Association between serum tumour necrosis factor-α concentrations and chronic obstructive pulmonary disease

Xiao-feng Xiong[1], Jia Wei[1], Yi-hua Lin[2] and De-yun Cheng[1,*]

[1]Department of Respiratory Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan, China
[2]Department of Respiratory Medicine, the First Affiliated Hospital of Xiamen University, Xiamen, Fujian, China

Tumour necrosis factor-α (TNF-α) is an important pro-inflammatory cytokine and has been implicated to play a role in the systemic inflammation of patients with chronic obstructive pulmonary disease (COPD). We conducted a meta-analysis to assess the association between serum TNF-α concentration and COPD. PubMed and Embase were searched for eligible studies. Data were extracted and standard mean differences (SMDs) and 95% confidence intervals (CI) were calculated. Thirty-three studies were included in the meta-analysis. The serum TNF-α concentrations were higher in patients with stable COPD than healthy controls (SMD = 0.64 pg/ml, 95%CI 0.43, 0.86). COPD patients with normal to high body mass index (BMI) and low BMI had increased TNF-α concentration compared with healthy controls (SMD = 1.14 pg/ml, 95%CI 0.36, 1.92; SMD = 1.62 pg/ml, 95%CI 0.89, 2.35 respectively). There was notable significance in serum TNF-α level between underweight and normal weight COPD patients (SMD = 0.68, 95%CI 0.43, 0.92). The meta-analysis indicates that patients with stable COPD have higher serum TNF-α concentration than healthy controls, and the higher circulating TNF-α levels in COPD patients with weight loss may suggest its valuable role in the evaluation of systemic inflammatory responses in stable COPD patients.

Keywords: Chronic obstructive pulmonary disease, meta-analysis, tumour necrosis factor-α systemic inflammation.

CHRONIC obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. It is characterized by persistent airflow limitation that is usually progressive and associated with enhanced chronic inflammatory responses in the airways and lung to noxious particles or gases[1]. The presence of chronic inflammation in both airways and lung parenchyma in COPD is well-known. Furthermore, there is increasing evidence of systemic inflammation in patients with COPD. Weight loss, muscle wasting and tissue depletion are common features reported in COPD patients, and they are all related to systemic inflammation[2]. Since there is evidence that a number of different inflammatory cells and mediators play a role in the progress of COPD, tumour necrosis factor (TNF)-α has become a subject of considerable research at present. TNF-α is a pleiotropic cytokine classically described as playing a central role in the pathophysiology of COPD[3]. Moreover, it is involved in the development of muscular abnormalities resulting in loss of skeletal muscle mass and function[4]. An earlier study showed that circulating TNF-α levels are significantly higher in COPD patients with weight loss when compared to healthy controls, and that the elevated TNF-α levels were correlated with body mass index (BMI) in these patients[5]. A number of studies have also shown that patients with COPD have higher serum concentrations of TNF-α than healthy controls[6–9]. However, results from different studies are not consistent. Some studies showed that serum TNF-α concentration is not a good marker in COPD patients with weight loss and that it does not correlate with BMI[10,11]. Besides, most of the studies undertaken to evaluate this potential relationship are small in size[12,13] and may lack sufficient statistical data to address this issue adequately. So it still remains controversial whether serum TNF-α concentrations are higher in COPD patients than in controls and whether serum TNF-α levels are correlated with BMI in patients with COPD. In an effort to overcome these limitations and have a better understanding on the relationship between serum TNF-α concentrations and COPD, a systemic review and meta-analysis is necessary.

Methods

Identification of relevant studies

Two investigators (X.X. and J.W.) independently searched PubMed, Embase and the Cochrane Database until March 2015 to identify potentially relevant articles. Disagreements were resolved through discussion or adjudicated by a third author (Y.L.). The following search terms were used both in keywords and free text words: ((((((((('Pulmonary Disease, Chronic Obstructive'

*For correspondence. (e-mail: chengdeyunscu@163.com)

[Mesh]) or (COPD[Title/Abstract]) or (((((((Chronic Obstructive Pulmonary Disease[Title/Abstract]) or (COAD[Title/Abstract]) or (Chronic Obstructive Airway Disease[Title/Abstract]) or (Chronic Obstructive Lung Disease[Title/Abstract]) or (Chronic Airflow Obstructions [Title/Abstract])))))))) AND ((((((((((Tumour Necrosis Factor-alpha[Mesh]) or (Cachectin-Tumour Necrosis Factor[Title/Abstract]) or (Cachectin Tumour Necrosis Factor[Title/Abstract]) or (Cachectin Tumour Necrosis Factor) or (Cachectin Tumour Necrosis Factor[Title/Abstract]) or (TNF alpha[Title/Abstract]) or TNF-alpha [Title/Abstract]) or Tumour Necrosis Factor[Title/Abstract]) or Tumour Necrosis Factor Ligand Superfamily Member 2[Title/Abstract]) or TNF Superfamily, Member 2[Title/Abstract])) AND "HUMANS" [Mesh]). TNF-α levels in the blood were retrieved manually. There was no restriction on languages and references for all selected articles were retrieved to identify other relevant studies.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) Prospective or retrospective observational studies reporting the serum concentrations of TNF-α. (2) COPD patients who met the criteria of the American Thoracic Society (ATS) or European Respiratory Society (ERS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD). (3) Healthy controls with no medical illness or abnormalities.

Exclusion criteria were as follows: (1) Patients who were in an acute phase or hospitalized. (2) Patients with a history or diagnosis of asthma, allergy or other respiratory diseases other than COPD. (3) Articles with no original data.

Data extraction

The data were extracted by two investigators (X.X. and J.W.) independently and a consensus was reached on all items. Any disagreement was resolved as described above. The following data were extracted: first author, year of publication, original country, sample size, age, BMI, smoking status, GOLD stages of cases, mean value, SD, SEM and 95% CI of both patients with COPD and healthy subjects. The SEM or 95% CI was transformed into SD using statistical formulas.

Statistical analysis

All the statistics was analysed using Review Manager (version 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 software (Stata Corp LP, College Station, TX, USA). Weighted mean differences (WMDs) were selected to combine statistics. If the difference in mean values was too large or resulted in large heterogeneity, then the standard mean differences (SMDs) were selected. The I^2 statistic was used for quantifying heterogeneity. $I^2 < 25\%$, 25–75% and >75% were considered to indicate low, moderate and high heterogeneity[14].

If the *P*-value for heterogeneity was >0.05, which showed low heterogeneity ($I^2 < 25\%$), the fixed-effects model was selected. Otherwise, the random-effects model was applied[15]. A two-tailed *Z*-test was performed to statistically assess differences between healthy subjects and a disease stage, and $P < 0.05$ was considered statistically significant. In order to assess the BMI effects, subgroup analyses were performed according to the BMI value (COPD with BMI ≥ 20 subgroup and COPD with BMI < 20 subgroup). Sensitivity analysis was performed by removing one study each time to see whether the results of the rest would be affected. Egger's test and funnel plot were used to assess the publication bias[16].

Results

Characteristics of the studies

We identified 832 relevant studies that fit our search strategy. Figure 1 shows the procedure for identifying and selecting eligible studies. Among all the potential studies, 45 duplicate records were removed, leaving 787 articles for screening. Furthermore, 676 articles were excluded by screening titles and abstracts. Two articles were not accessible and we only got 111 for full-text

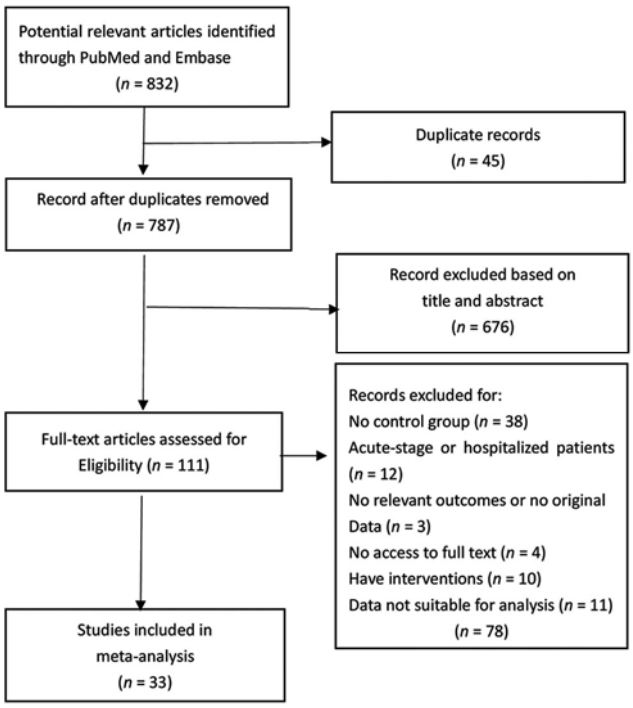

Figure 1. Flow chart of study identification, inclusion and exclusion.

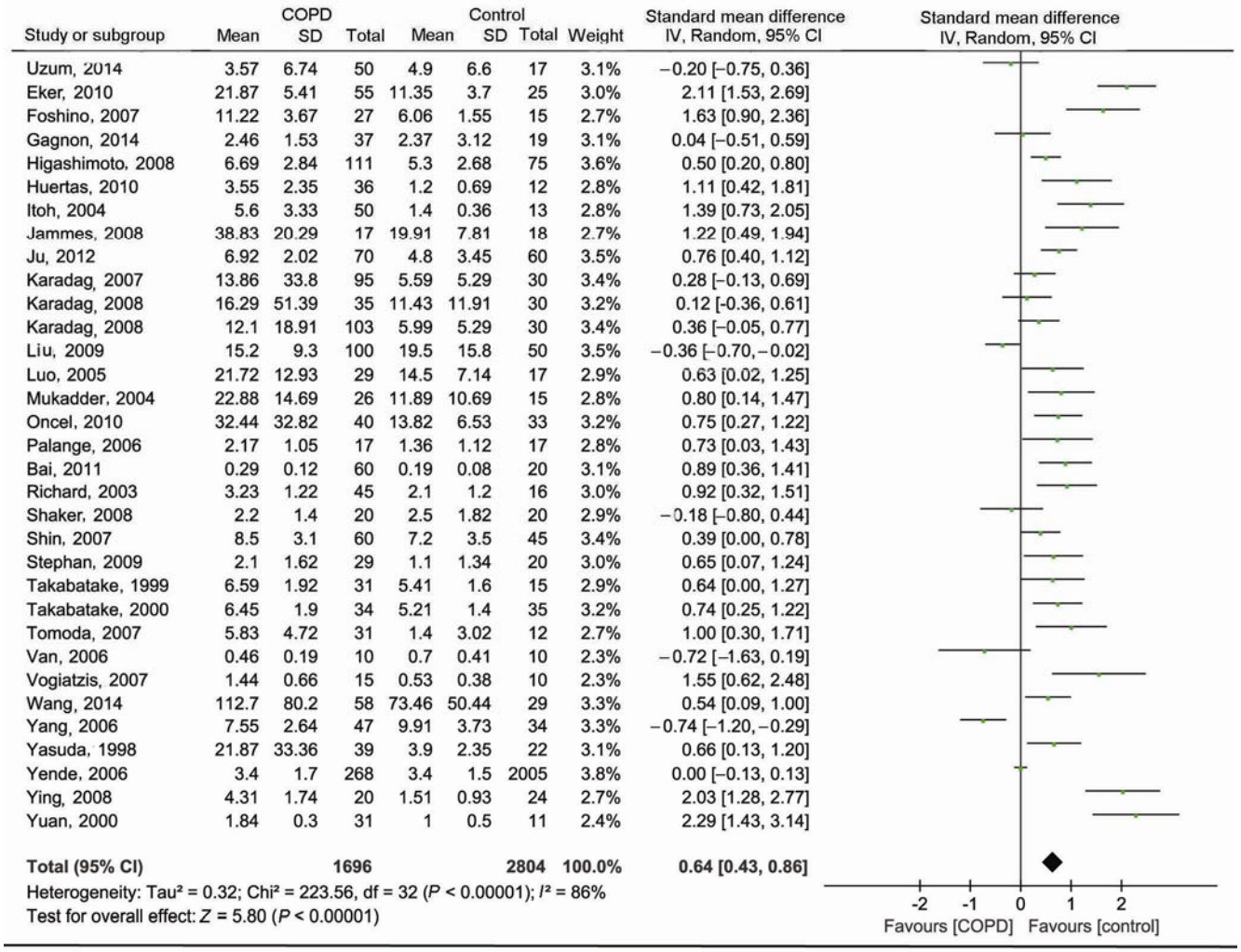

Figure 2. Forest plot of meta-analysis of 33 studies investigating the association between serum tumour necrosis factor-α (TNF-α) concentration and COPD, using a random-effects model. COPD, Chronic obstructive pulmonary disease; SD, Standard difference; SMD, Standard mean difference; CI, Confidence interval. IV, Inverse variance.

reading. After reading the full text, 78 articles were excluded according to our exclusion criteria. Finally, a total of 33 articles were included for our systematic review and meta-analysis[6–9,11,17–44].

Overall meta-analysis

Twelve articles contained subgroup analysis either in COPD patients or healthy controls, and we combined these data using the combination formula wherever possible. The statistical data which could not be combined was regarded as separate studies. Eventually, a total of 33 studies which contained 1696 stable COPD patients and 2804 healthy controls was included. The methodological design in different studies was not the same; therefore, the SMD was selected for quantitative analysis. The studies showed a positive result that the serum levels of TNF-α were higher in stable COPD patients than healthy controls (SMD = 0.64 pg/ml, 95% CI 0.43, 0.86, $P < 0.00001$; $I^2 = 86\%$, $P < 0.00001$; random effect model, Figure 2)[6–9,11,17–44].

Subgroup analysis by BMI value

Twelve studies had subgroups according to smoking status, BMI and severity of COPD. We only evaluated TNF-α levels by BMI in COPD. BMI was calculated by dividing the weight of the patient by the height squared (weight/height^2) using the Outlet index. A BMI of 20 or less was considered low. On the contrary, a BMI of 20 or more was considered normal to high. Seven studies showed data including COPD patients with underweight (BMI < 20) and normal weight (BMI ≥ 20)[9,20,22,24,29,38,41]. We compared COPD of normal weight and underweight patients with healthy controls respectively. Both demonstrated that stable COPD patients with normal to high,

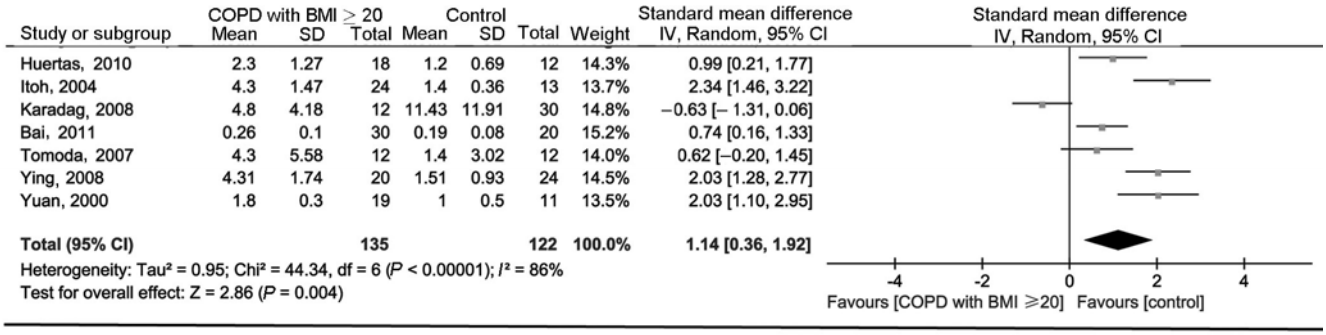

Figure 3. Forest plot of subgroup studies in the meta-analysis investigating the serum TNF-α concentration between COPD patients with normal to high body mass index (BMI) and healthy control, using a random-effects model.

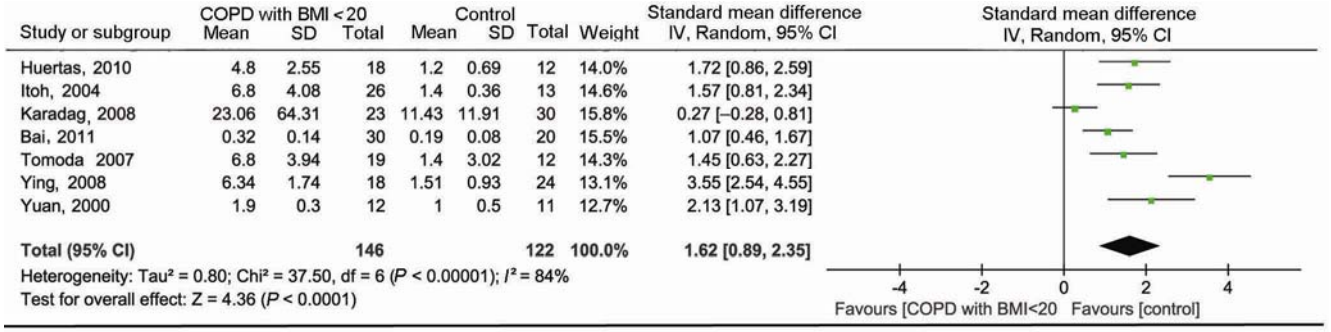

Figure 4. Forest plot of subgroup studies in the meta-analysis investigating the serum TNF-α concentration between COPD patients with low BMI and healthy control, using a random-effects model.

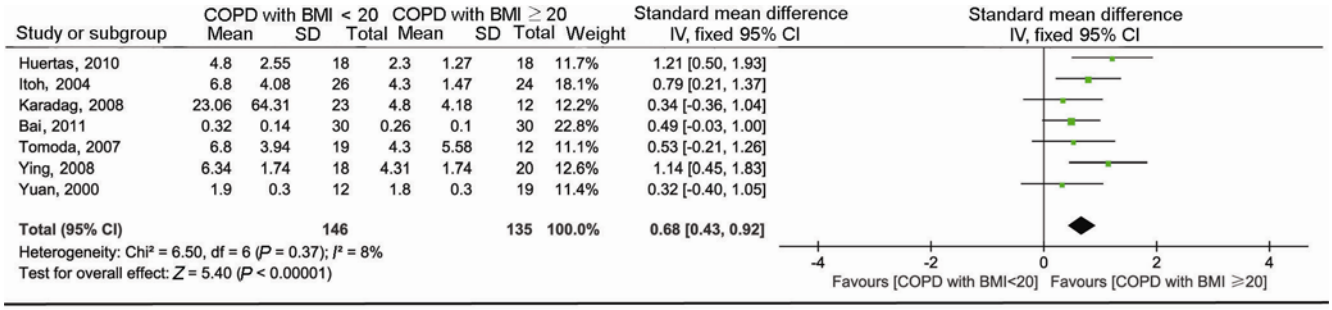

Figure 5. Forest plot of subgroup studies in the meta-analysis investigating the serum TNF-α concentration between COPD patients with low BMI and normal to high BMI, using a fixed-effects model.

and low BMI had increased TNF-α concentration compared with healthy controls (SMD = 1.44 pg/ml, 95% CI 0.36, 1.92, $P = 0.004$; $I^2 = 86\%$, $P < 0.00001$; SMD = 1.62, 95% CI 0.89, 2.35, $P < 0.0001$; $I^2 = 84\%$, $P < 0.00001$, random effect model respectively; Figures 3 and 4). Another subgroup analysis compared COPD patients with BMI ≥ 20 and BMI < 20; a notable significance in serum TNF-α level was found between them (SMD = 0.68, 95% CI 0.43, 0.92, $P < 0.0001$; $I^2 = 8\%$, $P < 0.00001$, fixed-effect model).

Sensitivity analysis

We performed a sensitivity analysis for the statistically significant result. Among the overall studies and subgroups, the observed significant result was not materially altered after sequentially excluding each study.

Heterogeneity and publication bias

Egger's test showed a publication bias in the overall meta-analysis ($P < 0.00001$) and group of COPD with low BMI versus healthy controls ($P = 0.006$); the shape of the funnel plot was asymmetrical. This may be explained by the presence of a language bias, inflated estimates by a flawed methodological design in smaller studies, and a lack of small trials with opposite results. However, there was no significant evidence of publication bias among COPD with normal to high BMI versus controls ($P = 0.201$), and COPD with low BMI versus normal to high BMI ($P = 0.729$).

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

Study (first author, year)	Country	Age (mean/range)		Numbers		Serum TNF-α levels (means ± SD; pg/ml)		Smoking status of subjects		BMI of cases
		Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	
Gagnon, 2014	Canada	65	62	37	19	2.46 ± 1.53	2.37 ± 3.12	≥15 pack-years	≥15 pack-years	27 ± 4
Wang, 2014	China	73.1	74.5	58	29	112.7 ± 80.20	73.46 ± 50.44	Mixed	Mixed	Not mentioned
Uzum, 2014.	Turkey	66.08	50.2	50	17	3.57 ± 6.73	4.9 ± 6.6	Mixed	Non-smokers	19.44 ± 1.65
Bai, 2011	China	66.5	58.4	60	20	0.29 ± 0.12	0.19 ± 0.08	Mixed	Mixed	24.8 ± 3.5
Ju, 2012	China	65.17	63.98	70	60	6.92 ± 2.02	4.80 ± 3.45	Ex-smokers	Smokers	19.36 ± 3.31
Eker, 2010	Turkey	64.47	63.84	55	25	21.87 ± 5.41	17.35 ± 3.7	Mixed	Non-smokers	24.034 ± 4.2
Huertas, 2010	Italy	68.8	63	36	12	3.35 ± 2.35	1.2 ± 0.69	Mixed	Mixed	24 ± 4.77
Oncel, 2010	Turkey	62.8	61.8	40	33	13.44 ± 32.82	13.82 ± 6.53	Mixed	Mixed	Not mentioned
Liu, 2009	China	69.1	61.9	100	50	15.2 ± 9.3	19.5 ± 15.8	≥10 Pack-years	Smokers	23.1 ± 3.9
Stephan, 2009	UK	64	58	29	20	2.1 ± 1.61	1.1 ± 1.34	Mixed	Mixed	Not mentioned
Jammes, 2008	France	53	48	17	18	36.83 ± 20.29	19.91 ± 7.81	Mixed	Mixed	26 ± 4
Ying, 2008	China	69.75	67.7	38	24	5.27 ± 2	1.51 ± 0.19	Mixed	Mixed	21.22 ± 11.52
Karadag, 2008	Turkey	65.6	63.2	35	30	16.27 ± 51.39	11.43 ± 11.91	Mixed	Mixed	24.06 ± 5.41
Karadag, 2008	Turkey	65.54	64.1	83	30	11.43 ± 11.91	5.99 ± 5.29	Mixed	Mixed	25.25 ± 4.84
Higashimoto, 2008	Japan	74.9	64.5	111	75	6.97 ± 2.84	5.30 ± 2.68	Mixed	Mixed	20.2 ± 3.16
Shaker, 2008	Denmark	64	58	20	20	2.2 ± 1.4	2.5 ± 1.81	≥20 Pack-years	≥20 Pack-years	24.1 ± 3.4
Foshino, 2007	UK	52	49	27	15	11.22 ± 3.67	6.06 ± 1.55	Ex-smokers	Ex-smokers	21.1 ± 2.4
Vogiatzis, 2007	Greece	66	61	15	10	1.44 ± 0.66	0.53 ± 0.38	Not mentioned	Not mentioned	25.9 ± 2.7
Tomoda, 2007	Japan	70.92	69.3	31	12	5.83 ± 1.43	1.4 ± 0.2	Not mentioned	Not mentioned	20.06 ± 3.05
Karadag, 2007	Turkey	63.5	61.1	95	30	13.86 ± 33.80	5.99 ± 5.29	Mixed	Mixed	25.34 ± 4.98
Shin, 2007	Korean	63.6	66.5	60	45	8.5 ± 3.1	7.2 ± 3.5	Not mentioned	Not mentioned	21.9 ± 3.0
Palange, 2006	Italy	68	63	18	12	2.17 ± 1.05	1.36 ± 1.12	Mixed	Non-smokers	26.8 ± 4.2
Van, 2006	The Netherlands	65.5	59	20	10	0.43 ± 0.26	0.7 ± 0.13	Former smokers	Non-smokers	23.5 ± 5.56
Yende, 2006	USA	73.6	73.2	268	2005	3.4 ± 1.7	3.4 ± 1.5	Mixed	Mixed	25.4 ± 4.7
Yang, 2006	China	67.56	64.8	83	34	7.55 ± 2.64	9.91 ± 3.37	Not mentioned	Not mentioned	22.76 ± 2.95
Luo, 2005	China	70	71	29	17	21.72 ± 12.93	14.50 ± 7.14	Not mentioned	Not mentioned	18.5 ± 3.2
Mukadder, 2004	Turkey	58.26	54.73	26	15	22.88 ± 2.88	11.89 ± 2.76	Not mentioned	Not mentioned	24.54 ± 0.60
Richard, 2003	Canada	67.4	65	45	16	3.23 ± 1.22	3.45 ± 0.23	Mixed	Ex-smokers	28 ± 1
Itoh, 2004	Japan	71	69	31	13	6.8 ± 0.9	1.4 ± 0.1	Mixed	Mixed	20.98 ± 3.88
Takabatake, 2000	Japan	71.9	68.6	34	35	6.45 ± 1.90	5.21 ± 1.40	Not mentioned	Not mentioned	18 ± 2.5
Yuan, 2000	China	67.3	62.9	31	11	1.84 ± 0.30	1 ± 0.5	Mixed	Non-smokers	21.08 ± 3.56
Takabatake, 1999	Japan	72.5	69.8	31	15	6.59 ± 1.92	5.41 ± 1.6	Not mentioned	Not mentioned	18.1 ± 2.7
Yasuda, 1998	Japan	66	42	39	22	21.87 ± 33.36	3.9 ± 0.5	Mixed	Mixed	Not mentioned

The word ‘mixed’ means that the subjects (both cases and controls) are composed of smokers and non-smokers. BMI, Body mass index.

Discussion

To our knowledge, the present study is the most comprehensive meta-analysis to assess the relationship between serum TNF-α concentration and stable COPD. The meta-analysis demonstrates that serum TNF-α level is significantly increased in stable COPD patients compared to healthy controls and BMI is the dominant determinant of circulating TNF-α levels in stable COPD patients.

TNF-α is produced from several cells, including T lymphocytes, mast cells and cells of the airway epithelium, which leads to a shift towards catabolism, resulting in muscle wasting and cachexia[45,46]. Some observational studies indicated that TNF-α levels were significantly elevated in the peripheral blood of patients with COPD[6–9] and it was associated with BMI[9,20,22,24,29,38,41]. On the other hand, some studies showed no such statistical significance[11,17,18]. Therefore, we performed this comprehensive meta-analysis that included the latest data, to examine the association between TNF-α levels and stable COPD. Our findings demonstrated that concentrations of serum TNF-α were higher in stable COPD than healthy controls and the serum TNF-α concentrations may have an association with BMI of COPD patients.

The pooled analysis of 23 studies showed that the levels of serum TNF-α were significantly elevated in COPD patients compared to healthy subjects, which suggests that systemic inflammatory activity exists in stable COPD patients. Ten studies showed no significant difference in the values of TNF-α between patients and controls[11,17,18,23,30,33,35,36,39,40], which differs from our results. A previous study showed that TNF-α levels are not increased in GOLD 2–4 COPD compared to smokers with normal lung function[47], which is not congruent with our findings. Shaker *et al.*[23] reported that TNF-α levels are not higher in patients with COPD compared to smokers and non-smokers. Shin *et al.*[30] also found that the serum TNF-α levels were higher in stable COPD patients than the controls, but there was no statistical difference. Obvious heterogeneity was observed in our study, which may be explained by methodological differences among the primary studies, and gender differences and difference in disease severity in the included population.

Thus, TNF-α has been shown to play a central role in muscle wasting and weight loss seen in COPD patients[5,42,48]. The present meta-analysis involved seven studies which compared the serum TNF-α concentrations between COPD patients with lower BMI, and normal to high BMI with healthy subjects. The results show that stable COPD patients with low BMI have increased TNF-α concentrations compared with healthy controls. When compared, there is notable significance in serum TNF-α levels between COPD patients with BMI $\geq$ 20 and those with BMI < 20. These findings demonstrate that BMI is the dominant determinant of circulating TNF-α levels in stable COPD patients, and serum concentrations of the cytokine are higher in COPD patients with weight loss. Furthermore, BMI has been shown to be an independent risk factor for mortality in COPD and has been associated with disease severity[49,50]. Increased skeletal muscle apoptosis has also been shown to be associated with a lower BMI and reduced exercise tolerance[51]. Moreover, a low BMI has been demonstrated to be a significant predictor of increased mortality[50]. So, it is a meaningful result which highlights the early systemic inflammation in stable COPD patients.

The present meta-analysis indicates that the serum of TNF-α levels are increased in underweight COPD patients compared with those with normal weight, and may be a better marker of early inflammation and associated comorbidities. Since TNF-α participates directly in inflammation, it may be regarded as a marker of low-grade systemic inflammation and an additional parameter for risk assessment together with smoking, number of exacerbations, hospitalization rate and mortality rate. More evidence of early interventions might be obtained by synthesizing all these parameters, thus decreasing the risk of possible complications.

There are certain limitations to the present study. First, publication bias has been detected in our study, but it is difficult for us to adjust the impact of these confounding factors such as age, gender and smoking status, which could influence the concentrations of TNF-α. Also, the control subjects are not matched for these confounders. It is important to minimize selection bias in future studies. Secondly, some studies had subgroup analysis and we used formulas to calculate these data without considering the confounding factors, which may have led to lower statistical power. Thirdly, some studies were of a small scale, which may affect the power to explore the real association. Lastly, nearly all the included studies were conducted in different institutions. Thus different methods/kits may have been used for measuring the serum TNF-α levels, and the detection limit varied, which could inconspicuously influence the data.

Conclusion

The present meta-analysis shows that stable COPD patients have higher serum TNF-α concentration than healthy controls, and the circulating TNF-α level is associated with the BMI value. Serum concentrations of cytokine are high in COPD patients with weight loss, which suggests that circulating TNF-α remains regulated physiologically in stable COPD and varies with the nutritional status. The higher circulating TNF-α levels in COPD patients with weight loss may suggest its valuable role in the evaluation of systemic inflammatory responses in stable COPD patients. These findings may partly explain the high prevalence of systemic complications such as cachexia, anorexia and atherosclerosis of COPD. In this

regard, more studies with larger sample sizes and those including different stages to evaluate the serum TNF-α levels and disease severity are needed to better identify the role of serum TNF-α. Whether early interventions would decrease the serum TNF-α levels and modify the risk of complications in COPD should also be determined in future studies.

1. Global initiative for chronic obstructive lung disease. Gold workshop report: Global strategy for diagnosis, management and prevention of COPD (updated 2015); http://www.Goldcopd.Org/guidelines/guidelines-global-strategy-for-diagnosis-management
2. Davidson, W. J., Verity, W. S., Traves, S. L., Leigh, R., Ford, G. T. and Eves, N. D., Effect of incremental exercise on airway and systemic inflammation in patients with COPD. *J. Appl. Physiol*., 2012, **112**, 2049–2056.
3. Matera, M. G., Martuscelli, E. and Cazzola, M., Pharmacological modulation of beta-adrenoceptor function in patients with coexisting chronic obstructive pulmonary disease and chronic heart failure. *Pulm. Pharmacol. Therap*., 2010, **23**, 1–8.
4. Bhatnagar, S., Panguluri, S. K., Gupta, S. K., Dahiya, S., Lundy, R. F. and Kumar, A., Tumour necrosis factor-alpha regulates distinct molecular pathways and gene networks in cultured skeletal muscle cells. *PLoS ONE*, 2010, **5**, e13262.
5. de Godoy, I., Donahoe, M., Calhoun, W. J., Mancino, J. and Rogers, R. M., Elevated TNF-alpha production by peripheral blood monocytes of weight-losing COPD patients. *Am. J. Resp. Crit. Care Med*., 1996, **153**, 633–637.
6. Uzum, A. K., Aydin, M. M., Tutuncu, Y., Omer, B., Kiyan, E. and Alagol, F., Serum ghrelin and adiponectin levels are increased but serum leptin level is unchanged in low weight chronic obstructive pulmonary disease patients. *Eur. J. Intern. Med*., 2014, **25**, 364–369.
7. Eker, S., Ayaz, L., Tamer, L. and Ulubas, B., Leptin, visfatin, insulin resistance, and body composition change in chronic obstructive pulmonary disease. *Scand. J. Clin. Lab. Invest*., 2010, **70**, 40–44.
8. Oncel, C., Baser, S., Cam, M., Akdag, B., Taspinar, B. and Evyapan, F., Peripheral neuropathy in chronic obstructive pulmonary disease. *COPD*, 2010, **7**, 11–16.
9. Huertas, A. *et al.*, Bone marrow-derived progenitors are greatly reduced in patients with severe COPD and low-bmi. *Respir. Physiol. Neurobiol*., 2010, **170**, 23–31.
10. Karadag, F., Karul, A. B., Cildag, O., Altun, C. and Gurgey, O., Determinants of BMI in patients with COPD. *Respirology*, 2004, **9**, 70–75.
11. Liu, S. F., Chin, C. H., Wang, C. C. and Lin, M. C., Correlation between serum biomarkers and BODE index in patients with stable COPD. *Respirology*, 2009, **14**, 999–1004.
12. Koechlin, C., Couillard, A., Cristol, J. P., Chanez, P., Hayot, M., Le Gallais, D. and Prefaut, C., Does systemic inflammation trigger local exercise-induced oxidative stress in COPD? *Eur. Respir. J*., 2004, **23**, 538–544.
13. Rabinovich, R. A. *et al.*, Increased tumour necrosis factor – plasma levels during moderate-intensity exercise in COPD patients. *Eur. Respir. J*., 2003, **21**, 789–794.
14. Higgins, J. P. and Thompson, S. G., Quantifying heterogeneity in a meta-analysis. *Stat. Med*., 2002, **21**, 1539–1558.
15. DerSimonian, R. and Laird, N., Meta-analysis in clinical trials. *Control Clin. Trials*, 1986, **7**, 177–188.
16. Egger, M., Davey Smith, G., Schneider, M. and Minder, C., Bias in meta-analysis detected by a simple graphical test. *BMJ*, 1997, **315**, 629–634.
17. Gagnon, P. *et al.*, Preserved function and reduced angiogenesis potential of the quadriceps in patients with mild COPD. *Respiratory Res*., 2014, **15**, 4.
18. Wang, X. R. *et al.*, Increased serum levels of lipocalin-1 and -2 in patients with stable chronic obstructive pulmonary disease. *Int. J. Chronic Obstr. Pulm. Dis*., 2014, **9**, 543–549.
19. Ju, C. R. and Chen, R. C., Serum myostatin levels and skeletal muscle wasting in chronic obstructive pulmonary disease. *Respir. Med*., 2012, **106**, 102–108.
20. Bai, P., Sun, Y., Jin, J., Hou, J., Li, R., Zhang, Q. and Wang, Y., Disturbance of the opg/rank/rankl pathway and systemic inflammation in COPD patients with emphysema and osteoporosis. *Respir. Res*., 2011, **12**, 157.
21. von Haehling, S., Hopkinson, N. S., Polkey, M. I., Niethammer, M., Anker, S. D. and Genth-Zotz, S., Elevated TNF-α production in whole blood in patients with severe COPD: the potential link to disease severity. *Wien. Klin. Wochenschr*., 2009, **121**, 303–308.
22. Ying, B. W. *et al.*, Plasma ghrelin levels and weight loss in chinese uygur patients with chronic obstructive pulmonary disease. *J. Int. Med. Res*., 2008, **36**, 1371–1377.
23. Shaker, S. B. *et al.*, Identification of patients with chronic obstructive pulmonary disease (COPD) by measurement of plasma biomarkers. *Clin. Respir. J*., 2008, **2**, 17–25.
24. Karadag, F., Kirdar, S., Karul, A. B. and Ceylan, E., The value of c-reactive protein as a marker of systemic inflammation in stable chronic obstructive pulmonary disease. *Eur. J. Int. Med*., 2008, **19**, 104–108.
25. Karadag, F., Karul, A. B., Cildag, O., Yilmaz, M. and Ozcan, H., Biomarkers of systemic inflammation in stable and exacerbation phases of COPD. *Lung*, 2008, **186**, 403–409.
26. Jammes, Y., Steinberg, J. G., Ba, A., Delliaux, S. and Bregeon, F., Enhanced exercise-induced plasma cytokine response and oxidative stress in COPD patients depend on blood oxygenation. *Clin. Physiol. Funct. Imaging*, 2008, **28**, 182–188.
27. Higashimoto, Y. *et al.*, Systemic inflammation in chronic obstructive pulmonary disease and asthma: similarities and differences. *Respirology*, 2008, **13**, 128–133.
28. Vogiatzis, I., Stratakos, G., Simoes, D. C., Terzis, G., Georgiadou, O., Roussos, C. and Zakynthinos, S., Effects of rehabilitative exercise on peripheral muscle TNF-α, IL-6, IGF-I and MyaD expression in patients with COPD. *Thorax*, 2007, **62**, 950–956.
29. Tomoda, K., Yoshikawa, M., Itoh, T., Tamaki, S., Fukuoka, A., Komeda, K. and Kimura, H., Elevated circulating plasma adiponectin in underweight patients with COPD. *Chest*, 2007, **132**, 135–140.
30. Shin, K. C., Chung, J. H. and Lee, K. H., Effects of TNF-alpha and leptinon weight loss in patients with stable chronic obstructive pulmonary disease. *Kor. J. Intern. Med*., 2007, **22**, 249–255.
31. Karadag, F., Ozcan, H., Karul, A. B., Ceylan, E. and Cildag, O., Correlates of erectile dysfunction in moderate-to-severe chronic obstructive pulmonary disease patients. *Respirology*, 2007, **12**, 248–253.
32. Foschino Barbaro, M. P., Carpagnano, G. E., Spanevello, A., Cagnazzo, M. G. and Barnes, P. J., Inflammation, oxidative stress and systemic effects in mild chronic obstructive pulmonary disease. *Int. J. Immunopathol. Pharmacol*., 2007, **20**, 753–763.
33. Yende, S. *et al.*, Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. *Thorax*, 2006, **61**, 10–16.
34. Yang, Y. M., Sun, T. Y. and Liu, X. M., The role of serum leptin and tumour necrosis factor-alpha in malnutrition of male chronic obstructive pulmonary disease patients. *Chin. Med. J*., 2006, **119**, 628–633.
35. Van Helvoort, H. A., Heijdra, Y. F., Thijs, H. M., Vina, J., Wanten, G. J. and Dekhuijzen, P. N., Exercise-induced systemic effects in muscle-wasted patients with COPD. *Med. Sci. Sports Exercise*, 2006, **38**, 1543–1552.
36. Palange, P. *et al.*, Circulating haemopoietic and endothelial progenitor cells are decreased in COPD. *Eur. Respir. J*., 2006, **27**, 529–541.

37. Luo, F. M., Liu, X. J., Li, S. Q., Wang, Z. L., Liu, C. T. and Yuan, Y. M., Circulating ghrelin in patients with chronic obstructive pulmonary disease. *Nutrition*, 2005, **21**, 793–798.
38. Itoh, T. *et al.*, Elevated plasma ghrelin level in underweight patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med*., 2004, **170**, 879–882.
39. Calikoglu, M. *et al.*, Leptin and TNF-alpha levels in patients with chronic obstructive pulmonary disease and their relationship to nutritional parameters. *Respir. Int. Rev. Thorac. Dis*., 2004, **71**, 45–50.
40. Debigare, R., Marquis, K., Cote, C. H., Tremblay, R. R., Michaud, A., LeBlanc, P. and Maltais, F., Catabolic/anabolic balance and muscle wasting in patients with COPD. *Chest*, 2003, **124**, 83–89.
41. Yuan, Y., Wang, Z. and Liu, C., [Preliminary investigation of effect of serum leptin on nutritional state of copd patients]. *Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chin. J. Tuberculosis Respir. Dis*., 2000, **23**, 292–295.
42. Takabatake, N. *et al.*, Circulating levels of soluble FAS ligand and soluble FAS in patients with chronic obstructive pulmonary disease. *Respir. Med*., 2000, **94**, 1215–1220.
43. Takabatake, N. *et al.*, Circulating leptin in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med*., 1999, **159**, 1215–1219.
44. Yasuda, N. *et al*., An increase of soluble FAS, an inhibitor of apoptosis, associated with progression of COPD. *Resp. Med*., 1998, **92**, 993–999.
45. Agusti, A. G., Noguera, A., Sauleda, J., Sala, E., Pons, J. and Busquets, X., Systemic effects of chronic obstructive pulmonary disease. *Eur. Res. J*., 2003, **21**, 347–360.
46. Wouters, E. F., Chronic obstructive pulmonary disease. 5: systemic effects of COPD. *Thorax*, 2002, **57**, 1067–1070.
47. Dickens, J. A., Miller, B. E., Edwards, L. D., Silverman, E. K., Lomas, D. A. and Tal-Singer, R., COPD association and repeatability of blood biomarkers in the eclipse cohort. *Respir. Res*., 2011, **12**, 146.
48. Di Francia, M., Barbier, D., Mege, J. L. and Orehek, J., Tumour necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med*., 1994, **150**, 1453–1455.
49. Landbo, C., Prescott, E., Lange, P., Vestbo, J. and Almdal, T. P., Prognostic value of nutritional status in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med*., 1999, **160**, 1856–1861.
50. Schols, A. M. W. J., Slangen, J., Volovics, L. and Wouters, E. F. M., Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med*., 1998, **157**, 1791–1797.
51. Agusti, A. G. *et al.*, Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med*., 2002, **166**, 485–489.

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