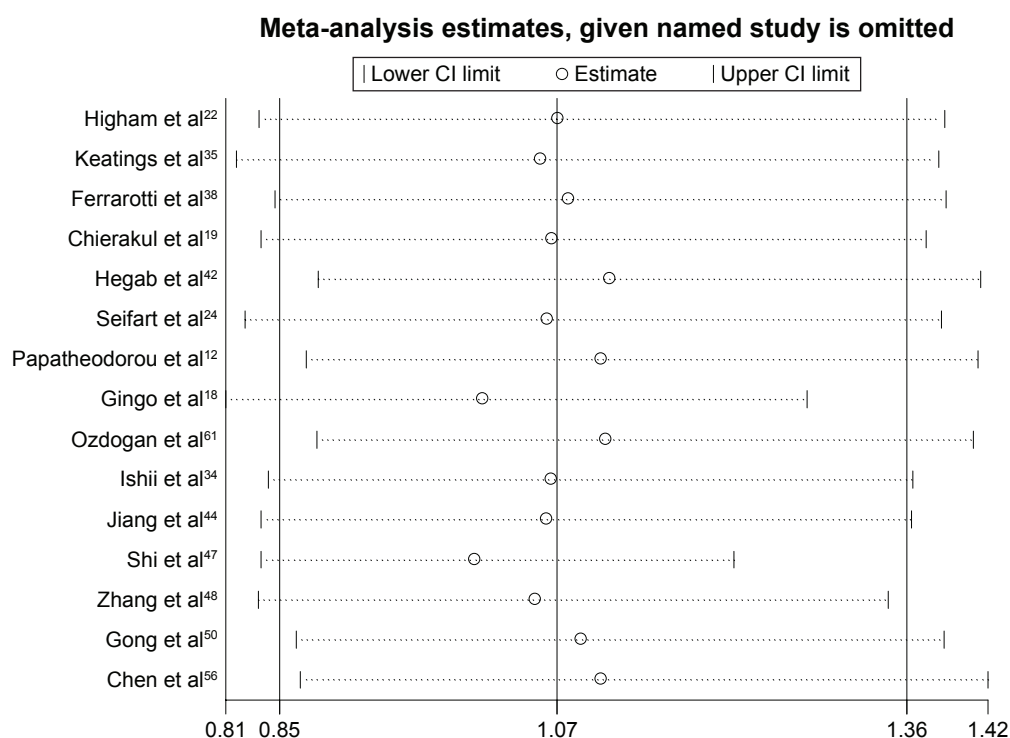


Figure 8 Sensitivity analysis for TNF- α -308 polymorphism with COPD in smoking subjects.

Abbreviation: CI, confidence interval.

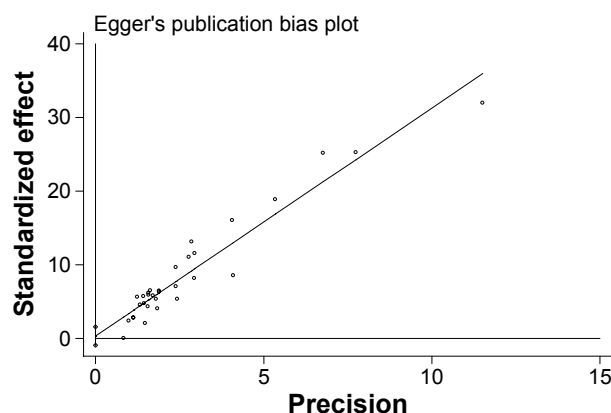


Figure 9 Publication bias on COPD risk and TNF- α -308 polymorphism.

heterogeneity was significantly decreased when the analysis stratified by ethnicity was performed. We speculated that it may be because that the A allele is more important for COPD susceptibility in Asians than in non-Asians.

To minimize the effect of smoking status on the association, a second meta-analysis restricted to smokers was conducted. Interestingly, no correlation was found between the TNF- α -308 G/A polymorphism and the risk of COPD in either Asian smokers or non-Asian smokers. This result was contrary to the previous meta-analysis which showed an obvious correlation between the TNF- α -308 G/A polymorphism and the risk of COPD in smokers. Although moderate heterogeneity was observed in Asian smokers in the allelic model, which may distort the result, the pooled OR did not vary significantly after the removal of two studies that were considered the origin of the heterogeneity. This indicated that the results of this meta-analysis in the smokers were reliable. The opposite results may be attributed to the following: 1) the codominant model was adopted in the current study, which was different from the previous study (dominant model); and 2) due to stricter inclusion criteria, several studies were excluded from the current meta-analysis. Based on the results of our study, it seems that other factors may contribute to COPD development in smokers, and we speculated that the A allele may be a risk factor in nonsmokers; however, a firm conclusion should not be drawn until a larger number of studies with a sufficient number of nonsmokers can be included in the meta-analysis.

There are several limitations of the present meta-analysis that should be considered when explaining the results: 1) Even though we followed a strict procedure for data collection and data analysis to minimize the heterogeneity, several pooled ORs were obtained from heterogeneous studies. 2) There were not enough nonsmokers in the case and control groups

to conduct a subgroup analysis to ascertain whether the A allele of TNF- α -308 was associated with the risk of COPD development in the nonsmoking population. 3) The numbers of studies were limited for this meta-analysis; some studies were excluded from the study. This selection bias may have an effect on the genotyping publication bias. What's more, more studies are needed to further improve the power of the study. 4) The genotyping methods in the studies included are different, which may cause some bias on the result.

In conclusion, this meta-analysis update suggested that the A allele of TNF- α -308 is a risk factor for developing COPD. Additionally, individuals with the AA genotype appeared to be more susceptible to developing COPD than those with the GA genotype. Additionally, the subgroup analysis in Asians (but not in non-Asians) supported the results. The data presented in the current report may provide insight for COPD treatment based on patients' genotype. In future, larger and more strictly controlled studies are needed to evaluate the relationship between gene polymorphisms and COPD. What's more, relationship between gene polymorphisms and COPD in nonsmoking populations should be explored to further elucidate if gene polymorphism is an independent risk factor associated with the development of COPD, which will favor the development of effective prevention and treatment methods for COPD in nonsmokers.

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Disclosure

The authors declare no conflicts of interest in this work.

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