REVIEW

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

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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]

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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 circulation[10] 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-Asians[18] 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 scale[32] 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
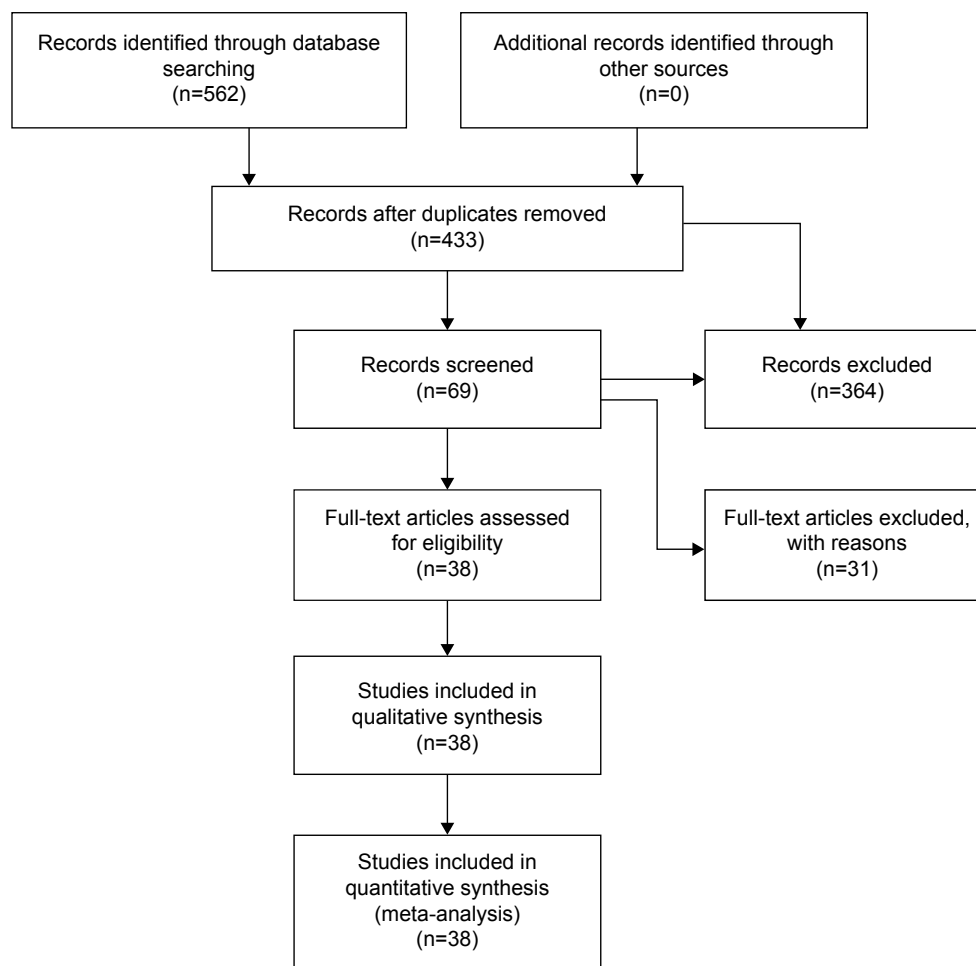

Figure I Study flow chart of identification, inclusion, and exclusion.

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							
	Smoking status	GG	GA	AA	Subtotal	G	A	Smoking status	GG	GA	AA	Subtotal	HWE (P-value)	G	A
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	60	4	1	65	124	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	28	8	0	36	64	8	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	19	5	1	25	43	7	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	I² (%)	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: [a]Only 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.
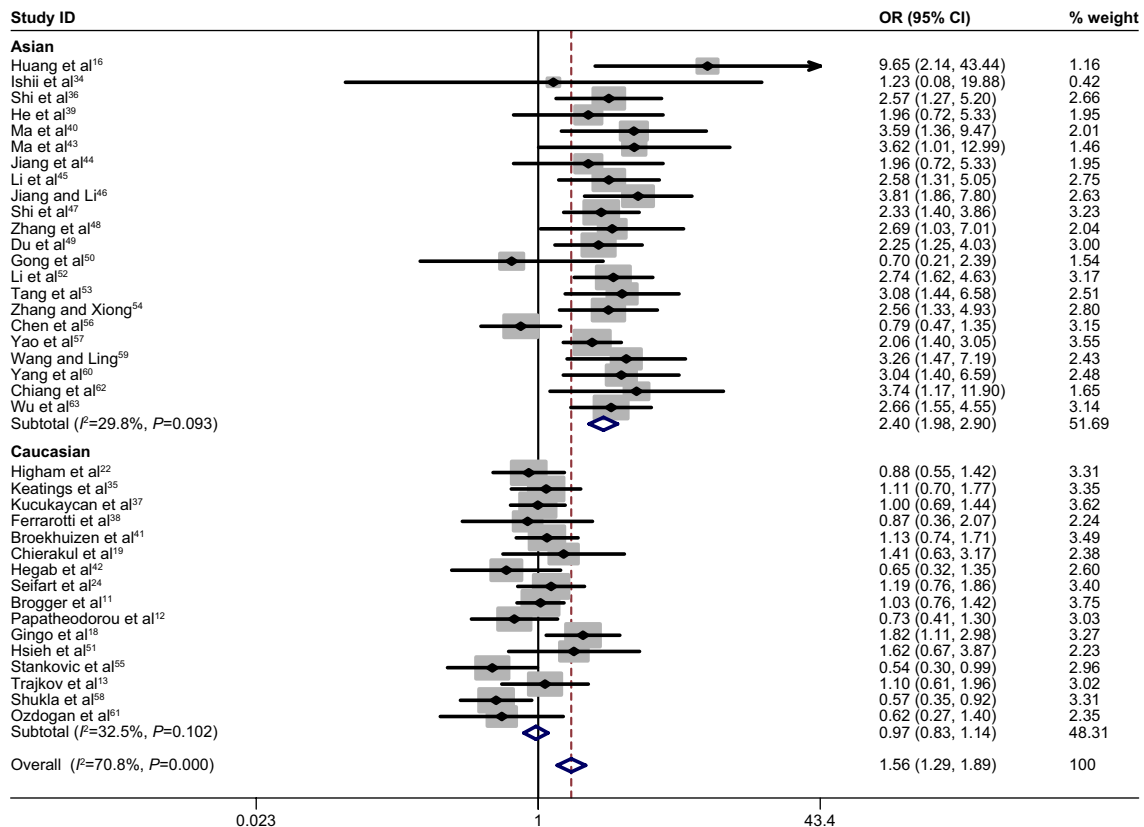
Figure 2 Forest plot for the association between TNF-α −308 polymorphism and COPD in all subjects using allelic model (G vs A).
Note: Weights are from random effects analysis.
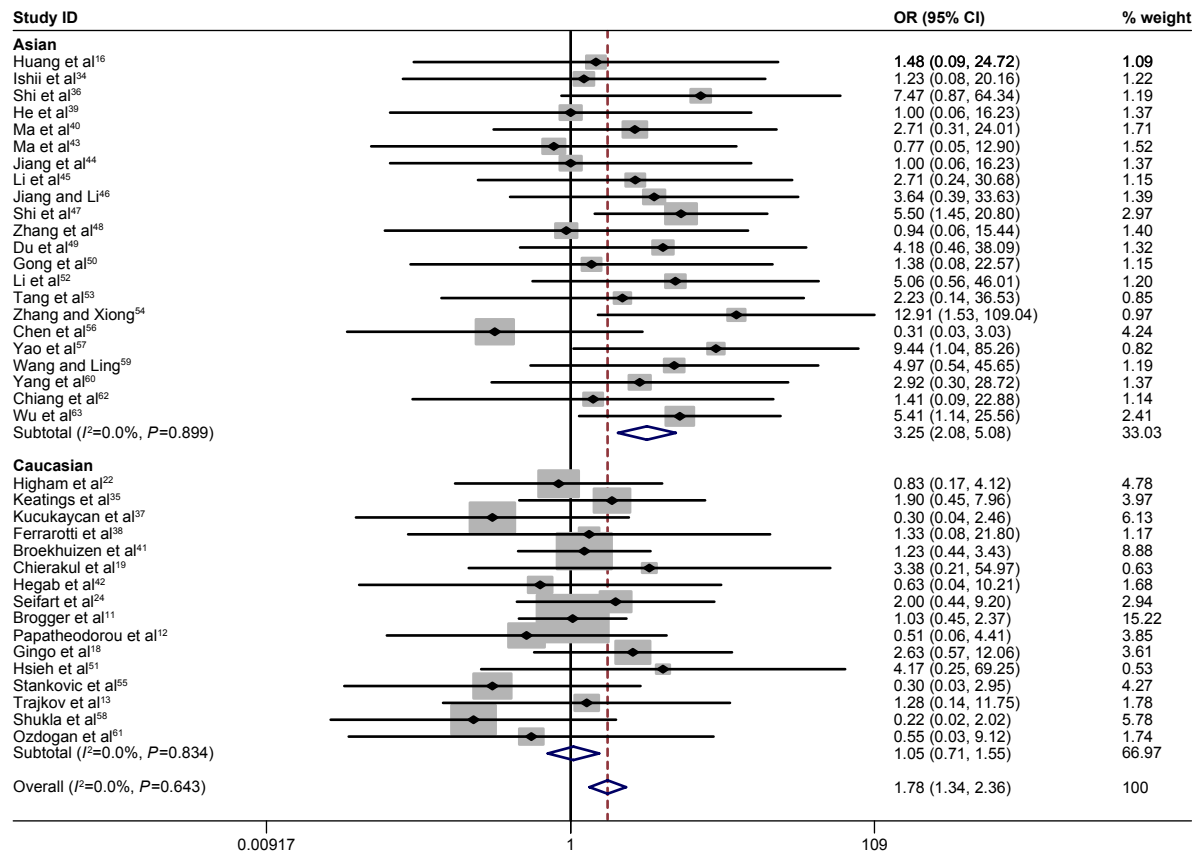**Abbreviations:** OR, odds ratio; CI, confidence interval.

Study ID	OR (95% CI)	% weight
Asian		
Huang et al[16]	1.48 (0.09, 24.72)	1.09
Ishii et al[34]	1.23 (0.08, 20.16)	1.22
Shi et al[36]	7.47 (0.87, 64.34)	1.19
He et al[39]	1.00 (0.06, 16.23)	1.37
Ma et al[40]	2.71 (0.31, 24.01)	1.71
Ma et al[43]	0.77 (0.05, 12.90)	1.52
Jiang et al[44]	1.00 (0.06, 16.23)	1.37
Li et al[45]	2.71 (0.24, 30.68)	1.15
Jiang and Li[46]	3.64 (0.39, 33.63)	1.39
Shi et al[47]	5.50 (1.45, 20.80)	2.97
Zhang et al[48]	0.94 (0.06, 15.44)	1.40
Du et al[49]	4.18 (0.46, 38.09)	1.32
Gong et al[50]	1.38 (0.08, 22.57)	1.15
Li et al[52]	5.06 (0.56, 46.01)	1.20
Tang et al[53]	2.23 (0.14, 36.53)	0.85
Zhang and Xiong[54]	12.91 (1.53, 109.04)	0.97
Chen et al[56]	0.31 (0.03, 3.03)	4.24
Yao et al[57]	9.44 (1.04, 85.26)	0.82
Wang and Ling[59]	4.97 (0.54, 45.65)	1.19
Yang et al[60]	2.92 (0.30, 28.72)	1.37
Chiang et al[62]	1.41 (0.09, 22.88)	1.14
Wu et al[63]	5.41 (1.14, 25.56)	2.41
Subtotal (I^2=0.0%, P=0.899)	3.25 (2.08, 5.08)	33.03
Caucasian		
Higham et al[22]	0.83 (0.17, 4.12)	4.78
Keatings et al[35]	1.90 (0.45, 7.96)	3.97
Kucukaycan et al[37]	0.30 (0.04, 2.46)	6.13
Ferrarotti et al[38]	1.33 (0.08, 21.80)	1.17
Broekhuizen et al[41]	1.23 (0.44, 3.43)	8.88
Chierakul et al[19]	3.38 (0.21, 54.97)	0.63
Hegab et al[42]	0.63 (0.04, 10.21)	1.68
Seifart et al[24]	2.00 (0.44, 9.20)	2.94
Brogger et al[11]	1.03 (0.45, 2.37)	15.22
Papatheodorou et al[12]	0.51 (0.06, 4.41)	3.85
Gingo et al[18]	2.63 (0.57, 12.06)	3.61
Hsieh et al[51]	4.17 (0.25, 69.25)	0.53
Stankovic et al[55]	0.30 (0.03, 2.95)	4.27
Trajkov et al[13]	1.28 (0.14, 11.75)	1.78
Shukla et al[58]	0.22 (0.02, 2.02)	5.78
Ozdogan et al[61]	0.55 (0.03, 9.12)	1.74
Subtotal (I^2=0.0%, P=0.834)	1.05 (0.71, 1.55)	66.97
Overall (I^2=0.0%, P=0.643)	1.78 (1.34, 2.36)	100

0.00917   1   109

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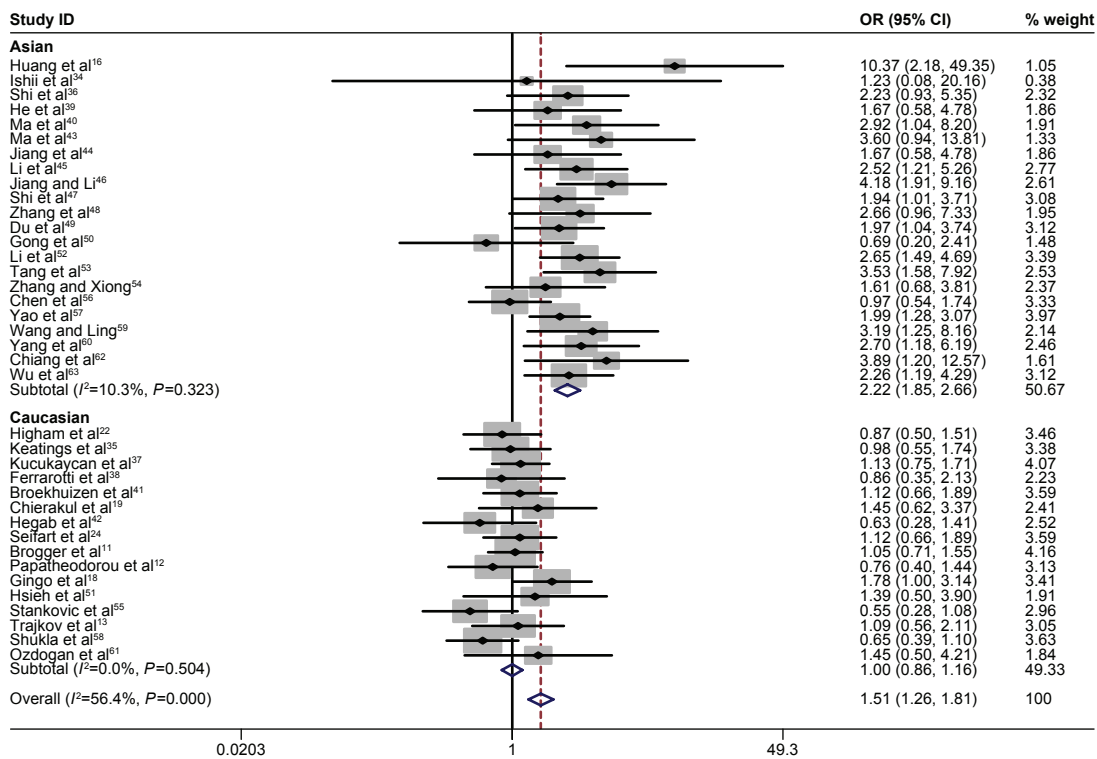**Abbreviations:** OR, odds ratio; CI, confidence interval.

Study ID	OR (95% CI)	% weight
Asian		
Huang et al[16]	10.37 (2.18, 49.35)	1.05
Ishii et al[34]	1.23 (0.08, 20.16)	0.38
Shi et al[36]	2.23 (0.93, 5.35)	2.32
He et al[39]	1.67 (0.58, 4.78)	1.86
Ma et al[40]	2.92 (1.04, 8.20)	1.91
Ma et al[43]	3.60 (0.94, 13.81)	1.33
Jiang et al[44]	1.67 (0.58, 4.78)	1.86
Li et al[45]	2.52 (1.21, 5.26)	2.77
Jiang and Li[46]	4.18 (1.91, 9.16)	2.61
Shi et al[47]	1.94 (1.01, 3.71)	3.08
Zhang et al[48]	2.66 (0.96, 7.33)	1.95
Du et al[49]	1.97 (1.04, 3.74)	3.12
Gong et al[50]	0.69 (0.20, 2.41)	1.48
Li et al[52]	2.65 (1.49, 4.69)	3.39
Tang et al[53]	3.53 (1.58, 7.92)	2.53
Zhang and Xiong[54]	1.61 (0.68, 3.81)	2.37
Chen et al[56]	0.97 (0.54, 1.74)	3.33
Yao et al[57]	1.99 (1.28, 3.07)	3.97
Wang and Ling[59]	3.19 (1.25, 8.16)	2.14
Yang et al[60]	2.70 (1.18, 6.19)	2.46
Chiang et al[62]	3.89 (1.20, 12.57)	1.61
Wu et al[63]	2.26 (1.19, 4.29)	3.12
Subtotal (I^2=10.3%, P=0.323)	2.22 (1.85, 2.66)	50.67
Caucasian		
Higham et al[22]	0.87 (0.50, 1.51)	3.46
Keatings et al[35]	0.98 (0.55, 1.74)	3.38
Kucukaycan et al[37]	1.13 (0.75, 1.71)	4.07
Ferrarotti et al[38]	0.86 (0.35, 2.13)	2.23
Broekhuizen et al[41]	1.12 (0.66, 1.89)	3.59
Chierakul et al[19]	1.45 (0.62, 3.37)	2.41
Hegab et al[42]	0.63 (0.28, 1.41)	2.52
Seifart et al[24]	1.12 (0.66, 1.89)	3.59
Brogger et al[11]	1.05 (0.71, 1.55)	4.16
Papatheodorou et al[12]	0.76 (0.40, 1.44)	3.13
Gingo et al[18]	1.78 (1.00, 3.14)	3.41
Hsieh et al[51]	1.39 (0.50, 3.90)	1.91
Stankovic et al[55]	0.55 (0.28, 1.08)	2.96
Trajkov et al[13]	1.09 (0.56, 2.11)	3.05
Shukla et al[58]	0.65 (0.39, 1.10)	3.63
Ozdogan et al[61]	1.45 (0.50, 4.21)	1.84
Subtotal (I^2=0.0%, P=0.504)	1.00 (0.86, 1.16)	49.33
Overall (I^2=56.4%, P=0.000)	1.51 (1.26, 1.81)	100

0.0203   1   49.3

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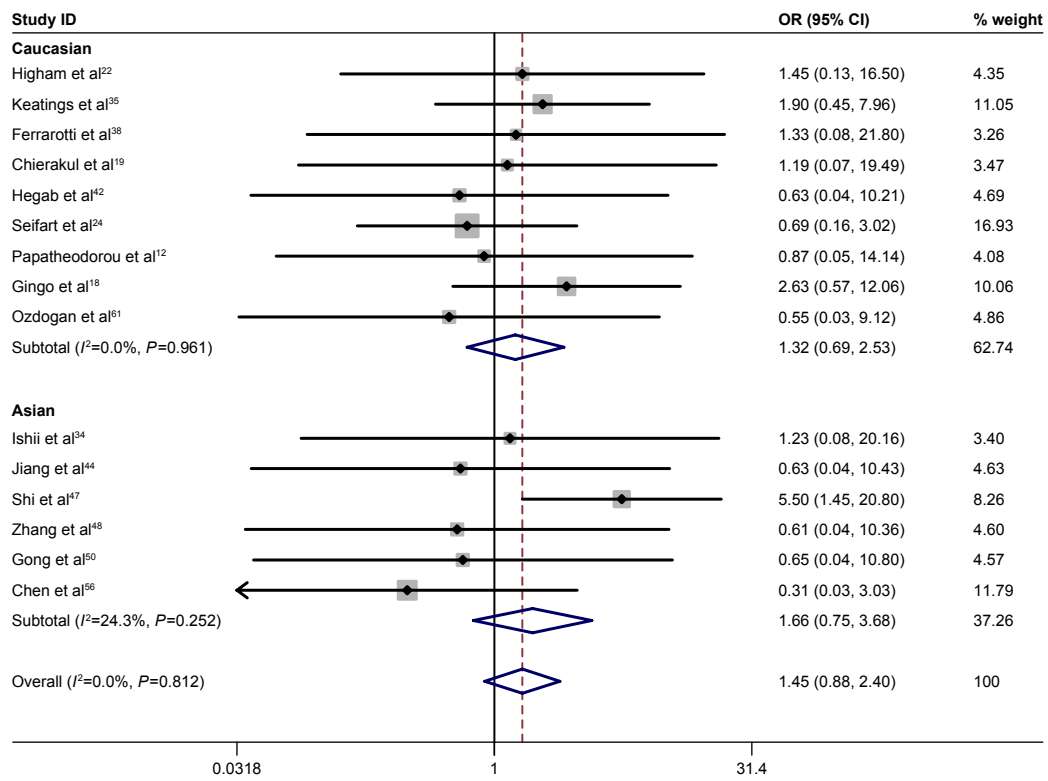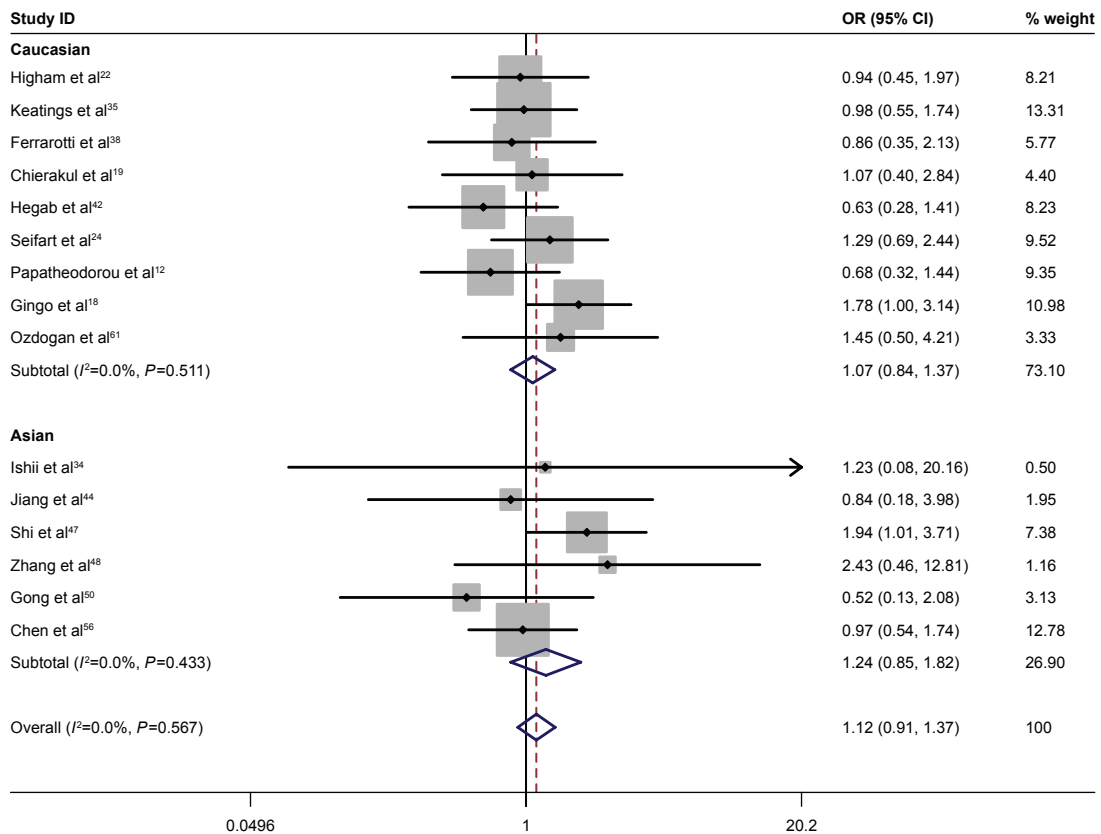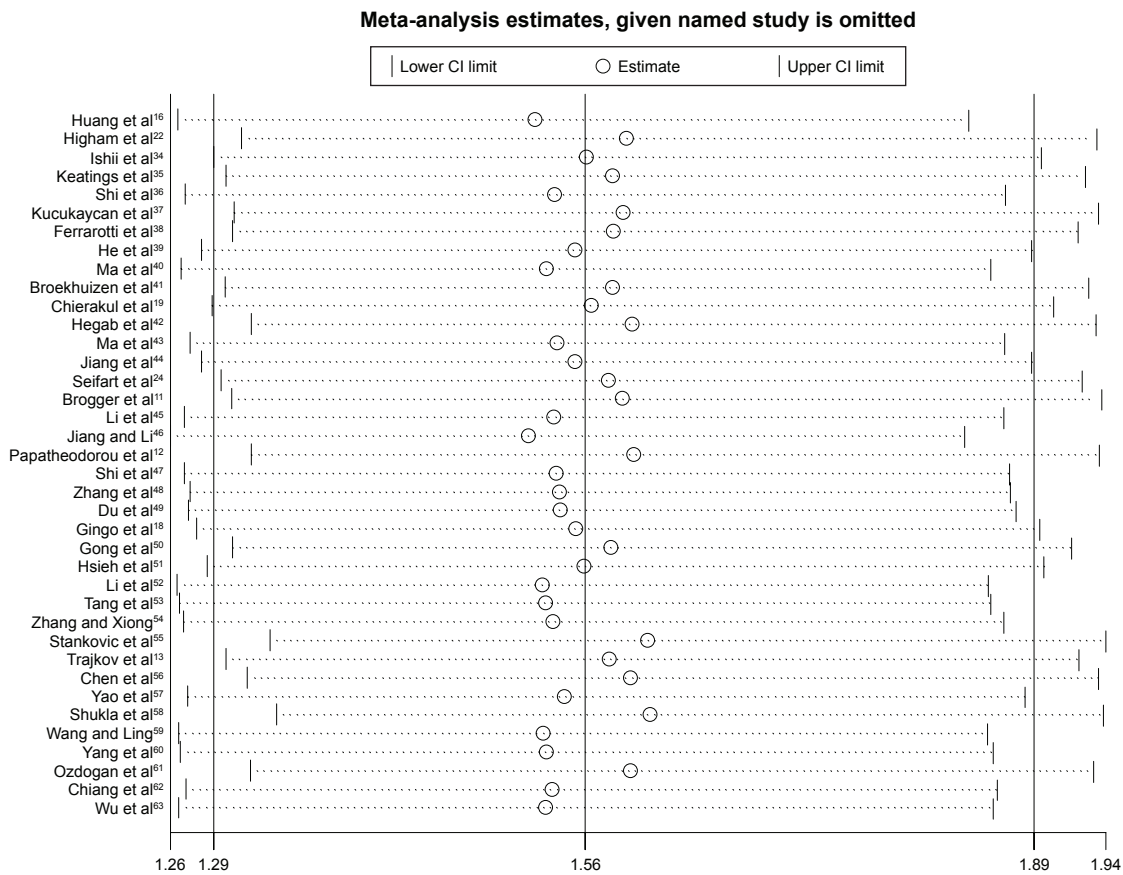**Abbreviations:** OR, odds ratio; CI, confidence interval.

Study ID	OR (95% CI)	% weight
Caucasian		
Higham et al[22]	1.45 (0.13, 16.50)	4.35
Keatings et al[35]	1.90 (0.45, 7.96)	11.05
Ferrarotti et al[38]	1.33 (0.08, 21.80)	3.26
Chierakul et al[19]	1.19 (0.07, 19.49)	3.47
Hegab et al[42]	0.63 (0.04, 10.21)	4.69
Seifart et al[24]	0.69 (0.16, 3.02)	16.93
Papatheodorou et al[12]	0.87 (0.05, 14.14)	4.08
Gingo et al[18]	2.63 (0.57, 12.06)	10.06
Ozdogan et al[61]	0.55 (0.03, 9.12)	4.86
Subtotal (I²=0.0%, P=0.961)	1.32 (0.69, 2.53)	62.74
Asian		
Ishii et al[34]	1.23 (0.08, 20.16)	3.40
Jiang et al[44]	0.63 (0.04, 10.43)	4.63
Shi et al[47]	5.50 (1.45, 20.80)	8.26
Zhang et al[48]	0.61 (0.04, 10.36)	4.60
Gong et al[50]	0.65 (0.04, 10.80)	4.57
Chen et al[56]	0.31 (0.03, 3.03)	11.79
Subtotal (I²=24.3%, P=0.252)	1.66 (0.75, 3.68)	37.26
Overall (I²=0.0%, P=0.812)	1.45 (0.88, 2.40)	100

0.0318   1   31.4

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.

Study ID	OR (95% CI)	% weight
Caucasian		
Higham et al[22]	0.94 (0.45, 1.97)	8.21
Keatings et al[35]	0.98 (0.55, 1.74)	13.31
Ferrarotti et al[38]	0.86 (0.35, 2.13)	5.77
Chierakul et al[19]	1.07 (0.40, 2.84)	4.40
Hegab et al[42]	0.63 (0.28, 1.41)	8.23
Seifart et al[24]	1.29 (0.69, 2.44)	9.52
Papatheodorou et al[12]	0.68 (0.32, 1.44)	9.35
Gingo et al[18]	1.78 (1.00, 3.14)	10.98
Ozdogan et al[61]	1.45 (0.50, 4.21)	3.33
Subtotal (I²=0.0%, P=0.511)	1.07 (0.84, 1.37)	73.10
Asian		
Ishii et al[34]	1.23 (0.08, 20.16)	0.50
Jiang et al[44]	0.84 (0.18, 3.98)	1.95
Shi et al[47]	1.94 (1.01, 3.71)	7.38
Zhang et al[48]	2.43 (0.46, 12.81)	1.16
Gong et al[50]	0.52 (0.13, 2.08)	3.13
Chen et al[56]	0.97 (0.54, 1.74)	12.78
Subtotal (I²=0.0%, P=0.433)	1.24 (0.85, 1.82)	26.90
Overall (I²=0.0%, P=0.567)	1.12 (0.91, 1.37)	100

0.0496   1   20.2

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.

Meta-analysis estimates, given named study is omitted

| Lower CI limit | ○ Estimate | Upper CI limit |

Huang et al[16]
Higham et al[22]
Ishii et al[34]
Keatings et al[35]
Shi et al[36]
Kucukaycan et al[37]
Ferrarotti et al[38]
He et al[39]
Ma et al[40]
Broekhuizen et al[41]
Chierakul et al[19]
Hegab et al[42]
Ma et al[43]
Jiang et al[44]
Seifart et al[24]
Brogger et al[11]
Li et al[45]
Jiang and Li[46]
Papatheodorou et al[12]
Shi et al[47]
Zhang et al[48]
Du et al[49]
Gingo et al[18]
Gong et al[50]
Hsieh et al[51]
Li et al[52]
Tang et al[53]
Zhang and Xiong[54]
Stankovic et al[55]
Trajkov et al[13]
Chen et al[56]
Yao et al[57]
Shukla et al[58]
Wang and Ling[59]
Yang et al[60]
Ozdogan et al[61]
Chiang et al[62]
Wu et al[63]

1.26 1.29   1.56   1.89 1.94

Figure 7 Sensitivity analysis for TNF-α −308 polymorphism with COPD in all subjects.
Abbreviation: CI, confidence interval.

Meta-analysis estimates, given named study is omitted

| Lower CI limit | ○ Estimate | Upper CI limit |

Higham et al[22]
Keatings et al[35]
Ferrarotti et al[38]
Chierakul et al[19]
Hegab et al[42]
Seifart et al[24]
Papatheodorou et al[12]
Gingo et al[18]
Ozdogan et al[61]
Ishii et al[34]
Jiang et al[44]
Shi et al[47]
Zhang et al[48]
Gong et al[50]
Chen et al[56]

0.81 0.85   1.07   1.36 1.42
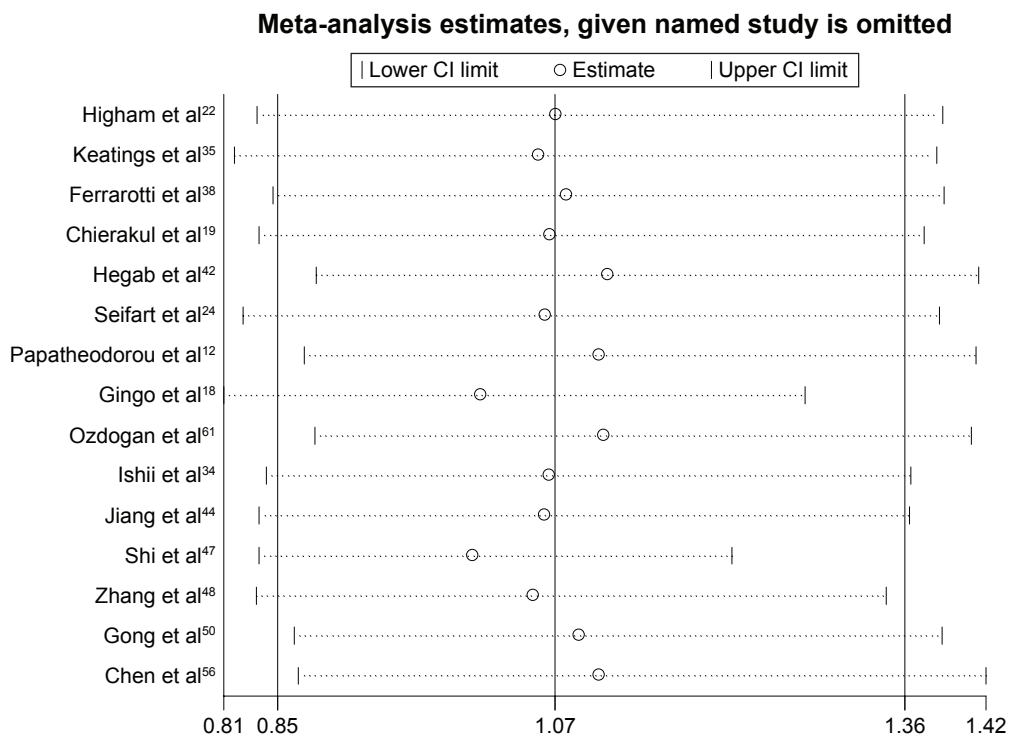
Figure 8 Sensitivity analysis for TNF-α −308 polymorphism with COPD in smoking subjects.
Abbreviation: CI, confidence interval.
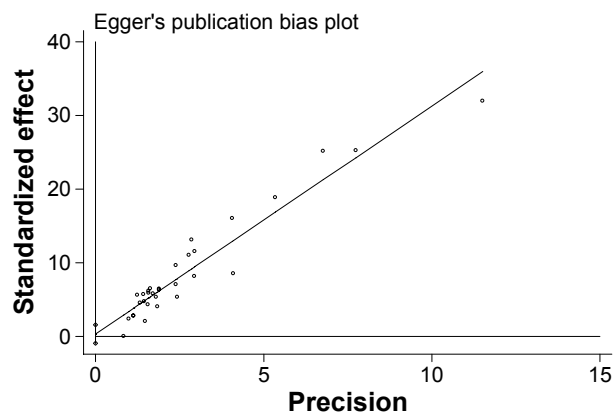
Figure 9 Publication bias on COPD risk and TNF-α −308 polymorphism.

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.

Acknowledgments

Disclosure

The authors declare no conflicts of interest in this work.

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