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Abstract

Background: Patients diagnosed with chronic obstructive pulmonary disease (COPD) have increased risks for a series of physical and mental illnesses. Tumor necrosis factor- α (TNF- α) has been reported to participate in the development of COPD and its complications. However, the values of blood TNF- α level used in the diagnosis of COPD remains controversial. In view of this, we performed a systematic review and meta-analysis to evaluate the correlation between TNF- α level and COPD.

Association between tumor necrosis factor- α

and chronic obstructive pulmonary disease:

a systematic review and meta-analysis

Methods: We searched PubMed, Web of Science, Embase and CNKI up to May 2018. The selection criteria were set according to the PICOS framework. A random-effects model was then applied to evaluate the overall effect sizes by calculating standard mean difference (SMD) and its 95% confidence intervals (CIs).

Results: A total of 40 articles containing 4189 COPD patients and 1676 healthy controls were included in this meta-analysis. The results indicated a significant increase in TNF- α level in the COPD group compared with the control group (SMD: 1.24, 95% CI: 0.78–1.71, p < 0.00001). According to the subgroup analyses, we noted that TNF- α level was associated with predicted first second of forced expiration (FEV₁) (%) and study region. However, no association between TNF- α level and COPD was found when the participants were nonsmokers, and the mean age was less than 60 years.

Conclusions: Our results indicated that TNF- α level was increased in COPD patients when compared with healthy controls. Illness progression and a diagnosis of COPD might contribute to higher TNF- α levels. However, the underlying mechanism still remains unknown and needs further investigation.

The reviews of this paper are available via the supplemental material section.

Keywords: biomarker, chronic obstructive pulmonary disease, meta-analysis, tumor necrosis factor- α

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Introduction

Chronic obstructive pulmonary disease (COPD) kills more than 3 million people worldwide every year.¹ Many factors have been reported to be associated with COPD, including systemic and local inflammation, air pollution and a sedentary lifestyle.^{2–4} However, the exact mechanisms underlying COPD still remain unclear. Since COPD is a chronic inflammatory disease, the relationship between inflammation and COPD

has been widely evaluated. Tumor necrosis factor- α (TNF- α), one of the major inflammatory factors, is implicated in the pathogenesis of many disorders, including COPD.^{5,6} However, due to the small sample sizes, most studies lack adequate statistical power to clarify the relationship between TNF- α and COPD. Moreover, currently available studies have provided inconsistent, or even contrary, results. For example, Karadag and colleagues have pointed out that raised serum level

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Category	Description	Search strategy terms
Population	COPD	COPD OR Chronic obstructive pulmonary disease
Intervention	TNF-α	TNF- α OR Tumor necrosis factor-alpha
Control	Healthy control or non-COPD	Healthy control or non-COPD
Outcome	Concentration of TNF- α	$TNF\text{-}\alpha$ concentration OR $TNF\text{-}\alpha$ level
Study Design	Case-control study	Case-Control study OR Case-Comparison Studies OR Case-compare study OR case-referent study OR Matched case-control study NOT animals

Table 1. PICOS table of included studies.	
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COPD, chronic obstructive pulmonary disease; PICOS, population, intervention, comparison, outcomes, study design; TNF- α , tumor necrosis factor-alpha

of TNF- α can be used as a biomarker for the systemic inflammatory response in stable COPD patients.⁷ But Franciosi and colleagues showed that healthy people and COPD patients at different stages had no statistical difference in TNF- α concentrations.⁸ To comprehensively investigate the association between TNF- α and COPD, and evaluate the diagnostic value of TNF- α in COPD, we conducted this meta-analysis to systematically evaluate the relationship between them.

Materials and methods

Literature search

We systematically searched four electronic databases (PubMed, Web of Science, EMBASE, and Cochrane library database CENTRAL) up to May 2018. The search terms were ['pulmonary disease, chronic obstructive' (MeSH Terms) or 'chronic obstructive pulmonary disease' or 'COPD' or 'COAD' or 'chronic obstructive airway disease' or 'chronic obstructive lung disease' or 'emphysema' or 'chronic bronchitis'] and ['Tumor necrosis factor-a' (MeSH Terms) or 'Tumor necrosis factor-a 'or 'TNF- α '] and ('systemic inflammation' or 'biological markers') (Supplementary Table S1). Only articles published in English were included. We also went through the references of eligible studies and review articles manually to identify possible relevant publications.

Study selection and inclusion and exclusion criteria

The inclusion criteria, set according to the PICOS framework (population, intervention, comparison,

outcomes, study design), were as follows (Table 1): population, COPD patients; intervention, TNF- α ; comparison, healthy control or non-COPD; outcomes, concentration of TNF- α ; study design, case-control study.

The eligible studies had to meet all of the following criteria: evaluation of the association between TNF- α and COPD was described; the specific concentration of TNF- α was provided; TNF- α level in both the control and COPD group was provided; sufficient patient data for calculating standard mean difference (SMD) and its 95% confidence intervals (CIs) were provided; COPD patients were diagnosed according to the criteria of the American Thoracic Society or Global Initiative for Chronic Obstructive Lung Disease; and healthy controls who had no medical illness or abnormalities in physical examination and laboratory date, and presented no symptoms of infection, were included. The exclusion criteria included: patients who received nutritional support with therapy; conference papers, reports, comments or review articles; studies without a control group; and patients with a history or diagnosis of asthma, allergy, or respiratory diseases other than COPD. The reasons for exclusion are shown in Table 2.

Quality assessment

Two reviewers (YY and ZJ) independently evaluated the quality of included studies according to the Newcastle-Ottawa Quality Assessment Scale (NOS). The NOS is a semiquantitative scale composed of three domains: selection, comparability, and exposure. The maximum NOS score is 9: a study with a total score of ≤ 3 was considered as poor

Table 2. Exclusion criteria.

Characteristics of excluded studies	Reasons
Patients who received nutritional support with therapy	Nutritional support is likely to affect the expression of TNF- $\!\alpha$
Conference papers, reports, comments or review articles	Conference papers, reports, comments, or review articles do not have enough case-control studies. These paper cannot provide enough data about PICOS
Without control group	All included studies are case-control studies, in which patients with COPD are diagnosed as cases, and individuals who do not have the disease or non-COPD are comparable as controls
Patients with a history or diagnosis of asthma, allergy, or respiratory diseases other than COPD	The aim of this review was to investigate the relationship between TNF- α and COPD rather than other respiratory diseases
COPD. chronic obstructive pulmonary disease: TNF	-α tumor necrosis factor-alpha

quality, those scoring 4–6 were of moderate quality, and a score of 7–9 was considered high quality.

Data extraction

Two investigators (DX and YY) independently extracted the following information from the original studies: first author's name, year of publication, country, sample size, clinical characteristics [including sex ratio, mean ages, smoking status, COPD status, body mass index (BMI), and the predicted first second of forced expiration (FEV₁)]. Disagreements between the two reviewers were resolved by consultation with a third reviewer (WSY).

Statistical analysis

The RevMan 5.3 software was used to perform the meta-analysis. The SMD and corresponding 95% CI were calculated to evaluate the relationships between TNF- α level and COPD. The Chisquared test and I^2 statistics were applied to detect the heterogeneity among studies. A p < 0.05 in Chi-squared test or $I^2 > 50\%$ indicated the presence of significant heterogeneity. A random effect model or fixed model was then used based on the presence or absence of significant heterogeneity. A sensitivity analysis was performed to explore the origins of heterogeneity. Publication bias was assessed using funnel plots with standard error.

Results

Study selection

The initial literature search returned a total of 949 articles. We excluded 143 duplicated studies. After a careful review of the titles and abstracts of remaining studies, a further 433 articles were excluded, and another 323 articles were also excluded for various reasons. Finally, 40 studies involving 4189 COPD patients and 1676 healthy controls were included in this meta-analysis.^{9–45} The flowchart for the literature search is presented in Figure 1.

The characteristics of the included studies are summarized in Table 3. Eight studies had a NOS score of 9^{25,29,33,36,37,40,42,45}; seven studies scored 813-15,17,18,22,44; nine studies scored 711,19,30,31,34,35,38,41,46; ten studies scored 6^{9,10,12,24,27,28,32,43,47,48}; four studies scored 5^{16,20,26,39}; and the last two studies scored 4.21,23 The NOS scores suggested that all included studies were of moderate or high quality. Regarding location, the majority of studies were from Europe,²⁶ two studies were from the US,14,26 one study was from eight studies were Africa,15 and from Asia.^{22,29,32,34,35,38,43,45} Patients in 9 studies were treated with steroids, while patients in the remaining 24 studies were not treated with steroids. The mean age, smoking status, COPD status, gender, and BMI of the study participants in the included studies are also provided in Table 3.

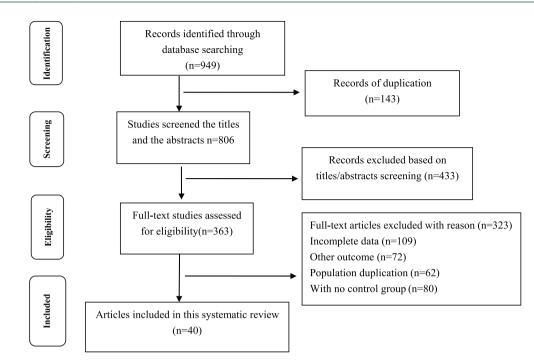


Figure 1. Flow diagram of the literature search process.

Meta-analysis

Due to the existence of significant heterogeneity $(p < 0.00001, I^2 = 98\%)$, this meta-analysis used a random effect model. Compared with the control group, the COPD patients had a significantly elevated level of TNF- α (SMD: 1.45, 95% CI: 0.44–2.27, p < 0.00001) (Figure 2).

Subgroup analysis

Subsequently, subgroup analyses stratified for FEV₁%, smoking history, COPD status, country, mean age, and BMI were performed to further understand the association between TNF- α level and COPD, and discover the source of heterogeneity (Table 4). A total of 36 studies were included in the subgroup analysis based on FEV₁%; the TNF- α level was 1.49 higher in COPD group compared with the control group (95% CI: 0.89-2.00, p < 0.00001) (Figure 3). The heterogeneity was still significant (>50%: p < 0.00001, $I^2 = 94\%$; < 50%: p < 0.0001, $I^2 = 98\%$). In the subgroup analysis based on smoking status (Figure 4), the TNF- α level in the ex-smokers/current smoker group was higher than those in the control and case groups (SMD: 1.63, 95% CI: 0.77–2.49, p=0.0002), but was not different for smoking patients (SMD: 0.70, 95% CI: -1.36 to 2.76, p=0.51). The

heterogeneity in both groups was still significant p < 0.00001, (ex-smokers/current smoker: $I^2 = 98\%$; No: p < 0.00001, $I^2 = 95\%$). A subgroup analysis was then performed according to COPD status (Figure 5). Patients with stable COPD and exacerbated COPD had higher TNF- α levels than the control group (stable: SMD: 1.33, 95% CI: 0.46-2.21, p=0.003; exacerbated: SMD: 2.43, 95% CI: 0.29-4.57, p = 0.03), but the heterogeneity was still significant regardless of COPD status (stable: $p < 0.00001, I^2 = 98\%$; exacerbated: p < 0.00001, $I^2 = 99\%$). Moreover, a subgroup analysis was carried out based on mean age (Figure 6). The TNF- α level in age >60 groups was 0.98 higher than that of the control group (SMD: 0.98 95% CI: 0.29-1.68, p=0.006). The heterogeneity was still significant in both groups (>60: $p < 0.00001, I^2 = 97\%;$ < 60: p < 0.00001, $I^2 = 91\%$) (Figure 6). In addition, in the country and BMI subgroup, the TNF- α level in the case group was significantly higher than that of the control group (Europe: SMD: 1.58, 95% CI: 0.94-2.23, p < 0.00001; others: SMD: 1.76, 95% CI: 0.78–2.74, p=0.0004) (BMI ≥ 20 : SMD: 8.53, 95% CI: 7.43–9.62, p<0.00001; BMI <20: SMD: 4.85, 95% CI: -3.22 to 12.93, p = 0.24). The heterogeneity was still obvious (Europe: p < 0.00001, $I^2 = 98\%;$ others:

Study	Year	Country	Sample size	Mean age		Sex(male/Female)	emale)	Smoking status	Reversibility test	Treat with	COPD status	NOS
				Case	Control	Case	Control			Steroids		
Calikoglu⁰	2004	Turkey	41	62.18±2.50	54.73 ± 2.23	NR	NR	NR	No	NR	Exacerbated	9
Agusti ¹⁰	2012	Spain	2409	63.5 ± 7.1	53.0 ± 8.6	1160/1004	76/169	NR	Yes	NR	NR	9
Once ¹¹	2010	Turkey	73	62.8 ± 5.5	61.8 ± 7.4	38/2	31/2	Ex-smokers	No	No	NR	7
Kleniewska ¹²	2016	Poland	42	59.8 ± 6.7	43.7 ± 14.4	20/0	15/7	NR	Yes	No	Stable	9
Rovina ¹³	2007	Greece	30	54 <u>+</u> 9	46 <u>+</u> 11	NR	NR	Current- smokers	Yes	No	N N	ω
Gagnon ¹⁴	2014	Canada	56	65±6	62 ± 8	25/12	13/6	Ex-smokers	No	NR	Mild	ω
Ben Anes ¹⁵	2017	Tunisia	285	61.58 ± 1.75	58.15 ± 0.7	50/6	203/26	Ex-smokers	Yes	NR	Exacerbated	ω
Perez-deLiano ¹⁶	2017	Spain	109	65.6 ± 10.1	59.8 ± 10.5	18/26	53/12	NR	Yes	NR	NR	£
FoschinoBarbaro ¹⁷	2007	UK	42	NR	NR	24/3	12/3	Ex-smokers	Yes	No	Stable	œ
Barreiro ¹⁸	2013	Spain	21	59 ± 8	58 ± 14	6	12	Ex-smokers	No	No	NR	œ
Beeh ¹⁹	2003	Germany	26	59 ± 9.25	31 ± 8.75	8/4	8/6	Ex-smokers	Yes	No	Stable	7
Di Stefano ²⁰	2018	Italy	41	NR	NR	19/4	8/10	Ex-smokers	Yes	No	Exacerbated	ъ
Breyer ²¹	2011	Netherlands	127	NR	NR	NR	NR	Ex-smokers	No	No	Exacerbated	4
Zhang ²²	2016	China	89	61.14 ± 10.21	60.92 ± 9.62	30/20	23/16	NR	Yes	No	Moderate	œ
Dima ²³	2010	Greece	38	58.4 ± 2.0	41.5 ± 3.5	NR	NR	Ex-smokers	Yes	No	NR	4
Kawayama ²⁴	2016	UK	20	62.2 ± 6.6	64.2 ± 6.6	7/3	5/5	Ex-smokers	No	Inhaled	NR	9
Gaki ²⁵	2011	Greece	354	6 3 ± 1.86	60 ± 1.71	169/53	97/35	Ex-smokers	No	Inhaled	Stable	6
Godoy ²⁶	2003	Brazi	24	62 ± 2.25	54 ± 1.5	14/0	5/5	NR	No	No	NR	2
Hacievliyagil ²⁷	2012	Turkey	40	61.2±1.7	59.1 ± 5.4	17/3	14/6	NR	Yes	Oral	Stable	9
Huertas ²⁸	2010	Italy	33	69 <u>+</u> 8	63 ± 7	NR	NR	NR	No	No	Stable	9
Ju ²⁹	2011	China	130	65.17 ± 6.79	63.98 ± 5.77	54/16	21/39	Ex-smokers	Yes	No	Stable	6
Karadag ³⁰	2007	Turkey	125	63.5 ± 7.59	61.10 ± 7.68	NR	NR	NR	Yes	Inhaled	Stable	7

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atuay	Year	Country	Sample	Mean age		Sex(male/Female)	Female)	Smoking	Reversibility	Treat	COPD	NOS
			216	Case	Control	Case	Control	chibic	1631	Steroids	chield	
Karadag ³¹	2008	Turkey	65	65.6 ± 7.8	63.2 ± 7.6	RN	NR	Ex-smokers	Yes	No	Stable	2
Shin ³²	2007	Korea	105	63.6±7.4	66.5 ± 8.9	NR	NR	NR	No	No	Stable	9
Kythreotis ³³	2008	Greece	77	65.8 ± 8.3	65.9 ± 9.6	43/9	19/6	Ex-smokers	No	No	Exacerbation	6
Liu ³⁴	2009	China	63	70 ± 7	70 ± 7	NR	NR	No-smoker	No	No	Stable	7
Huang ³⁵	2016	China	67	60.2 ± 10.1	55.7 ± 10.3	21/11	19/16	NR	Yes	NR	NR	7
Moermans ³⁶	2011	Belgium	128	62 ± 12	40 ± 12	73/21	24/10	Ex-smokers	Yes	Yes	Stable	6
Piehl-Aulin ³⁷	2008	Sweden	40	64 ± 8.7	61.9±7.9	11/15	7/7	Ex-smokers	No		Stable	6
Tan ³⁸	2016	China	20	65 ± 3	50 -+ 5	6/4	4/6	Ex-smokers	Yes	Yes	Stable	7
Guiot ³⁹	2017	Belgium	62	63 ± 9	55 ± 9	24/8	11/19	NR	No	NR	NR	വ
Sarioglu ⁴⁰	2015	Turkey	175	64.0 ± 8.9	61.5 ± 9.2	100/10	55/10	Ex-smokers	Yes	No	Stable	6
Uzum ⁴¹	2013	Turkey	49	65.9 ± 10.0	50.2 ± 8.4	RN	NR	No-smoker	No	No	Stable	7
Kosacka ⁴²	2015	Poland	210	62.2 ± 9.37	49.48 ± 13.68	121/60	18/11	Ex-smokers	No	NR	Stable	6
Cheng ⁴³	2008	China	343	71.9 ± 8.0	74.7 ± 3.7	152/32	129/30	Ex-smokers	Yes	NR	NR	9
Valipour ⁴⁴	2008	Austria	60	62 <u>+</u> 9	59 ± 8	23/7	23/7	NR	Yes	No	Exacerbation	ω
Zhang ⁴⁵	2010	China	65	70.93 ± 5.58	69.16 ± 7.43	38/8	13/6	Ex-smokers	Yes	No	Stable	6
Soler ⁴⁶	1999	Spain	21	68 ± 9	51 ± 11	13/0	5/3	Ex-smokers	No	No	Stable	7
Vera ⁴⁷	1996	UK	30	62.5 ± 3.2	39.4 ± 3.1	NR	NR	Ex-smokers	No	No	NR	9
De Godoy ⁴⁸	1996	US	23	67.0 ± 4.9	63.5 ± 5.8	6/4	11/2	NR	No	No	NR	9

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Table 3. (Contiuned)

		COPD	-		control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	57998	100000000	Mean	1.2.12.1	10000	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
gusti A 2012	2.35	1.36	2164	2.35	1.12	245	2.7%	0.00 [-0.13, 0.13]	ſ
arreiro E 2013	13.5	3.56	9	13.6	2.89	12	2.5%	-0.03 [-0.89, 0.83]	T
eeh KM 2003	69	31	12	61	12	14	2.5%	0.34 [-0.44, 1.12]	T
en Anes A 2017	1.55	0.46	56	1.33	0.46	229	2.7%	0.48 [0.18, 0.77]	-
reyer MK 2011	1.59	0.17	91	1.41	0.17	36	2.7%	1.05 [0.64, 1.46]	-
alikoglu M 2004	62.41	8.02	26	11.89	2.76	15	1.9%	7.47 [5.66, 9.29]	
heng SL 2008	205.7	46.1	305	17.2	184	159	2.7%	1.65 [1.43, 1.87]	-
e Godoy I 1996	7.1	1.8	10	5.8	1.56	13	2.5%	0.75 [-0.11, 1.61]	t-
i Stefano A 2018	3.2	13.8	23	2.7	21.2	18	2.6%	0.03 [-0.59, 0.64]	+
Dima E 2010	47.9	29.2	21	13.7	8.33	17	2.6%	1.49 [0.76, 2.22]	
oschino Barbaro MP 2007	11.17	3.41	27	6.22	0.82	15	2.5%	1.74 [1.00, 2.48]	
agnon P 2014	2.46	1.53	37	2.37	3.12	19	2.6%	0.04 [-0.51, 0.59]	+
aki E 2011	2.9	0.36	222	1.5	0.09	132	2.7%	4.81 [4.39, 5.23]	-
odoy AO 2003	2	0.3	14	2	0.4	10	2.5%	0.00 [-0.81, 0.81]	+
Juiot J 2017	14	121.75	32	6.9	5.6	30	2.6%	0.08 [-0.42, 0.58]	+
lacievliyagil SS 2012	90.8	19.6	20	13.7	0.4	20	2.2%	5.45 [4.05, 6.85]	
luang AX 2016	82.68	15.32	32		9.68	35	2.5%	3.91 [3.07, 4.74]	
luertas A 2010	2.3	0.3	21	1.2	0.2	12	2.3%	3.99 [2.74, 5.24]	
u CR 2011	6.92	2.02	70	4.8	3.45	60	2.7%	0.76 [0.40, 1.12]	-
(aradag F 2007	13.86	33.8	95	5.99	5.29	30	2.7%	0.26 [-0.15, 0.68]	-
(aradag F 2008	16.27	51.39	35	11.43	11.91	30	2.6%	0.12 [-0.36, 0.61]	Ļ
(awayama T 2016	8.15	20.2	10	1.3	8.42	10	2.5%	0.42 [-0.46, 1.31]	+
Kleniewska A 2016	8.7	7.2	20	2.42	4.2	22	2.6%	1.06 [0.41, 1.71]	
	2.91	3.23		2.42	1.48	29	2.7%		+
Kosacka M 2015			181					0.12 [-0.27, 0.51]	
(ythreotis P 2008	63.9	5.4	52	14	1.65	25	1.9%	10.86 [9.03, 12.68]	
iu XJ 2009	24.35	9.99	35	9.44	5.94	28	2.6%	1.74 [1.16, 2.33]	-
loermans C 2011	1.12	0.21	94	2.25	0.34	34	2.6%	-4.48 [-5.16, -3.80]	_
once L 2010	32.44	32.82	40	13.82	6.53	33	2.6%	0.75 [0.27, 1.22]	
erez-de- Liano L 2017	4	0.5	44	3.22	0.53	65	2.7%	1.49 [1.06, 1.93]	~
Piehl-Aulin K 2008	5.2	0.68	26	4.4	0.3	14	2.6%	1.35 [0.63, 2.08]	
Rovina N 2007	50	14.5	14	18.6	6.25	16	2.4%	2.81 [1.76, 3.85]	
arioglu N 2015	109.5	58	110	14.6	18	65	2.7%	2.00 [1.62, 2.37]	~
Shin KC 2007	8.5	3.1	60	7.2	3.5	45	2.7%	0.39 [0.00, 0.78]	~
Soler N 1999	15.7	12.4	13	7.1	2.2	8	2.5%	0.83 [-0.09, 1.75]	-
an CT 2016	21.35	1.73	10	13.9	0.77	10	1.8%	5.33 [3.29, 7.37]	
Jzum AK 2013	2.6	5.9	18	65.9	10	17	1.8%	-7.59 [-9.59, -5.59]	
alipour A 2008	1	0.15	30	1.4	0.18	30	2.6%	-2.38 [-3.05, -1.71]	
/era M 1996	5.8	2.1	14	0.9	0.13	16	2.3%	3.32 [2.17, 4.48]	
hang M 2010	126.3	104.84	46	16.63	17.52	19	2.6%	1.22 [0.64, 1.79]	
hang X 2016	16.05	20.39	50	14.77		39	2.7%	0.06 [-0.36, 0.48]	†
otal (95% CI)			4189			1676	100.0%	1.24 [0.78, 1.71]	•
leterogeneity: Tau ² = 2.07; C	hi ² = 142	7.24. df	= 39 (P	< 0.000	01); I ² =	97%			-20 -10 0 10
est for overall effect: Z = 5.23									-20 -10 0 10 Favours [COPD] Favours [Control]

Figure 2. Comparison of tumor necrosis factor- α level between COPD patients and controls in the included studies.

CI, Confidence interval; COPD, chronic obstructive pulmonary disease; SD, standard deviation.

 $p < 0.00001, I^2 = 98\%$) (BMI $\ge 20: p < 0.00001, I^2 = 100\%$; BMI $< 20: p < 0.00001, I^2 = 95\%$). (Figures 7 and 8). Finally, subgroup analysis was performed based on sample source. The TNF- α level in the case group was significantly higher than that of the control group in serum and BAL; the difference has statistical significance (serum: $p < 0.00001, I^2 = 100\%$; BAL: $p < 0.00001, I^2 = 100\%$) (Figure 9).

Meta-regression analysis

To further determine the source of heterogeneity, meta-regression analyses were conducted. The results indicated that publication year, region, BMI, NOS, study sample size, and smoking status were not potential sources of heterogeneity (Table 5).

Sensitivity analysis and publication bias

The sensitivity analysis showed that removing each of the 40 included studies did not result in significant change in the pooled effect size, indicating that the results of the present meta-analysis were stable (Table 6). Potential publication bias in this meta-analysis was evaluated with a funnel plot. The result showed that the included studies were symmetrically distributed, excluding the presence of significant publication bias (Figure 10).

Discussion

COPDs induced by chronic bronchitis and emphysema are characterized by not fully reversible and progressive airflow limitation, and represent one of the most serious public health concerns in the world.^{49,50} As an inflammatory disease,

Table 4.	Subgroup	analysis	of TNF- α	level in	COPD.
10000	Cubgroup	anacyoro	01 1111 0		001 D.

Subgroups	N	SMD (95%CI)	р	Test o	f heterogeneity
				1 2	р
COPD Status					
Stable	1654	1.33 (0.46–2.21)	<i>p</i> = 0.003	98	p < 0.00001
Exacerbated	590	2.43 (0.29–4.57)	<i>p</i> = 0.03	99	p < 0.00001
FEV1 %					
>50%	1046	1.49 (0.88–2.10)	p<0.00001	94	p<0.00001
<50%	4154	1.39 (0.56–2.22)	<i>p</i> = 0.0010	98	p<0.00001
Current smoking status Ex-smokers/current smokers	2352	1.63 (0.77–2.49)	<i>p</i> =0.0002	98	p<0.00001
No	98	0.70 (–1.36 to 2.76)	<i>p</i> =0.51	95	p<0.00001
Country					
Europe	4461	1.58 (0.94–2.23)	p<0.00001	98	p<0.00001
Others	1190	1.76 (0.78–2.74)	<i>p</i> = 0.0004	98	p<0.00001
Mean age					
>60	1585	0.98 (0.29–1.68)	<i>p</i> = 0.006	97	p<0.00001
<60	157	0.58 (-0.59 to 1.74)	<i>p</i> =0.33	91	p<0.00001
BMI					
>20	2146	0.72 (0.69–0.76)	p<0.00001	100	p<0.00001
<20	228	2.61 (1.67–3.55)	p<0.00001	95	p<0.00001

BMI, Body mass index; COPD, chronic obstructive pulmonary disease; FEV1, first second of forced expiration; TNF-α, tumor necrosis factor-alpha

inflammation of airways and lung parenchyma have been identified as one of the major pathogenic mechanisms of COPD.⁵¹ Inflammation is a complex process, in which a variety of cells and molecules are involved and a series of inflammatory signaling pathways are activated.

Previously, several meta-analyses have evaluated the association between TNF- α levels and COPD; however, the conclusions were conflicting. Gan and colleagues performed a meta-analysis including 14 studies and reported a significant correlation between systemic inflammatory markers, including TNF- α , and lung function.⁵² Bin and colleagues, however, indicated that there was no significant correlation between COPD and TNF- α level in a meta-analysis of 24 studies.⁵³ The main limitation of the previous meta-analyses is the relatively small number of the included studies, which leads to a small size of participant cohort. To overcome this limitation, we conducted the updated meta-analysis presented here, which includes 40 articles with 4152 COPD patients and 1639 healthy controls, to better evaluate the potential associations between TNF- α level and COPD. We found that COPD patients had significantly higher TNF- α levels than healthy controls. To explain this result, the following factors need to be taken into account. First, common genetic or constitutional differences between COPD patients and controls probably exist, and these differences predispose COPD patients to both systemic and

		Case			ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
2.1.1 >50%									
Barreiro E 2013	13.5	3.56	9	13.6	2.89	12	2.8%	-0.03 [-0.89, 0.83]	-
Calikoglu M 2004	62.41	8.02		11.89	2.76	15	2.2%	7.47 [5.66, 9.29]	-
Di Stefano A 2018	23	18	23	3.2	13.8	18	2.8%	1.19 [0.52, 1.86]	[
Dima E 2010	21	17	21	47.9	29.2	17	2.8%	-1.13 [-1.83, -0.44]	1
Foschino Barbaro MP 2007	11.17	3.41	27	6.22	0.82	15	2.8%	1.74 [1.00, 2.48]	
Gagnon P 2014	2.46	1.53	37	2.37	3.12	19	2.9%	0.04 [-0.51, 0.59]	
Huang AX 2016	82.68	15.32	32		9.68	35	2.8%	3.91 [3.07, 4.74]	-
Huertas A 2010	2.3	0.3	21	1.2	0.2	12	2.6%	3.99 [2.74, 5.24]	*
Karadag F 2008	16.27	51.39	35	11.43		30	2.9%	0.12 [-0.36, 0.61]	1
Kleniewska A 2016	8.7	7.2	20	2.42	4.2	22	2.9%	1.06 [0.41, 1.71]	
Kosacka M 2015	2.91	3.23	181	2.55	1.48	29	2.9%	0.12 [-0.27, 0.51]	1
Liu XJ 2009	24.35	9.99	35	9.44	5.94	28	2.9%	1.74 [1.16, 2.33]	t t
Once L 2010	32.44	32.82	40	13.82	6.53	33	2.9%	0.75 [0.27, 1.22]	
Rovina N 2007	50	14.5	14	18.6	6.25	16	2.7%	2.81 [1.76, 3.85]	-
Shin KC 2007	8.5	3.1	60	7.2	3.5	45	2.9%	0.39 [0.00, 0.78]	t
Tan CT 2016	21.35	1.73	10	13.9	0.77	10	2.1%	5.33 [3.29, 7.37]	~
Zhang X 2016	16.05	20.39	50	14.77	22.07	49	2.9%	0.06 [-0.33, 0.45]	
Subtotal (95% CI)			641			405	46.8%	1.49 [0.88, 2.10])
Heterogeneity: Tau ² = 1.45; C Test for overall effect: Z = 4.7			16 (P <	0.0000	1); F = !	94%			
2.1.2 <50%									
Agusti A 2012	2.35	1.36	2164	2.35	1.12	245	3.0%	0.00 [-0.13, 0.13]	
Ben Anes A 2017	1.55	0.46	56	1.33	0.38	229	3.0%	0.55 [0.26, 0.85]	ł
Breyer MK 2011	91	36	91	1.59	0.17	36	2.9%	2.91 [2.38, 3.44]	-
Cheng SL 2008	205.7	46.1	184	30.5	17.2	159	2.9%	4.89 [4.47, 5.32]	•
De Godoy I 1996	7.1	1.8	10	5.8	1.56	13	2.8%	0.75 [-0.11, 1.61]	ł
Godoy AO 2003	14	10	14	2	0.3	10	2.7%	1.51 [0.57, 2.44]	ŀ
			22	6.9	5.6	30	2.9%	0.08 [-0.42, 0.58]	
Guiot J 2017	14	121.75	32						
						20	2.5%	5.45 [4.05, 6.85]	7
Hacievliyagil SS 2012	90.8	19.6	20	13.7	0.4	20 60	2.5%	5.45 [4.05, 6.85] 0.76 [0.40, 1.12]	
Hacievliyagil SS 2012 Ju CR 2011	90.8 6.92	19.6 2.02	20 70	13.7 4.8	0.4 3.45	60	2.9%	0.76 [0.40, 1.12]	
Hacievliyagil SS 2012 Ju CR 2011 Karadag F 2007	90.8 6.92 13.86	19.6 2.02 33.8	20 70 95	13.7 4.8 5.99	0.4 3.45 5.29	60 30	2.9% 2.9%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68]	
Hacievliyagil SS 2012 Ju CR 2011 Karadag F 2007 Kawayama T 2016	90.8 6.92 13.86 8.15	19.6 2.02 33.8 20.2	20 70 95 10	13.7 4.8 5.99 1.3	0.4 3.45 5.29 8.42	60 30 10	2.9% 2.9% 2.8%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31]	
Hacievliyagil SS 2012 Ju CR 2011 Karadag F 2007 Kawayama T 2016 Kythreotis P 2008	90.8 6.92 13.86 8.15 63.9	19.6 2.02 33.8 20.2 5.4	20 70 95 10 52	13.7 4.8 5.99 1.3 14	0.4 3.45 5.29 8.42 1.65	60 30 10 25	2.9% 2.9% 2.8% 2.2%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [9.03, 12.68]	-
Hacievliyagil SS 2012 Ju CR 2011 Karadag F 2007 Kawayama T 2016 Kythreotis P 2008 Moermans C 2011	90.8 6.92 13.86 8.15 63.9 1.12	19.6 2.02 33.8 20.2 5.4 0.21	20 70 95 10 52 94	13.7 4.8 5.99 1.3 14 2.25	0.4 3.45 5.29 8.42 1.65 0.34	60 30 10 25 34	2.9% 2.9% 2.8% 2.2% 2.8%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [9.03, 12.68] -4.48 [-5.16, -3.80]	-
Hacievliyagii SS 2012 Ju CR 2011 (aradag F 2007 (awayama T 2016 (ythreotis P 2008 Moermans C 2011 Piehl-Aulin K 2008	90.8 6.92 13.86 8.15 63.9 1.12 5.2	19.6 2.02 33.8 20.2 5.4 0.21 0.68	20 70 95 10 52 94 26	13.7 4.8 5.99 1.3 14 2.25 4.4	0.4 3.45 5.29 8.42 1.65 0.34 0.3	60 30 10 25 34 14	2.9% 2.9% 2.8% 2.2% 2.8% 2.8%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [9.03, 12.68] -4.48 [-5.16, -3.80] 1.35 [0.63, 2.08]	-
Hacievliyagii SS 2012 Ju CR 2011 Karadag F 2007 Kawayama T 2016 Kythreotis P 2008 Moermans C 2011 Piehl-Aulin K 2008 Sarioglu N 2015	90.8 6.92 13.86 8.15 63.9 1.12 5.2 109.5	19.6 2.02 33.8 20.2 5.4 0.21 0.68 58	20 70 95 10 52 94 26 110	13.7 4.8 5.99 1.3 14 2.25 4.4 14.6	0.4 3.45 5.29 8.42 1.65 0.34 0.3 18	60 30 10 25 34 14 65	2.9% 2.9% 2.8% 2.2% 2.8% 2.8% 2.8% 2.9%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [9.03, 12.68] -4.48 [-5.16, -3.80] 1.35 [0.63, 2.08] 2.00 [1.62, 2.37]	-
Hacievliyagii SS 2012 Ju CR 2011 Karadag F 2007 Kawayama T 2016 Kythreotis P 2008 Moermans C 2011 Piehl-Aulin K 2008 Sarloglu N 2015 Soler N 1999	90.8 6.92 13.86 8.15 63.9 1.12 5.2 109.5 15.7	19.6 2.02 33.8 20.2 5.4 0.21 0.68 58 12.4	20 70 95 10 52 94 26 110 13	13.7 4.8 5.99 1.3 14 2.25 4.4 14.6 7.1	0.4 3.45 5.29 8.42 1.65 0.34 0.3 18 2.2	60 30 25 34 14 85 8	2.9% 2.9% 2.8% 2.2% 2.8% 2.8% 2.8% 2.9% 2.7%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [9.03, 12.68] -4.48 [-5.16, -3.80] 1.35 [0.63, 2.08] 2.00 [1.62, 2.37] 0.83 [-0.09, 1.75]	
Hacievliyagil SS 2012 Ju CR 2011 Karadag F 2007 Kawayama T 2016 Kyhreotis P 2008 Moermans C 2011 Piehl-Aulin K 2008 Sariogiu N 2015 Soler N 1999 Juum AK 2013	90.8 6.92 13.86 8.15 63.9 1.12 5.2 109.5 15.7 2.6	19.6 2.02 33.8 20.2 5.4 0.21 0.68 58 12.4 5.91	20 70 95 10 52 94 26 110 13 18	13.7 4.8 5.99 1.3 14 2.25 4.4 14.6 7.1 4.9	0.4 3.45 5.29 8.42 1.65 0.34 0.3 18 2.2 6.6	60 30 25 34 14 85 8 17	2.9% 2.9% 2.8% 2.2% 2.8% 2.8% 2.9% 2.7% 2.9%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [9.03, 12.68] -4.48 [-5.16, -3.80] 1.35 [0.63, 2.08] 2.00 [1.62, 2.37] 0.83 [-0.09, 1.75] -0.36 [-1.03, 0.31]	
Hacievilyagii SS 2012 Ju CR 2011 Kavadag F 2007 Kawayama T 2016 Kyhtheotis P 2008 Moermans C 2011 Pieht-Aulin K 2008 Sariogiu N 2015 Soler N 1999 Uzum AK 2013 Valipour A 2008	90.8 6.92 13.86 8.15 63.9 1.12 5.2 109.5 15.7 2.6 1	19.6 2.02 33.8 20.2 5.4 0.21 0.68 58 12.4 5.91 0.15	20 70 95 10 52 94 26 110 13 18 30	13.7 4.8 5.99 1.3 14 2.25 4.4 14.6 7.1 4.9 1.4	0.4 3.45 5.29 8.42 1.65 0.34 0.3 18 2.2 6.6 0.18	60 30 10 25 34 14 65 8 17 30	2.9% 2.9% 2.8% 2.2% 2.8% 2.8% 2.9% 2.7% 2.9% 2.8%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [9.03, 12.68] -4.48 [-5.16, -3.80] 1.35 [0.63, 2.08] 2.00 [1.62, 2.37] 0.83 [-0.09, 1.75] -0.36 [-1.03, 0.31] -2.38 [-3.05, -1.71]	
Hacievliyagil SS 2012 Ju CR 2011 Kawayama T 2016 Kykhreotis P 2008 Moermans C 2011 Pieht-Aulin K 2008 Sarloglu N 2015 Soler N 1999 Uzum AK 2013 Valipour A 2008	90.8 6.92 13.86 8.15 63.9 1.12 5.2 109.5 15.7 2.6	19.6 2.02 33.8 20.2 5.4 0.21 0.68 58 12.4 5.91	20 70 95 10 52 94 26 110 13 18 30 14	13.7 4.8 5.99 1.3 14 2.25 4.4 14.6 7.1 4.9	0.4 3.45 5.29 8.42 1.65 0.34 0.3 18 2.2 6.6	60 30 10 25 34 14 65 8 17 30 16	2.9% 2.9% 2.8% 2.2% 2.8% 2.8% 2.9% 2.7% 2.9% 2.9% 2.8% 2.6%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [9.03, 12.68] -4.48 [-5.16, -3.80] 1.35 [0.63, 2.08] 2.00 [1.62, 2.37] 0.83 [-0.09, 1.75] -0.36 [-1.03, 0.31] -2.38 [-3.05, -1.71] 3.32 [2.17, 4.48]	
Hacievilyagil SS 2012 Ju CR 2011 Kavadag F 2007 Kavayama T 2016 Kyhtreolis P 2008 Moermans C 2011 Piehi-Aulin K 2008 Sariogiu N 2015 Soler N 1999 Uzum AK 2013 Valipour A 2008 Vera M 1996 Subtotal (95% Cl)	90.8 6.92 13.86 8.15 63.9 1.12 5.2 109.5 15.7 2.6 1 5.8 Chi [#] = 109	19.6 2.02 33.8 20.2 5.4 0.21 0.68 58 12.4 5.91 0.15 2.1 9.05, df=	20 70 95 10 52 94 26 110 13 18 30 14 3103	13.7 4.8 5.99 1.3 14 2.25 4.4 14.6 7.1 4.9 1.4 0.9	0.4 3.45 5.29 8.42 1.65 0.34 0.3 18 2.2 6.6 0.18 0.13	60 30 10 25 34 14 85 8 17 30 16 1051	2.9% 2.9% 2.8% 2.2% 2.8% 2.8% 2.9% 2.7% 2.9% 2.8%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [9.03, 12.68] -4.48 [-5.16, -3.80] 1.35 [0.63, 2.08] 2.00 [1.62, 2.37] 0.83 [-0.09, 1.75] -0.36 [-1.03, 0.31] -2.38 [-3.05, -1.71]	
Guiot J 2017 Hacievilyagil SS 2012 Ju CR 2011 Karadag F 2007 Kkythreotis P 2008 Moermans C 2011 Piehi-Aulin K 2008 Sarioglu N 2015 Soler N 1999 Uzum AK 2013 Valipour A 2008 Vera M 1996 Subtota (95% Cl) Heterogeneilty: Tau ^s = 3.24; C Test for overail effect. Z = 3.2 Total (95% Cl)	90.8 6.92 13.86 8.15 63.9 1.12 5.2 109.5 15.7 2.6 1 5.8 Chi [#] = 109	19.6 2.02 33.8 20.2 5.4 0.21 0.68 58 12.4 5.91 0.15 2.1 9.05, df=	20 70 95 10 52 94 26 110 13 18 30 14 3103	13.7 4.8 5.99 1.3 14 2.25 4.4 14.6 7.1 4.9 1.4 0.9	0.4 3.45 5.29 8.42 1.65 0.34 0.3 18 2.2 6.6 0.18 0.13	60 30 10 25 34 14 65 8 17 30 16 1051 98%	2.9% 2.9% 2.8% 2.2% 2.8% 2.8% 2.9% 2.7% 2.9% 2.9% 2.8% 2.6%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [0.03, 12.68] 4.48 [-516, -3.80] 1.35 [0.53, 2.08] 2.00 [1.62, 2.37] 0.83 [-0.09, 1.75] -0.36 [-1.03, 0.31] 3.32 [2.17, 4.48] 1.39 [0.56, 2.22]	
Hacievilyagill SS 2012 Ju CR 2011 Kawagama T 2016 Kawagama T 2016 Kawagama T 2018 Moermans C 2011 Piehi-Aulin K 2008 Sariogiu N 2015 Soler N 1999 Uzum AK 2013 Valipour A 2008 Vera M 1996 Subtotal (95% C1) Heterogeneity: Tau ² = 3.24; C Test for overall effect: Z = 3.2	90.8 6.92 13.86 8.15 63.9 1.12 5.2 109.5 15.7 2.6 1 5.8 Chi [#] = 109 9 (P = 0.0	19.6 2.02 33.8 20.2 5.4 0.68 58 12.4 5.91 0.15 2.1 9.05, df= 010)	20 70 95 10 52 94 26 110 13 18 30 14 3103 = 18 (P	13.7 4.8 5.99 1.3 14 2.25 4.4 14.6 7.1 4.9 1.4 0.9 < 0.000	0.4 3.45 5.29 8.42 1.65 0.34 0.3 18 2.2 6.6 0.18 0.13	60 30 10 25 34 14 65 8 17 30 16 1051 98%	2.9% 2.9% 2.8% 2.8% 2.8% 2.9% 2.7% 2.9% 2.8% 2.6% 53.2%	0.76 [0.40, 1.12] 0.26 [-0.15, 0.68] 0.42 [-0.46, 1.31] 10.86 [9.03, 12.68] -4.48 [-5.16, -3.80] 1.35 [0.63, 2.08] 2.00 [1.62, 2.37] 0.83 [-0.09, 1.75] -0.36 [-1.03, 0.31] -2.38 [-3.05, -1.71] 3.32 [2.17, 4.48]	

Figure 3. Subgroup analyses of the relationship between tumor necrosis factor- α and chronic obstructive pulmonary disease according to first second of forced expiration (%).

Charles and Carl and Carl		Case	Tetel		ontrol	Tetel		Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	lotal	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.2.1 ex-smokers/current si		0.50		10.0	0.00	10	1.000		
Barreiro E 2013	13.5	3.56	9	13.6	2.89	12	4.0%	-0.03 [-0.89, 0.83]	
Beeh KM 2003	69	31	12	61	12	14	4.0%	0.34 [-0.44, 1.12]	T
Ben Anes A 2017	1.55	0.46	56	1.33	0.38	229	4.2%	0.55 [0.26, 0.85]	
Breyer MK 2011	91	36	91	1.59	0.17	36	4.1%	2.91 [2.38, 3.44]	
Cheng SL 2008	205.7	46.1	184	30.5	17.2	159	4.1%	4.89 [4.47, 5.32]	
Di Stefano A 2018	23	18	23	3.2	13.8	18	4.1%	1.19 [0.52, 1.86]	
Dima E 2010	21	17	21	47.9	29.2	17	4.0%	-1.13 [-1.83, -0.44]	
Foschino Barbaro MP 2007	11.17	3.41	27	6.22	0.82	15	4.0%	1.74 [1.00, 2.48]	
Gagnon P 2014	2.46	1.53	37	2.37	3.12	19	4.1%	0.04 [-0.51, 0.59]	-
Gaki E 2011	2.9	0.36	222	1.5	0.09	132	4.1%	4.81 [4.39, 5.23]	
Ju CR 2011	6.92	2.02	70	4.8	3.45	60	4.1%	0.76 [0.40, 1.12]	-
Karadag F 2008	16.27			11.43		30	4.1%	0.12 [-0.36, 0.61]	+
Kawayama T 2016	8.15	20.2	10	1.3	8.42	10	4.0%	0.42 [-0.46, 1.31]	
Kosacka M 2015	2.91	3.23	181	2.55	1.48	29	4.1%	0.12 [-0.27, 0.51]	+
Kythreotis P 2008	63.9	5.4	52	14	1.65	25	3.4%	10.86 [9.03, 12.68]	
Moermans C 2011	1.12	0.21	94	2.25	0.34	34	4.1%	-4.48 [-5.16, -3.80]	
Once L 2010	32.44	32.82	40	13.82	6.53	33	4.1%	0.75 [0.27, 1.22]	
Piehl-Aulin K 2008	5.2	0.68	26	4.4	0.3	14	4.0%	1.35 [0.63, 2.08]	
Rovina N 2007	50	14.5	14	18.6	6.25	16	3.9%	2.81 [1.76, 3.85]	
Sarioglu N 2015	109.5	58	110	14.6	18	65	4.1%	2.00 [1.62, 2.37]	-
Soler N 1999	15.7	12.4	13	7.1	2.2	8	4.0%	0.83 [-0.09, 1.75]	
Tan CT 2016	21.35	1.73	10	13.9	0.77	10	3.3%	5.33 [3.29, 7.37]	
Vera M 1996	5.8	2.1	14	0.9	0.13	16	3.8%	3.32 [2.17, 4.48]	
Subtotal (95% CI)			1351			1001	91.9%	1.63 [0.77, 2.49]	•
Heterogeneity: Tau ² = 4.26; C	hi ² = 119	95.95, d	f= 22 (P < 0.00	001); I ²	= 98%			
Test for overall effect: Z = 3.7	1 (P = 0.0	0002)							
2.2.2 No									
Liu XJ 2009	24.35	9.99	35	9.44	5.94	28	4.1%	1.74 [1.16, 2.33]	
Uzum AK 2013	2.6	5.91	18	4.9	6.6	17	4.1%	-0.36 [-1.03, 0.31]	
Subtotal (95% CI)			53			45	8.1%	0.70 [-1.36, 2.76]	
Heterogeneity: Tau ² = 2.11; C	hi ² = 21.	44, df =	1 (P <	0.00001); I ² = 9	5%			
Test for overall effect: Z = 0.6	6 (P = 0.5	51)	10.2261 18		envo so				
Total (95% CI)			1404			1046	100.0%	1.55 [0.74, 2.35]	•
Heterogeneity: Tau ² = 4.04; C	hi ² = 123	22.42, d	f= 24 (P < 0.00	001); lª	= 98%		-	-4 -2 0 2 4
Test for overall effect: Z = 3.7									
Test for subgroup differences			= 1 (P :	= 0.41)	P = 0.96				Favours [Case] Favours [control]

Figure 4. Subgroup analyses of the relationship between tumor necrosis factor- α and chronic obstructive pulmonary disease according to smoking status.

		Case		C	ontrol		8	Std. Mean Difference	Std. N	lean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, R	andom, 95% Cl
2.3.1 Stable										
Beeh KM 2003	69	31	12	61	12	14	4.4%	0.34 [-0.44, 1.12]		t
Foschino Barbaro MP 2007	11.17	3.41	27	6.22	0.82	15	4.4%	1.74 [1.00, 2.48]		-
Gaki E 2011	2.9	0.36	222	1.5	0.09	132	4.5%	4.81 [4.39, 5.23]		
Hacievliyagil SS 2012	90.8	19.6	20	13.7	0.4	20	4.0%	5.45 [4.05, 6.85]		-
Huertas A 2010	2.3	0.3	21	1.2	0.2	12	4.1%	3.99 [2.74, 5.24]		-
Ju CR 2011	6.92	2.02	70	4.8	3.45	60	4.5%	0.76 [0.40, 1.12]		t
Karadag F 2007	13.86	33.8	95	5.99	5.29	30	4.5%	0.26 [-0.15, 0.68]		
Karadag F 2008	16.27	51.39	35	11.43	11.91	30	4.5%	0.12 [-0.36, 0.61]		
Kleniewska A 2016	8.7	7.2	20	2.42	4.2	22	4.4%	1.06 [0.41, 1.71]		1
Kosacka M 2015	2.91	3.23	181	2.55	1.48	29	4.5%	0.12 [-0.27, 0.51]		
Liu XJ 2009	24.35	9.99	35	9.44	5.94	28	4.5%	1.74 [1.16, 2.33]		•
Moermans C 2011	1.12	0.21	94	2.25	0.34	34	4.4%	-4.48 [-5.16, -3.80]		-
Piehl-Aulin K 2008	5.2	0.68	26	4.4	0.3	14	4.4%	1.35 [0.63, 2.08]		
Sarioglu N 2015	109.5	58	110	14.6	18	65	4.5%	2.00 [1.62, 2.37]		•
Shin KC 2007	8.5	3.1	60	7.2	3.5	45	4.5%	0.39 [0.00, 0.78]		t
Soler N 1999	15.7	12.4	13	7.1	2.2	8	4.3%	0.83 [-0.09, 1.75]		ł
Tan CT 2016	21.35	1.73	10	13.9	0.77	10	3.5%	5.33 [3.29, 7.37]		-
Uzum AK 2013	2.6	5.91	18	4.9	6.6	17	4.4%	-0.36 [-1.03, 0.31]		1
Subtotal (95% CI)			1069			585	78.5%	1.33 [0.46, 2.21]		1
Heterogeneity: Tau ² = 3.43; C	chi ² = 759	3.78, df	= 17 (P	< 0.000	01); I ² =	98%				
Test for overall effect: Z = 2.9	8 (P = 0.0	003)								
2.3.2 Exacerbated										
Ben Anes A 2017	1.55	0.46	56	1.33	0.38	229	4.5%	0.55 [0.26, 0.85]		t
Breyer MK 2011	91	36	91	1.59	0.17	36	4.5%	2.91 [2.38, 3.44]		-
Di Stefano A 2018	23	18	23	3.2	13.8	18	4.4%	1.19 [0.52, 1.86]		1
Kythreotis P 2008	63.9	5.4	52	14	1.65	25	3.7%	10.86 [9.03, 12.68]		-
Valipour A 2008	1	0.15	30	1.4	0.18	30	4.4%	-2.38 [-3.05, -1.71]		•
Subtotal (95% CI)			252			338	21.5%	2.43 [0.29, 4.57]		•
Heterogeneity: Tau ² = 5.75; C	chi ² = 267	7.52, df	= 4 (P <	0.0000	1); =	99%				
Test for overall effect: Z = 2.2	2 (P = 0.0	03)								
Total (95% CI)			1321			923	100.0%	1.55 [0.77, 2.33]		
Heterogeneity: Tau ² = 3.47; C	chi ² = 102	28.99, d	f= 22 (P < 0.00	001); I ^z	= 98%			1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	
Test for overall effect: Z = 3.8			1.			1000			-100 -50	<u>0</u> 50 1
Test for subaroup difference:			= 1 (P	= 0.35)	F = 0%				Favours [C	ase] Favours [control]

Figure 5. Subgroup analyses of the relationship between TNF- α and chronic obstructive pulmonary disease (COPD) according to COPD status.

		Case			Control			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.4.1 >60									
Ju CR 2011	6.92	2.02	70	4.8	3.45	60	4.4%	0.76 [0.40, 1.12]	
Karadag F 2007	13.86	33.8	95	5.99	5.29	30	4.4%	0.26 [-0.15, 0.68]	t
Karadag F 2008	16.27	51.39	35	11.43	11.91	30	4.4%	0.12 [-0.36, 0.61]	
Kawayama T 2016	8.15	20.2	10	1.3	8.42	10	4.1%	0.42 [-0.46, 1.31]	t
Kosacka M 2015	2.91	3.23	181	2.55	1.48	29	4.4%	0.12 [-0.27, 0.51]	
Kythreotis P 2008	63.9	5.4	52	14	1.65	25	3.2%	10.86 [9.03, 12.68]	-
Liu XJ 2009	24.35	9.99	35	9.44	5.94	28	4.3%	1.74 [1.16, 2.33]	
Moermans C 2011	1.12	0.21	94	2.25	0.34	34	4.3%	-4.48 [-5.16, -3.80]	•
Once L 2010	32.44	32.82	40	13.82	6.53	33	4.4%	0.75 [0.27, 1.22]	
Perez-de- Liano L 2017	4	0.5	44	3.22	0.53	65	4.4%	1.49 [1.06, 1.93]	•
Piehl-Aulin K 2008	5.2	0.68	26	4.4	0.3	14	4.2%	1.35 [0.63, 2.08]	ł
Sarioglu N 2015	109.5	58	110	14.6	18	65	4.4%	2.00 [1.62, 2.37]	ŀ
Shin KC 2007	8.5	3.1	60	7.2	3.5	45	4.4%	0.39 [0.00, 0.78]	+
Soler N 1999	15.7	12.4	13	7.1	2.2	8	4.1%	0.83 [-0.09, 1.75]	ł
Tan CT 2016	21.35	1.73	10	13.9	0.77	10	3.0%	5.33 [3.29, 7.37]	-
Uzum AK 2013	2.6	5.91	18	4.9	6.6	17	4.3%	-0.36 [-1.03, 0.31]	4
Valipour A 2008	1	0.15	30	1.4	0.18	30	4.3%	-2.38 [-3.05, -1.71]	
Vera M 1996	5.8	2.1	14	0.9	0.13	16	3.9%	3.32 [2.17, 4.48]	-
Zhang X 2016	16.05	20.39	50	14.77	22.07	49	4.4%	0.06 [-0.33, 0.45]	4
Subtotal (95% CI)			987			598	79.2%	0.98 [0.29, 1.68])
Heterogeneity: Tau ² = 2.2	4: Chi ² =	570.94	. df = 1	8 (P < 0	.00001)	: 12 = 97	7%	182 8 8	
Test for overall effect: Z =				-N.S.					
2.4.2 <60									
Barreiro E 2013	13.5	3.56	9	13.6	2.89	12	4.1%	-0.03 [-0.89, 0.83]	ł
Beeh KM 2003	69	31	12	61	12	14	4.2%	0.34 [-0.44, 1.12]	+
Dima E 2010	21	17	21	47.9	29.2	17	4.2%	-1.13 [-1.83, -0.44]	1
Kleniewska A 2016	8.7	7.2	20	2.42	4.2	22	4.3%	1.06 [0.41, 1.71]	}
Rovina N 2007	50	14.5	14	18.6	6.25	16	4.0%	2.81 [1.76, 3.85]	•
Subtotal (95% CI)			76			81	20.8%	0.58 [-0.59, 1.74]	•
Heterogeneity: Tau ² = 1.6	0; Chi ² =	43.99.	df = 4 (P < 0.00	0001); I ^z	= 91%		101210 - 191000 - 58	
Test for overall effect: Z =			en) (10)						
Total (95% CI)			1063			679	100.0%	0.89 [0.29, 1.50]	
Heterogeneity: Tau ² = 2.1	2; Chi ² =	615.64	, df = 2	3 (P < 0	.00001)	; I2 = 98	5%		
Test for overall effect: Z =							0.002		-100 -50 0 50 11
Test for subaroup differen				(P = 0)	56) IZ-	0%			Favours [experimental] Favours [control]

Figure 6. Subgroup analyses of the relationship between tumor necrosis factor- α and chronic obstructive pulmonary disease according to age.

		Case			ontrol			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.5.1 Europe	0.05	4.00		0.05			0.70		1
Agusti A 2012	2.35		2164	2.35	1.12	245	2.7%	0.00 [-0.13, 0.13]	Ī
Barreiro E 2013	13.5	3.56	9	13.6	2.89	12	2.5%	-0.03 [-0.89, 0.83]	
Beeh KM 2003	69	31	12	61	12	14	2.5%	0.34 [-0.44, 1.12]	
Breyer MK 2011	91	36	91	1.59	0.17	36	2.6%	2.91 [2.38, 3.44]	
Calikoglu M 2004	62.41	8.02	26	11.89	2.76	15	2.0%	7.47 [5.66, 9.29]	,
De Godoy I 1996	7.1	1.8	10	5.8	1.56	13	2.5%	0.75 [-0.11, 1.61]	
Di Stefano A 2018	23	18	23	3.2	13.8	18	2.6%	1.19 (0.52, 1.86)	
Dima E 2010	21	17	21	47.9	29.2	17	2.5%	-1.13 [-1.83, -0.44]	
Foschino Barbaro MP 2007	11.17	3.41	27	6.22	0.82	15	2.5%	1.74 [1.00, 2.48]	
Gaki E 2011	2.9	0.36	222	1.5	0.09	132	2.6%	4.81 [4.39, 5.23]	
Godoy AO 2003	14	10	14	2	0.3	10	2.5%	1.51 [0.57, 2.44]	
Guiot J 2017	14	121.75	32	6.9	5.6	30	2.6%	0.08 [-0.42, 0.58]	
Hacievliyagil SS 2012	90.8	19.6	20	13.7	0.4	20	2.2%	5.45 [4.05, 6.85]	
Huertas A 2010	2.3	0.3	21	1.2	0.2	12	2.3%	3.99 [2.74, 5.24]	
Karadag F 2007	13.86	33.8	95	5.99	5.29	30	2.6%	0.26 [-0.15, 0.68]	+-
Karadag F 2008	16.27	51.39	35	11.43	11.91	30	2.6%	0.12 [-0.36, 0.61]	+-
Kawayama T 2016	8.15	20.2	10	1.3	8.42	10	2.5%	0.42 [-0.46, 1.31]	
Kleniewska A 2016	8.7	7.2	20	2.42	4.2	22	2.6%	1.06 [0.41, 1.71]	
Kosacka M 2015	2.91	3.23	181	2.55	1.48	29	2.6%	0.12 [-0.27, 0.51]	
Kythreotis P 2008	63.9	5.4	52	14	1.65	25	2.0%	10.86 [9.03, 12.68]	,
Moermans C 2011	1.12	0.21	94	2.25	0.34	34	2.6%	-4.48 [-5.16, -3.80]	←
Once L 2010	32.44	32.82	40	13.82	6.53	33	2.6%	0.75 [0.27, 1.22]	
Perez-de- Liano L 2017	4	0.5	44	3.22	0.53	65	2.6%	1.49 [1.06, 1.93]	
Piehl-Aulin K 2008	5.2	0.68	26	4.4	0.33	14	2.5%	1.35 [0.63, 2.08]	
Rovina N 2007	50	14.5	14	18.6	6.25	16	2.4%	2.81 [1.76, 3.85]	
Sarioqlu N 2015	109.5	58	110	14.6	18	65	2.6%	2.00 [1.62, 2.37]	
Soler N 1999	109.5	12.4	13	7.1	2.2	8	2.5%	0.83 [-0.09, 1.75]	
Uzum AK 2013	2.6	5.91	13	4.9	6.6	17	2.5%		
	2.0			4.9	0.13	16	2.6%	-0.36 [-1.03, 0.31]	
Vera M 1996 Subtatal (05% CI)	5.8	2.1	14 3458	0.9	0.13	1003	72.3%	3.32 [2.17, 4.48]	
Subtotal (95% CI)							12.3%	1.58 [0.94, 2.23]	
Heterogeneity: Tau² = 2.94; (Test for overall effect: Z = 4.8			= 28 (P	< U.UUU	101); 1-=	98%			
2.5.2 Others									
Ben Anes A 2017	1.55	0.46	56	1.33	0.38	229	2.6%	0.55 [0.26, 0.85]	
Cheng SL 2008	205.7	46.1	184	30.5	17.2	159	2.6%	4.89 [4.47, 5.32]	→
Gagnon P 2014	2.46	1.53	37	2.37	3.12	19	2.6%	0.04 [-0.51, 0.59]	
Godoy AO 2003	14	10	14	2	0.3	10	2.5%	1.51 [0.57, 2.44]	
	82.68	15.32		32.54	9.68	35	2.5%	3.91 [3.07, 4.74]	
Huang AX 2016		2.02	70	4.8	3.45	60	2.6%	0.76 [0.40, 1.12]	
Huang AX 2016 Ju CR 2011	692			9.44	5.94	28	2.6%	1.74 [1.16, 2.33]	
Ju CR 2011	6.92 24 35		36		0.04			0.39 [0.00, 0.78]	
Ju CR 2011 Liu XJ 2009	24.35	9.99	35		3.5				
Ju CR 2011 Liu XJ 2009 Shin KC 2007	24.35 8.5	9.99 3.1	60	7.2	3.5	45	2.6%		
Ju CR 2011 Liu XJ 2009 Shin KC 2007 Tan CT 2016	24.35 8.5 21.35	9.99 3.1 1.73	60 10	7.2 13.9	0.77	10	1.9%	5.33 [3.29, 7.37]	│ →
Ju CR 2011 Liu XJ 2009 Shin KC 2007 Tan CT 2016 Zhang M 2010	24.35 8.5 21.35 126.3	9.99 3.1 1.73 104.84	60 10 46	7.2 13.9 16.63	0.77 17.52	10 19	1.9% 2.6%	5.33 [3.29, 7.37] 1.22 [0.64, 1.79]	·
Ju CR 2011 Llu XJ 2009 Shin KC 2007 Tan CT 2016 Zhang M 2010 Zhang X 2016	24.35 8.5 21.35	9.99 3.1 1.73	60 10 46 50	7.2 13.9	0.77 17.52	10 19 49	1.9% 2.6% 2.6%	5.33 [3.29, 7.37] 1.22 [0.64, 1.79] 0.06 [-0.33, 0.45]	
Ju CR 2011 Llu XJ 2009 Shin KC 2007 Tan CT 2016 Zhang X 2010 Zhang X 2016 Subtotal (95% CI)	24.35 8.5 21.35 126.3 16.05	9.99 3.1 1.73 104.84 20.39	60 10 46 50 594	7.2 13.9 16.63 14.77	0.77 17.52 22.07	10 19 49 663	1.9% 2.6%	5.33 [3.29, 7.37] 1.22 [0.64, 1.79]	
Ju CR 2011 Lu XJ 2009 Shin KC 2007 Tan CT 2016 Zhang X 2016 Zhang X 2016 Subtotal (95% CI) Heterogeneity: Tau ² = 2.60; C	24.35 8.5 21.35 126.3 16.05 Chi ² = 439	9.99 3.1 1.73 104.84 20.39	60 10 46 50 594	7.2 13.9 16.63 14.77	0.77 17.52 22.07	10 19 49 663	1.9% 2.6% 2.6%	5.33 [3.29, 7.37] 1.22 [0.64, 1.79] 0.06 [-0.33, 0.45]	
Ju CR 2011 Llu XJ 2009 Shin KC 2007 Tan CT 2016 Zhang M 2010 Zhang X 2016	24.35 8.5 21.35 126.3 16.05 Chi ² = 439	9.99 3.1 1.73 104.84 20.39	60 10 46 50 594	7.2 13.9 16.63 14.77	0.77 17.52 22.07	10 19 49 663 98%	1.9% 2.6% 2.6%	5.33 [3.29, 7.37] 1.22 [0.64, 1.79] 0.06 [-0.33, 0.45]	
Ju CR ⁷ 2011 Lu XJ 2009 Shin KC 2007 Tan CT 2016 Zhang M 2010 Zhang X 2016 Subtotal (95% Cl) Heterogeneity: Tau ² = 2.80; (Test for overall effect: Z = 3.5	24.35 8.5 21.35 126.3 16.05 Chi ² = 439 i1 (P = 0.0 Chi ² = 166	9.99 3.1 1.73 104.84 20.39 1.42, df = 1004)	60 10 46 50 594 10 (P <	7.2 13.9 16.63 14.77	0.77 17.52 22.07 11); I ² = 9	10 19 663 38% 1666	1.9% 2.6% 2.6% 27.7%	5.33 [3.29, 7.37] 1.22 [0.64, 1.79] 0.06 [-0.33, 0.45] 1.76 [0.78, 2.74]	

Figure 7. Subgroup analyses of the relationship between tumor necrosis factor- α and chronic obstructive pulmonary disease according to country.

		Case			control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
2.6.1 ≥20									
Barreiro E 2013	13.5	3.56	9	13.6	2.89	12	4.3%	-0.10 [-2.94, 2.74]	Ť
Ben Anes A 2017	1.55	0.46	56	1.33	0.38	229	6.4%	0.22 [0.09, 0.35]	t
Calikoglu M 2004	62.41	8.02	26	11.89	2.76	15	3.8%	50.52 [47.14, 53.90]	-
Foschino Barbaro MP 2007	11.17	3.41	27	6.22	0.82	15	5.8%	4.95 [3.60, 6.30]	-
Gagnon P 2014	2.46	1.53	37	2.37	3.12	19	5.6%	0.09 [-1.40, 1.58]	t
Gaki E 2011	2.9	0.36	222	1.5	0.09	132	6.4%	1.40 [1.35, 1.45]	
Huang AX 2016	82.68	15.32	32	32.54	9.68	35	1.9%	50.14 [43.94, 56.34]	
Huertas A 2010	2.3	0.3	21	1.2	0.2	12	6.4%	1.10 [0.93, 1.27]	
Karadag F 2007	13.86	33.8	95	5.99	5.29	30	1.6%	7.87 [0.81, 14.93]	
Karadag F 2008	16.27	51.39	35	11.43	11.91	30	0.3%	4.84 [-12.71, 22.39]	
Kosacka M 2015	2.91	3.23	181	2.55	1.48	29	6.2%	0.36 [-0.36, 1.08]	•
Kythreotis P 2008	63.9	5.4	52	14	1.65	25	5.5%	49.90 [48.30, 51.50]	-
Liu XJ 2009	24.35	9.99	35	9.44	5.94	28	3.3%	14.91 [10.94, 18.88]	
Moermans C 2011	1.12	0.21	94	2.25	0.34	34	6.4%	-1.13 [-1.25, -1.01]	-
Piehl-Aulin K 2008	5.2	0.68	26	4.4	0.3	14	6.4%	0.80 [0.50, 1.10]	-
Sarioglu N 2015	109.5	58	110	14.6	18	65	0.7%	94.90 [83.21, 106.59]	-
Shin KC 2007	8.5	3.1	60	7.2	3.5	45	5.8%	1.30 [0.01, 2.59]	
Uzum AK 2013	2.6	5.91	18	4.9	6.6	17	3.1%	-2.30 [-6.46, 1.86]	
Valipour A 2008	1	0.15	30	1.4	0.18	30	6.4%	-0.40 [-0.48, -0.32]	4
Zhang M 2010	126.3	104.84		16.63		19		109.67 [78.37, 140.97]	
Zhang X 2016	16.05	20.39		14.77		49	1.2%	1.28 [-7.09, 9.65]	
Subtotal (95% CI)			1262			884	87.6%	8.53 [7.43, 9.62]	•
Heterogeneity: Tau ² = 4.25; C	$hi^2 = 744$	1 56 df:		< 0.000	101) [,] I ² =				
Test for overall effect: Z = 15.			20 0	0.000					
2.6.2 <20									
Ju CR 2011	6.92	2.02	70	4.8	3.45	60	6.0%	2.12 [1.13, 3.11]	-
Liu XJ 2009	24.35	9.99	35	9.44	5.94	28	3.3%	14.91 [10.94, 18.88]	-
Uzum AK 2013	2.6	5.91	18	4.9	6.6	17	3.1%	-2.30 [-6.46, 1.86]	-
Subtotal (95% CI)	2.0	0.01	123		0.0	105	12.4%		•
Heterogeneity: Tau ² = 47.99;	$Chi^2 = 43$	19 df=		0 00001) = 9				
Test for overall effect: $Z = 1.1$									
Total (95% CI)			1385			989	100.0%	8.02 [6.99, 9.04]	•
Heterogeneity: Tau ² = 4.27; C	hi ² = 750	0.10, df :	= 23 (P	< 0.000	001); I ^z =	100%			
Test for overall effect: Z = 15.									-100 -50 0 50 1

Figure 8. Subgroup analyses of the relationship between tumor necrosis factor- α and chronic obstructive pulmonary disease according to body mass index.

	COPD	-		ontrol			Mean Difference	Mean Difference
Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
2.35			2.35	1.12	245	5.5%	0.00 [-0.15, 0.15]	1
1.55	0.46	56	1.33	0.38	229	7.4%	0.22 [0.09, 0.35]	1
62.41	8.02	26	11.89	2.76	15	0.0%	50.52 [47.14, 53.90]	
7.1	1.8	10	5.8	1.56	13	0.1%	1.30 [-0.10, 2.70]	÷
23	18	23	3.2	13.8	18	0.0%		
								•
								-
								-
							49.90 [48.30, 51.50]	-
32.44		40			33		18.62 [8.21, 29.03]	
4	0.5	44	3.22	0.53	65	3.3%	0.78 [0.58, 0.98]	
5.2	0.68	26	4.4	0.3	14	1.4%	0.80 [0.50, 1.10]	
109.5	58	110	14.6	18	65	0.0%	94.90 (83.21, 106.59)	_
		60	7.2	3.5	45			•
								-
								-
120.5	104.04		10.05	17.52				
				N/	1120	09.0%	1.17 [1.13, 1.21]	
		0001),1	-= 100	70				
91	36	91	1.59	0.17	36	0.0%	89.41 [82.01, 96.81]	
11.17	3.41	27	6.22	0.82	15	0.1%		-
								Ļ
16.05	20.39		14.77	22.07				T
					224	22.4%	-0.07 [-0.15, 0.00]	
		001); l²	= 99%					
69	31	12	61	12	14	0.0%	8.00 [-10.63 26.63]	
50	14.5		18.6	6.25				
					141	8.5%	-1.11 [-1.23, -0.99]	
		01); I² =	98%					
13.5	3.56	9	13.6	2.89	12	0.0%	-0.10 [-2.94, 2.74]	+
5.8	2.1		0.9	0.13				1
			= 100%		195	0.1%	7.70 [6.69, 8.71]	'
00 (P < 0)	.00001)							
					0000			
		4068			1686	100.0%	0.71 [0.67, 0.74]	
19, df = 3	89 (P < 0.		; I ² = 10	0%	1686	100.0%	0.71 [0.67, 0.74]	-100 -50 0 50 10
7 6	Mean 2.35 1.55 62.41 7.1 23 2.91 13.86 6.92 13.86 7.91 14 6.92 13.86 8.7 2.91 6.92 109.5 8.5 2.135 8.5 2.6.3 9.1 11.17 2.46 2.3 2.435 82.68 2.3 2.435 6.99 91 11.1.7 2.435 7.07 (P = 0.0 69 921 14 90.8 1.12 50 00 13.55 205.7 15.7 5.8	Mean SD 2.35 1.36 1.55 0.46 82.41 8.02 2.3 1.8 2.3 1.8 2.3 1.8 2.3 1.8 2.3 1.8 2.3 1.8 2.3 1.8 2.3 0.36 1.4 10 6.92 2.02 13.86 33.8 16.27 51.39 8.7 7.2 2.91 3.23 63.9 5.4 0.55 5.2 0.8 6.5 5.2 0.88 10.5 1.73 2.6 5.91 12.6.3 104.84 .df = 20 (P < 0.0	Mean SD Total 2.35 1.36 2164 1.55 0.46 56 62.41 8.02 26 7.1 1.8 10 23 18 23 2.9 0.36 222 14 10 14 6.92 2.02 70 13.86 33.8 95 16.27 51.39 35 8.7 7.2 20 2.91 3.23 181 63.9 5.4 52 32.44 32.82 40 4 0.5 44 5.2 0.68 26 10.5 5.1 10 2.6 5.91 18 126.3 10.48.4 46 322 2.3 0.3 41 1.53 37 82.68 15.23 32 2.3 0.3 21 2.46 5.20	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean SD Total Mean SD 2.35 1.36 2164 2.35 1.12 1.55 0.46 56 1.33 0.38 82.41 8.02 26 11.89 2.76 7.1 1.8 10 58 1.56 23 18 2.3 3.2 13.8 2.9 0.36 222 1.5 0.09 14 10 14 2 0.3 6.92 2.02 70 4.8 3.45 13.86 33.8 95 5.99 5.29 16.27 51.39 35 1.43 11.91 8.7 7.2 2.42 4.2 2.91 3.86 5.6 11.0 14.8 1.82 5.5 2.91 3.23 181 2.25 1.48 0.3 5.2 0.68 2.6 4.4 0.3 10.95 51 11.48 10.22 0.77	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Mean SD Total Mean SD Total Weight 2.35 1.36 2164 2.35 1.12 245 5.5% 1.55 0.46 56 1.33 0.38 229 7.4% 82.41 8.02 28 11.89 2.76 15 0.0% 7.1 1.8 10 58 1.56 0.1% 2.50.8% 2.3 0.36 222 1.5 0.09 132 50.8% 1.4 10 1.4 2 0.3 0.0% 6.92 2.02 70 4.8 3.45 60 0.1% 1.3.86 33.8 95 5.99 5.29 30 0.0% 6.16.27 51.38 3181 2.55 1.48 29 0.2% 63.3 5.4 52 1.48 1.85 5 0.0% 32.44 32.82 40 13.82 6.53 33 0.0% 5.2 <t< td=""><td>Mean SD Total Meinth N. Fixed. 95% CI 2.35 1.36 2164 2.35 1.12 245 5.5% 0.00 [-0.15, 0.15] 1.55 0.46 56 1.33 0.38 229 7.4% 0.22 [0.09, 0.35] 82.41 8.02 26 11.89 2.76 15 0.0% 50.52 [47.14, 53.90] 7.1 1.8 10 58 1.56 0.0% 19.80 [10.07, 29.53] 2.9 0.36 222 1.5 0.09 132 50.8% 1.40 [1.35, 1.45] 1.4 10 14 2 0.3 10 0.0% 12.01 [6.76, 17.24] 8.7 7.2 20 4.4 2 20.0% 6.28 [2.67, 9.89] 2.91 3.23 181 2.55 1.48 29 0.2% 0.36 [6.36, 1.08] 63.3 5.4 52 1.4 1.65 25 0.0% 4.80 [0.50, 1.10] 10.52 0.68 2.4 0.3 <t< td=""></t<></td></t<>	Mean SD Total Meinth N. Fixed. 95% CI 2.35 1.36 2164 2.35 1.12 245 5.5% 0.00 [-0.15, 0.15] 1.55 0.46 56 1.33 0.38 229 7.4% 0.22 [0.09, 0.35] 82.41 8.02 26 11.89 2.76 15 0.0% 50.52 [47.14, 53.90] 7.1 1.8 10 58 1.56 0.0% 19.80 [10.07, 29.53] 2.9 0.36 222 1.5 0.09 132 50.8% 1.40 [1.35, 1.45] 1.4 10 14 2 0.3 10 0.0% 12.01 [6.76, 17.24] 8.7 7.2 20 4.4 2 20.0% 6.28 [2.67, 9.89] 2.91 3.23 181 2.55 1.48 29 0.2% 0.36 [6.36, 1.08] 63.3 5.4 52 1.4 1.65 25 0.0% 4.80 [0.50, 1.10] 10.52 0.68 2.4 0.3 <t< td=""></t<>

Figure 9. Subgroup analyses of the relationship between tumor necrosis factor- α and chronic obstructive pulmonary disease according to sample source.

Table 5. M	eta-regression	analysis	coefficients	for	TNF-α l	evels.
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Covariates	Coefficient	p	95% confidence interval			
Year	-0.44053	0.593	(-0.21028 to 0.12217)			
Region	-0.20124	0.843	(-2.25307 to 1.85058)			
BMI	-0.33315	0.724	(-2.23490 to 1.56859)			
Sample size	-0.000526	0.659	(-0.00293 to 0.00187)			
Smoking status	-0.203374	0.810	(-1.91399 to 1.50724)			
NOS	0.556458	0.886	(-7245434 to 0.83583)			
BMI, Body mass index; NOS, Newcastle-Ottawa Quality Assessment Scale; TNF- α , tumor necrosis factor-alpha						

Table 6.Sensitivity analysis.

Study	SMD (95% CI)	p Heterogeneity	I ²
Calikoglu 2004 ⁹	0.69 (0.62–0.76)	p<0.00001	97
Agusti 2012 ¹⁰	1.00 (0.91–1.08)	p<0.00001	97
Once 2010 ¹¹	0.70 (0.63–0.77)	p<0.00001	98
Kleniewska 2016 ¹²	0.70 (0.63–0.77)	p<0.00001	98
Rovina 2007 ¹³	0.69 (0.62–0.77)	p<0.00001	97
Gagnon 2014 ¹⁴	0.71 (0.64–0.79)	p<0.00001	98
Ben Anes 2017 ¹⁵	0.72 (0.64–0.79)	p<0.00001	98
Perez-de-Liano 2017 ¹⁶	0.68 (0.61–0.75)	p<0.00001	97
Foschino Barbaro 2007 ¹⁷	0.69 (0.62–0.77)	p<0.00001	97
Barreiro 2013 ¹⁸	0.71 (0.64–0.78)	p<0.00001	98
Beeh 2003 ¹⁹	0.71 (0.63–0.78)	p<0.00001	98
Di Stefano 2018 ²⁰	0.71 (0.64–0.78)	p<0.00001	98
Breyer 2011 ²¹	0.69 (0.62–0.77)	p<0.00001	98
Zhang 2016 ²²	0.72 (0.65–0.80)	p<0.00001	97
Dima 2010 ²³	0.70 (0.62–0.77)	p<0.00001	98
Kawayama 2016 ²⁴	0.71 (0.63–0.78)	p<0.00001	98
Gaki 2011 ²⁵	0.58 (0.50–0.65)	p<0.00001	97
Godoy 2003 ²⁶	0.71 (0.64–0.78)	p<0.00001	98
Hacievliyagil 2012 ²⁷	0.69 (0.62–0.76)	p<0.00001	97
Huertas 2010 ²⁸	0.69 (0.62-0.76)	p<0.00001	97
Ju 2011 ²⁹	0.70 (0.63–0.77)	p<0.00001	98
Karadag 2007 ³⁰	0.72 (0.64–0.79)	p<0.00001	98
Karadag 2008 ³¹	0.72 (0.64–0.79)	p<0.00001	98
Shin 2007 ³²	0.71 (0.64–0.79)	p<0.00001	98
Kythreotis 2008 ³³	0.69 (0.62–0.76)	p<0.00001	97
Liu 2009 ³⁴	0.69 (0.62–0.76)	p<0.00001	97
Huang 20162 ³⁵	0.68 (0.61–0.75)	p<0.00001	97
Moermans 2011 ³⁶	0.76 (0.69–0.83)	p<0.00001	97
Piehl-Aulin 2008 ³⁷	0.70 (0.62–0.77)	p<0.00001	98
Tan 2016 ³⁸	0.70 (0.63–0.77)	p<0.00001	97

(Continued)

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Table 6. (Continued)			
Study	SMD (95% CI)	p Heterogeneity	1 ²
Guiot 2017 ³⁹	0.72 (0.64–0.79)	p<0.00001	98
Sarioglu 201540	0.65 (0.58–0.73)	p<0.00001	97
Uzum 2013 ⁴¹	0.71 (0.64–0.79)	p<0.00001	97
Kosacka 2015 ⁴²	0.72 (0.64–0.80)	p<0.00001	97
Cheng 2008 ⁴³	0.59 (0.51–0.67)	p<0.00001	97
Valipour 200844	0.74 (0.64–0.81)	p<0.00001	97
Zhang 2010 ⁴⁵	0.70 (0.62–0.77)	p<0.00001	98
Vera 1996 ⁴⁶	1.19 (0.72–1.66)	p<0.00001	97
Soler 199947	1.25 (0.78–1.73)	p<0.00001	97
De Godoy 199648	1.25 (0.78–1.73)	p<0.00001	97
SMD, Standard mean difference; (CI, 95% confidence intervals		



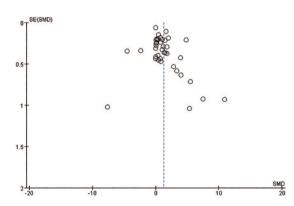


Figure 10. A funnel plot analysis of publication bias.

pulmonary inflammation.⁵⁴ Second, during inflammation processes, activated inflammatory cells and a variety of released inflammatory mediators, such as IL-8, IL-6, and TNF- α , can destroy lung structure and promote the inflammatory response of neutrophils.⁵⁵ Third, the elevated blood inflammatory factors might be explained by several previously proposed mechanisms, such as local pulmonary inflammation due to smoking, oxidative stress, and tissue hypoxia.⁵⁶

Due to the high heterogeneity, a subgroup analysis was then performed to minimize heterogeneity among the included studies. FEV_1 is the most widely used parameter for diagnosis and evaluation of treatment effect in severe COPD, and the current COPD staging system is based mainly on this parameter.8 Therefore, we subclassified the patients into two subgroups: FEV₁% >50% and FEV₁% <50% to perform subgroup analysis. The results showed that TNF- α level was elevated in COPD patients with both FEV₁% >50% and FEV₁% <50% compared with controls. Smoking is known to be one of the main causes of COPD; thus, a subgroup analysis based on smoking status was performed. We found a significant association between TNF-a level and COPD in participants with smoking history, but we failed to find this association in nonsmoking participants. This result was consistent with that of a study by Mosran and colleagues, who showed that, compared with non-COPD smokers, smokers with COPD had markedly higher levels of TNF- α ,⁵⁷ suggesting that smoking can further increase TNF- α levels. In addition, the level of TNF- α was also associated with COPD status, region of study, and BMI of participants. However, no association was found between TNF- α level and COPD if the mean age was less than 60 years.

Although our results reached the same conclusion as many studies, some other studies report different results. Schmidt-loanas and colleagues suggested there were no significant differences in the correlation between TNF- α levels and COPD exacerbation.⁵⁸ Monika and colleagues also did

not observe any obvious difference in serum TNF- α levels between COPD patients and controls.⁴² This inconsistency among studies could be explained by differences in study design; different COPD status of enrolled patients across the included studies, since early-stage COPD are insensitive to TNF- α ; and the inclusion of studies with different baseline characteristics.

Before we draw any firm conclusions, there are several limitations of this study that need to be considered. First, the significant heterogeneity in the present meta-analysis may limit generalization of the pooled results. Second, the methods for measuring TNF- α level were inconsistent. Third, since we limited the language of publication to English, we may have missed other related studies published in other languages. For example, the literature search for CNKI found several related studies in Chinese, but we excluded them from this study according to the exclusion criteria. Finally, the association between TNF- α level and patient quality of life was not evaluated due to the limited information available.

Conclusion

In this meta-analysis, a significant association between COPD and elevated TNF- α level was identified. These results encourage further exploration of the roles of TNF- α in COPD formation and development, and the potential of TNF- α as a novel biomarker and therapeutic target for COPD.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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