

# Efficacy of Vitamin C Supplementation on Chronic Obstructive Pulmonary Disease (COPD): A Systematic Review and Meta-Analysis

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**Background:** In recent years, the pleiotropic roles of antioxidants have drawn extensive attention in various diseases. Vitamin C is a well-known antioxidant, and it has been used to treat patients with chronic obstructive pulmonary disease (COPD). This systematic review and meta-analysis aim to demonstrate the impact of vitamin C supplementation in patients with COPD.

**Methods:** We searched PubMed, Embase, Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI), SinoMed, Wanfang, and China Science and Technology Journal Database (cqvip.com) for eligible randomized controlled trials (RCTs) from their respective inception to May 18<sup>th</sup>, 2021, by using the searching terms of COPD, vitamin C, and RCTs. A meta-analysis was performed to evaluate the effects of vitamin C on lung function, antioxidant levels, and nutritional conditions in COPD patients by using Review Manager (Version 5.4).

**Results:** Ten RCTs including 487 participants were eligible for our study. Meta-analysis results showed that vitamin C supplementation ( $\geq 400$  mg/day) can significantly improve the forced expiratory volume in one second as a percentage (FEV1%) in COPD (SMD:1.08, 95% CI:0.03, 2.12,  $P=0.04$ ). Moreover, vitamin C supplementation significantly improved the ratio of forced expiratory volume in 1 second and forced vital capacity (FEV1/FVC) (WMD:0.66, 95% CI: 0.26, 1.06,  $P=0.001$ ), vitamin C level in serum (SMD:0.63, 95% CI: 0.02, 1.24,  $P=0.04$ ) and glutathione (GSH) level in serum (SMD:2.47, 95% CI: 1.06, 3.89,  $P=0.0006$ ). While no statistically significant difference was observed in body mass index (BMI), fat-free mass index (FFMI), vitamin E level and superoxide dismutase (SOD) level in serum.

**Conclusion:** Vitamin C supplementation could increase the levels of antioxidation in serum (vitamin C and GSH) and improve lung function (FEV1% and FEV1/FVC), especially in patients treated with vitamin C supplementation greater than 400 mg/day. However, further prospective studies are needed to explore the role of vitamin C in improving nutritional status.

**Keywords:** vitamin C, COPD, RCTs, lung function, meta-analysis

## Introduction

Chronic obstructive pulmonary disease (COPD) is now the third leading cause of death worldwide.<sup>1</sup> The increasing social and economic burdens associated with it make its comprehensive control a major public health goal.<sup>2,3</sup> COPD is characterized by airflow limitation and persistent respiratory symptoms. These symptoms are the consequences of airway and/or alveolar abnormalities, which are usually caused by smoking gases or significant exposure to noxious particles.<sup>1</sup> Oxidative stress is defined as the disturbance of the oxidant/antioxidant balance, and it has been suggested to play

a critical role in the pathogenesis of COPD.<sup>4–6</sup> Antioxidants are the first line of defense against oxidants by preventing the lung from the delirious consequences resulting from various oxidants and/or reactive oxygen.<sup>7</sup> Antibiotics, systemic corticosteroids and short-acting bronchodilators are the three commonly used treatments to manage exacerbations of COPD, but no evidence supports the notion that these medications work against oxidative stress. Meanwhile, most COPD patients respond poorly to cortices due to the steroid refractoriness in their body.<sup>8</sup>

Vitamin C is a widely consumed natural supplement and is well known for its antioxidant properties.<sup>9</sup> It exerts its antioxidant function by keeping both transient oxidants, such as  $O_2^{\bullet-}$  and nitric oxide, and long-lived oxidants, such as semiquinone radicals, in their corresponding reduced state.<sup>7,10,11</sup> Our objective is to evaluate the clinical therapeutic effect of vitamin C supplementation in patients with COPD.

The study conducted by Kanani et al identified a positive correlation between vitamin C intake and adult lung function.<sup>12–14</sup> However, a negative correlation between supplemented vitamin C and the antioxidation level of vitamin C and SOD in serum was reported by Liu et al<sup>13</sup> while the study of Gouzi et al demonstrated a positively correlated between the two parameters.<sup>15</sup> Furthermore, although lots of studies have shown that COPD can cause malnutrition,<sup>16,17</sup> no significant change in body mass (BMI) or fat-free mass index (FFMI) after vitamin C supplementation has been found. Therefore, the relationship between vitamin C supplementation and antioxidative stress in COPD patients is conclusive. Thus, we conducted this systematic review and meta-analyses to separately evaluate the efficacy of vitamin C supplementation in improving lung function, antioxidation level in serum and nutrition level in patients with COPD.

## Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. The protocol for this study has been pre-registered to the PROSPERO database (registration number: CRD42021259220).

## Search Strategy

Two investigators independently searched PubMed, EMBASE, Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI), SinoMed, Wanfang, and China Science and Technology Journal Database for publications related to vitamin C and COPD from their corresponding inception until May 18th, 2021 without language restrictions. The search terms were “vitamin C”, or “ascorbic acid”, and “COPD”. Qualified articles must be studies in human. Moreover, we manually checked the reference lists of the retrieved articles and reviews for potentially eligible studies. Detailed search strategies are reported in [Appendix 1](#).

## Inclusion Criteria and Exclusion Criteria

Two investigators (LT and YHC) determined the eligibility of potential studies, and any disagreement was resolved by discussion with a third investigator.<sup>18–20</sup> The inclusion criteria were: (1) patients in the eligible studies were diagnosed with COPD and were 18 years old or older; (2) the studies compared vitamin C supplementation with a placebo; (3) randomized controlled trials (RCTs) that provided outcomes of lung function, nutrition or serum antioxidant data. Exclusion criteria were: (1) patients in the studies had other accompanying diseases such as diabetes, kidney disease, lung cancer and other complications in addition to COPD. (2) the studies were conducted in cell assays or animal experiments; (3) reviews, case reports, conference abstracts, letters, or editorials; (4) duplicated publications or publications with incomplete data.

## Data Extraction and Quality Assessment

Two authors (LT and YHC) independently extracted the following information: from each eligible study: first author, publication year, country of origin, study design, participant characteristics, vitamin C intake and trial duration. According to the Global GOLD guidelines,<sup>1</sup> the primary outcome was lung function, and the lung function index included were FEV1% (forced expiratory volume in one second as a percentage) and FEV1/FVC (the ratio of forced expiratory volume in 1 second and forced vital capacity). The secondary outcomes analyzed in the present study included

the concentrations of serum vitamin C, vitamin E, GSH (Glutathione), and SOD (Superoxide dismutase), the body mass index (BMI), and Fat-Free Mass Index (FFMI).

Two investigators assessed the risk of bias using the Cochrane risk of bias tool for randomized controlled trials,<sup>21</sup> which included random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other potential risk of bias. Each domain was graded as low, unclear or high in terms of risk of bias. GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) was used to assess the certainty of evidence in the meta-analysis.

## Statistical Analysis

For continuous variables, the random effect model was used to calculate the standardized mean difference (SMD), weighted mean difference (WMD) and 95% CI confidence interval (CI). Statistical heterogeneity was assessed by using the  $I^2$  test and Cochran Q test, and values of over 50% indicated substantial heterogeneity. Direct comparisons were performed using the Review Manager (version 5.4).  $P < 0.05$  for the overall effect was considered statistically significant. Subgroup analysis of the FEV1% was performed based on the dosage ( $< 400$  mg/d or  $\geq 400$  mg/d of vitamin C supplementation). Subgroup analysis of GSH concentration was performed based on the different duration of vitamin C supplementation ( $< 3$  months, 3–6 months,  $> 6$  months). Sensitivity analysis was performed by excluding low-quality studies to explore potential sources of heterogeneity. As for each assessed outcome there were less than ten articles; we could not assess publication bias by funnel plots.

## Results

### Study Screening and Characterization

Literature search following the search strategy yielded 1269 studies, including 190 duplicated. Title and abstract reviewing led to the exclusion of 1056 studies and a total of 23 articles for full-text review. Finally, ten articles were eligible for the present study.<sup>6,13–15,22–27</sup> The PRISMA flow diagram is shown in Figure 1.

All studies were RCTs and described an adequate random sequence generation process. Seven studies<sup>6,13,14,22,24–26</sup> described the methods used for allocation concealment. A total number of 487 patients were included in the present meta-analysis, including 248 patients who received vitamin C treatment and 239 patients who were given a placebo. Four studies<sup>13,14,23,26</sup> reports included the male of patients, and another four studies<sup>6,15,22,24</sup> included male-female ratio. But two studies<sup>25,27</sup> did not report the gender of patients. In two studies, patients were treated with a daily supplemented vitamin C of less than 400 mg/day,<sup>6,15</sup> while in the other studies, patients took vitamin C at 400 mg/day or more.<sup>13,14,22–27</sup> Seven studies reported the lung function as the primary outcome,<sup>6,13,14,22,24–26</sup> eight studies reported the levels of serum antioxidation,<sup>6,13–15,22–24,27</sup> and three studies reported the nutrition levels<sup>15,23,27</sup> as the secondary outcomes. The characteristics of the included RCTs are shown in Table 1.

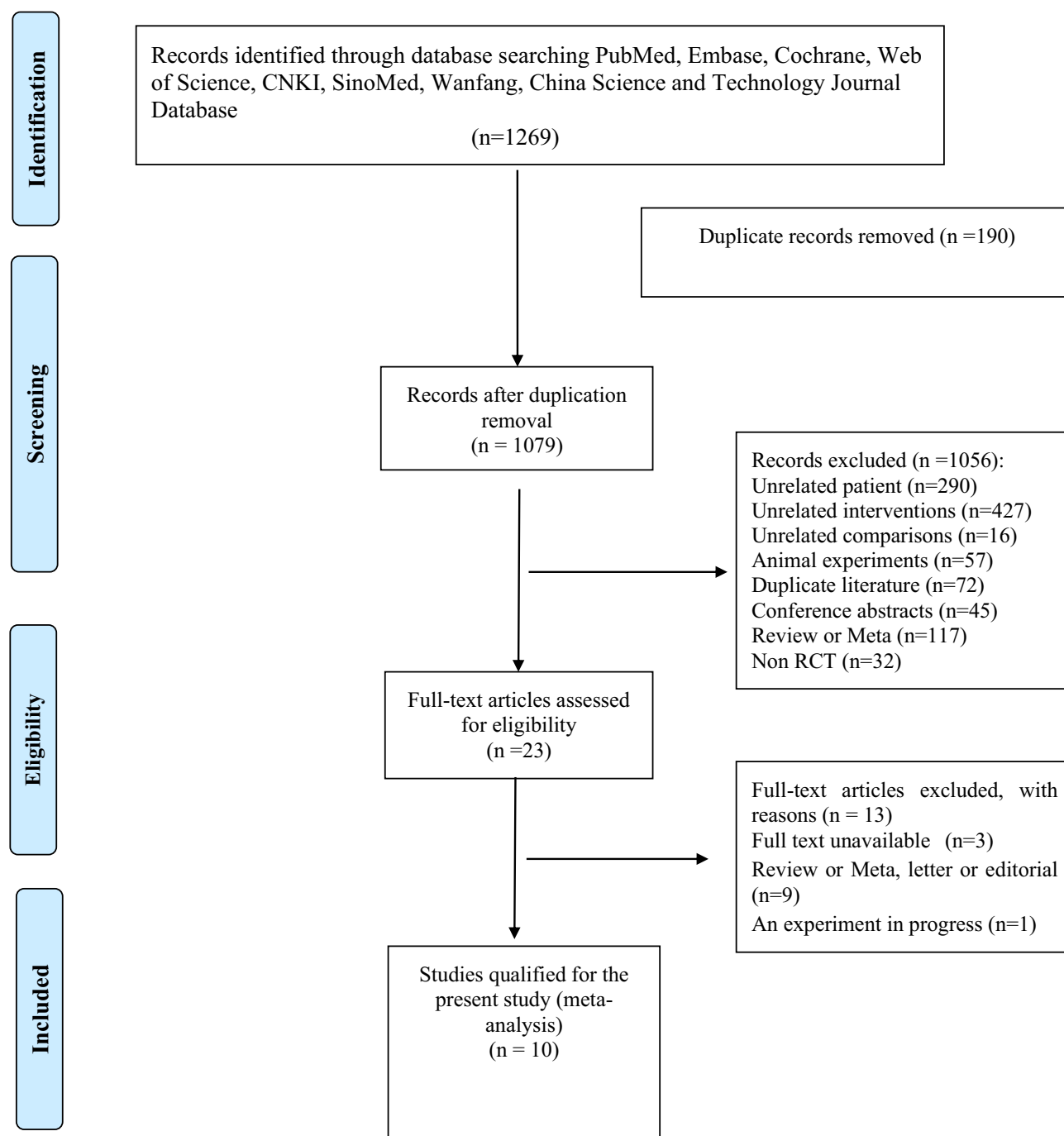
### Risk of Bias Assessments

Except for the study conducted by Zou et al,<sup>25</sup> the risk of bias in allocation concealment for the other studies was low. For the domain of blinding, the risk of bias was low in four studies (40%),<sup>13,15,26,27</sup> and it was unclear in the rest of the studies. The risk of bias for all included RCTs (100%) was low regarding the incomplete outcome data and other bias. With respect to the selective reporting outcomes, the risk of bias was unclear for five studies (50%),<sup>13,22–25</sup> and it was low for the rest of the studies. The quality assessments based on the risk of bias are shown in Figure 2, and the quality of evidence for the included studies, which were based on the GRADE was presented in Table 2.

## Meta-Analysis

### Lung Function Levels in COPD Patients

It has been pointed out in The Global Gold guide (2021) that the goals of COPD assessment are to determine the level of airflow limitation.<sup>1</sup> Spirometry is required to make the diagnosis. FEV1%, which means the forced expiratory volume in the first second expressed as a percentage of the forced vital capacity (FVC), and the ratio of FEV1% and FVC (FEV1/FVC)



**Figure 1** PRISMA 2009 Flow Diagram.

**Notes:** PRISMA figure adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. 72.

can be used to diagnose the presence of persistent airflow limitation.<sup>1,6</sup> These two diagnostic factors were affected by the supplementation of vitamin C in COPD patients. Among the ten eligible studies,<sup>6,13–15,22–27</sup> seven of them reported lung function as an outcome by measuring the FEV1% or FEV1/FVC.<sup>6,13,14,22,24–26</sup>

### Fev1%

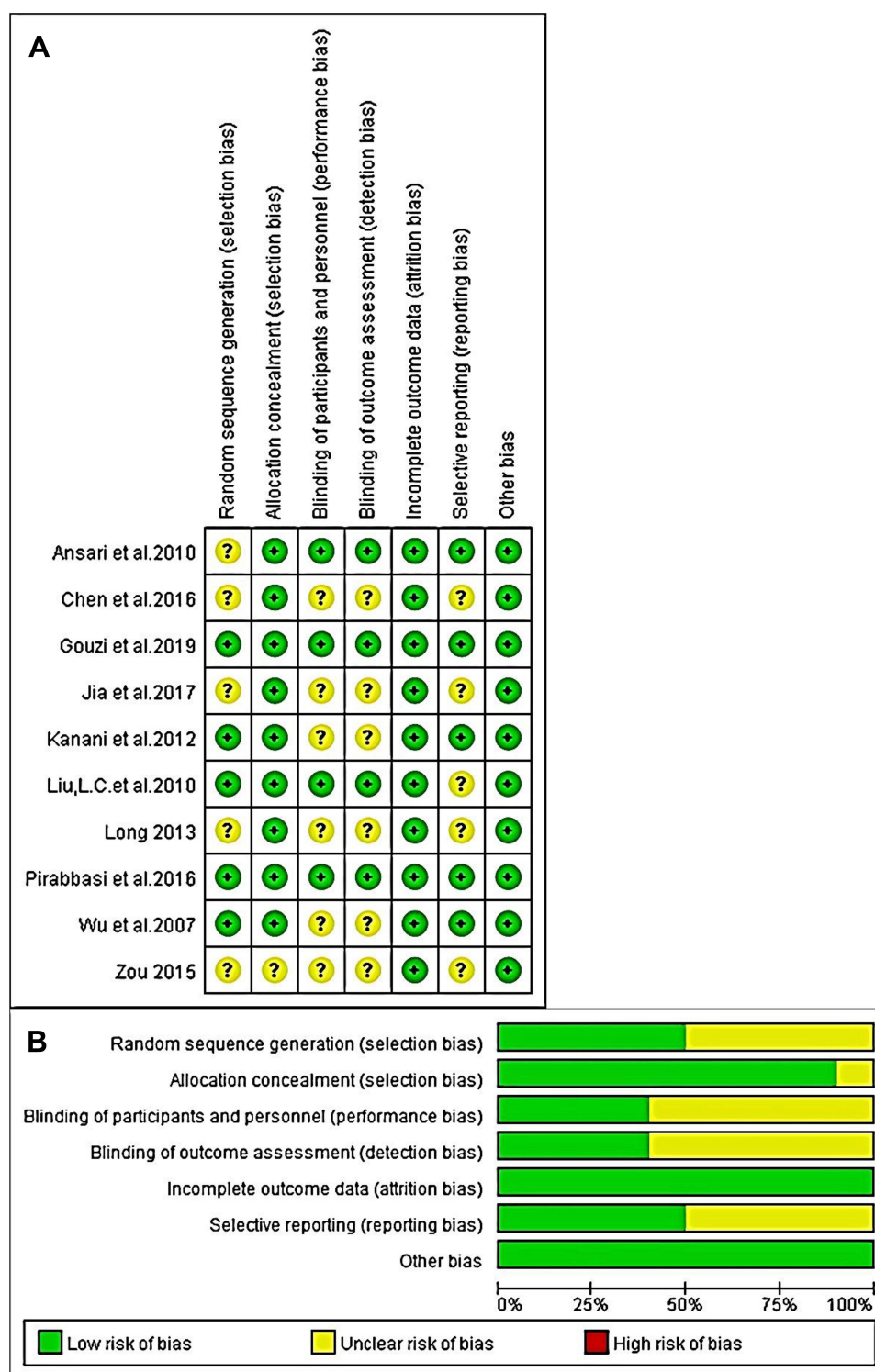
FEV1% was used to evaluate lung function. The study conducted by Ansari et al,<sup>26</sup> was excluded for lung function analysis since the original raw data could not be obtained. Since the dosage of vitamin C varies dramatically, we divided the pooled

**Table 1** Characteristics of Included Studies

Study	Design	Country	Group	Sample Size	Average Age	Sex (Male/Female)	Intervention	Primary Outcome	Secondary Outcome	Mean Follow-Up (Weeks)
Wu et al 2007 <sup>6</sup>	RCT	China, Taiwan	Vitamin C	9	14.05±12.12	7:2	Vitamin C 250mg/d	ab	ef	12
Ansari et al 2010 <sup>26</sup>	RCT, Single blind	Pakistan	Placebo	8	9.41±7.87	7:1	Placebo			
			Vitamin C	22	55.33±2.19	Male	Vitamin C 1000mg/d	ab	NA	36 (9months)
			Placebo	23	53.46±1.94	Male	salbutamol 100µg and beclomethasone 50µg			
Liu, L.C. et al 2010 <sup>13</sup>	RCT, Double blind	China, Taiwan	Vitamin C	12	68–72	Male	Vitamin C 500mg/d +Vitamin E 400IU/d	ab	efh	13
Kanani et al 2012 <sup>14</sup>	RCT	India	Placebo	9	68–72	Male	Vitamin E 400IU/d			
			Vitamin C	18	71.24±0.56	Male	Vitamin C 500mg/d +Vitamin E 200mg/d	ab	g	12 (3months)
Long et al 2013 <sup>24</sup>	RCT	China	Placebo	16	71.24±0.56	Male	Vitamin E 200mg/d			
			Vitamin C	25	45.5±13.2	15:1	Conventional therapy+exercise +vc400–800mg/d+ve8–10iu/d	a	ef	NA
Zou et al 2015 <sup>25</sup>	RCT	China	Placebo	20	46.4±3.6	12:8	Conventional therapy+exercise			
			Vitamin C	58	NA	NA	Vitamin C 300–600mg/d	ab	NA	24 (6months)
Pirabbasi et al 2016 <sup>27</sup>	RCT, Single blind	Malaysia	Placebo	59	NA	NA	Nothing			
			Vitamin C	13	64.5±10.2	Male	Vitamin C 500mg/d	NA	cfefg	24 (6months)
Chen et al 2016 <sup>22</sup>	RCT	China	Placebo	18	64.17±8.3	Male	NA			
			Vitamin C	30	71.27±3.32	14:16	Conventional therapy+Vitamin C 500mg/d	a	gh	20d
Jia et al 2017 <sup>23</sup>	RCT	China	Placebo	30	71.57 ± 2.69	13:17	Conventional therapy			
			Vitamin C	30	64.17±8.3	Male	Vitamin C 1500mg/d	NA	cdefg	24 (6months)
Gouzi et al 2019 <sup>15</sup>	RCT, Double blind	France	Placebo	30	64.17±8.3	Male	Blank control group			
			Vitamin C	31	40–78	13:13	Vitamin C 180mg/d	NA	cdefh	28d
			Placebo	26	40–78	15:16	Placebo			

**Notes:** Conventional therapy: anti-infection; oxygen therapy: antiasthmatic routine treatment. <sup>a</sup>FEV1%; <sup>b</sup>FEV1/FVC; <sup>c</sup>BMI; <sup>d</sup>FFMI; <sup>e</sup>Vitamin C; <sup>f</sup>Vitamin E; <sup>g</sup>GSH; <sup>h</sup>SOD.

**Abbreviations:** FEV1%, forced expiratory volume in 1 second; RCT, Randomized Clinical Trial; GSH, glutathione; SOD, Superoxide Dismutase.



**Figure 2 (A)** Summary of risk of bias for each included study. **(B)** bar graph of the risk of bias showing the percentage of risk level for each characterized risk. Each color represents a different level of bias: red for high risk, green for low risk, and yellow for unclear risk of bias.

data into two subgroups by the amount of supplemented vitamin C: the subgroup with a daily vitamin C supplementation of less than 400 mg (Vitamin C<400 mg) and the subgroup with a daily vitamin C supplementation greater than 400 mg (Vitamin C ≥400 mg). The results showed that no statistical difference was found between the vitamin C group and the placebo group in the vitamin C<400 mg subgroup (SMD: -0.05, 95% CI: -1.00, 0.91,  $P=0.92$ ). While in the vitamin C ≥



**Table 2** GRADE Evaluation Results

Outcome	No of Participants (Studies)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Relative Effect (95% CI)	GRADE
FEV1%	256 (6)	Not serious	Serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Not serious	SMD:1.34, (0.01, 2.67)	⊕⊕○○
FEV1/FVC	234 (5)	Not serious	Serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Not serious	SMD:0.66, (0.26, 1.06)	⊕⊕○○
Serum vitamin C levels	231 (6)	Not serious	Serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Not serious	SMD:0.63, (0.02, 1.24)	⊕⊕○○
Serum vitamin E levels	231 (6)	Not serious	Serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Not serious	SMD: 0.83, (−0.08, 1.74)	⊕⊕○○
Serum GSH levels	185 (4)	Not serious	Serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Not serious	SMD:2.47, (1.06, 3.89)	⊕⊕○○
Serum SOD levels	138 (3)	Not serious	Serious <sup>a</sup>	Not serious	Serious <sup>b</sup>	Not serious	SMD: 0.42, (−1.31, 2.15)	⊕⊕○○
BMI	148 (3)	Not serious	Not serious	Not serious	Serious <sup>b</sup>	Not serious	WMD: −0.17, (−1.5, 1.16)	⊕⊕⊕○
FFMI	148 (3)	Not serious	Not serious	Not serious	Serious <sup>b</sup>	Not serious	WMD: −0.17, (−1.06, 0.72)	⊕⊕⊕○

Notes: <sup>a</sup> $I^2 > 50\%$ ; <sup>b</sup>The sample size is less than 300.

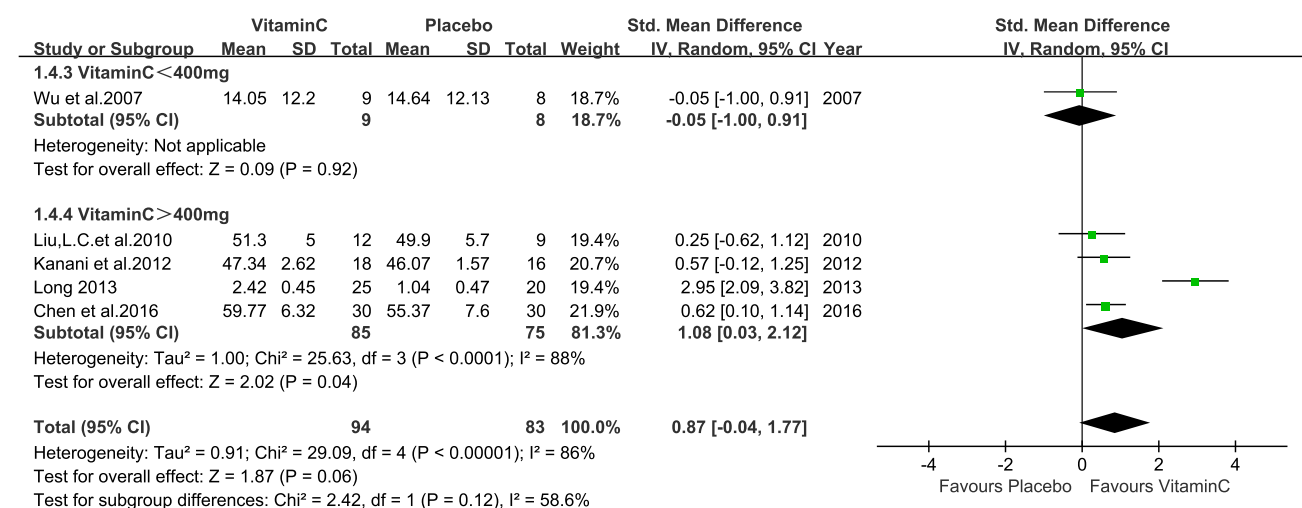
Abbreviation: GRADE, Grading of Recommendations Assessment Development and Evaluation.

400 mg subgroup, an improved FEV1% was found in the vitamin C treatment group compared to that of the placebo group. The difference was statistically significant (SMD: 1.08, 95% CI: 0.03, 2.12,  $P=0.04$ ). The result is shown in [Figure 3](#).

The sensitivity analysis result showed that the study conducted by Long et al<sup>24</sup> significantly influenced the pooled results ([Figure 4](#)). If this study was excluded from our analysis, the  $I^2$  dropped from 86% to 0%. However, we did not exclude this study from our analysis. The reason was as follows: although respiratory rehabilitation training was used to treat COPD in Long et al study as the placebo treatment, which was different from the placebo treatments used in other analyzed studies,<sup>24</sup> respiratory rehabilitation training alone would not have a significant impact on the lung function in COPD patients in clinical practice.<sup>15</sup> Therefore, we concluded that the breathing exercise might not be a main source of heterogeneity.

### FEV1/Fvc

FEV1/FVC ratio was measured in five studies (n=234 patients)<sup>6,13,14,25,26</sup> (SMD:0.66, 95% CI: 0.26,1.06,  $P=0.001$ ; [Figure 5](#)), with a significant heterogeneity among these studies ( $I^2=98\%$ ,  $P<0.00001$ ). Sensitivity analyses showed that no individual study significantly influenced the results from the pooled data.

**Figure 3** FEV1% in lung function.

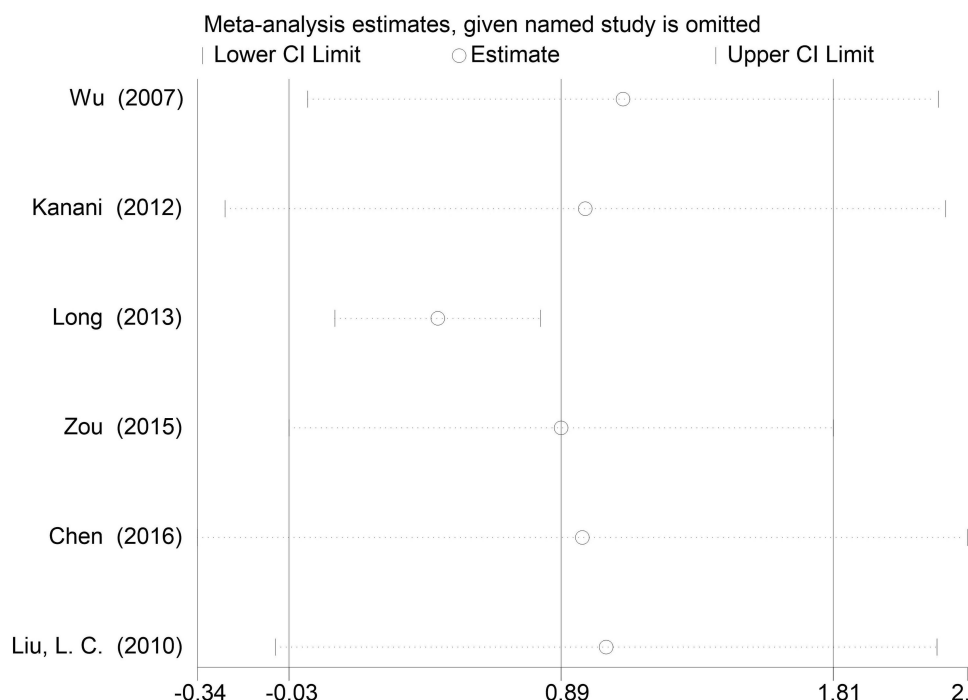


Figure 4 Sensitivity Analysis FEV1%.

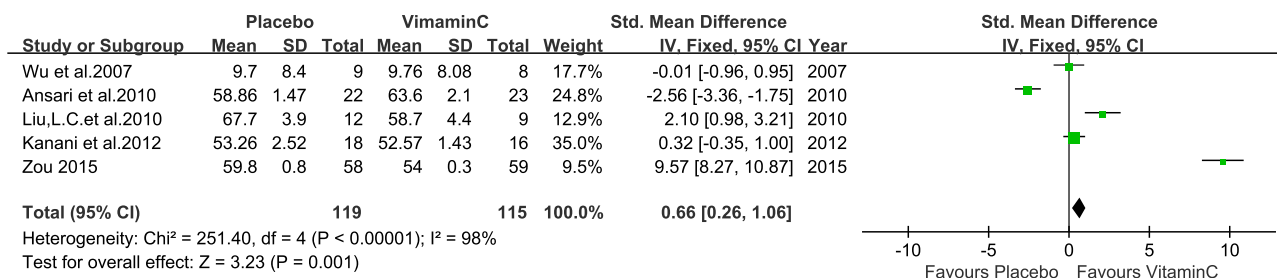


Figure 5 FEV1/FVC in lung function.

## Antioxidation Levels in Serum in COPD Patients

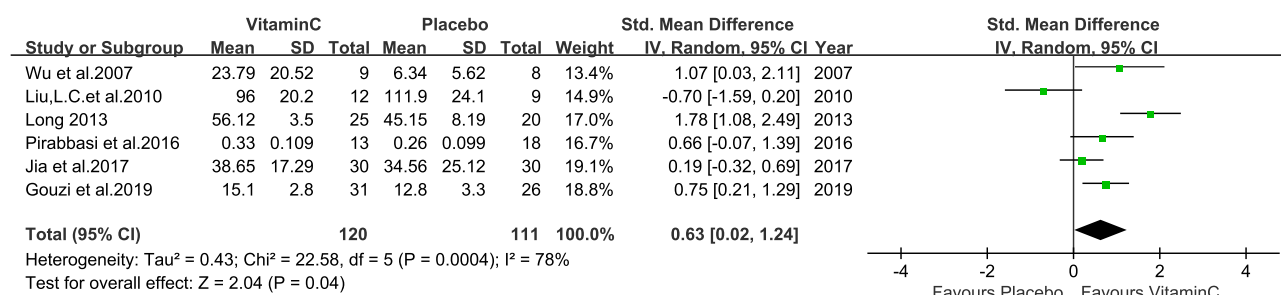
Different antioxidants were measured in different studies. Six studies including 231 patients, measured the levels of vitamin C and vitamin E in serum,<sup>6,13,15,23,24,27</sup> and four studies, including 185 patients<sup>14,22,23,27</sup> measured the level of GSH. Vitamin C, E and GSH are all non-enzymatic antioxidants in the lung. Three studies including 138 patients, measured the level of SOD, which belongs to the family of enzymatic antioxidants in lung.<sup>13,15,22</sup>

## Vitamin C Level in Serum

Six studies reported the levels of vitamin C and vitamin E in serum in 120 COPD patients in the vitamin C group and in 111 patients in the placebo group.<sup>6,13,15,23,24,27</sup>

The result from the pooled data from the six studies showed that serum vitamin C level was higher in the vitamin C group than that of the placebo group (SMD:0.63, 95% CI: 0.02, 1.24,  $P=0.04$ ; Figure 6), with significant heterogeneity among these studies ( $I^2=78\%$ ,  $P=0.0004$ ).





**Figure 6** Vitamin C level in serum.

## Serum Vitamin E Level

A random effect model was used to analyze the data on serum vitamin E levels, and the result demonstrated that the serum vitamin E level was higher in the vitamin C supplementation group than that in the placebo group (SMD:0.83, 95% CI: -0.08, 1.74,  $P=0.07$ ; Figure 7), with significant heterogeneity among these studies ( $I^2=90\%$ ,  $P<0.00001$ ). Sensitivity analyses showed that no individual study significantly influenced the results from the pooled data.

## GSH Level in Serum in COPD Patients

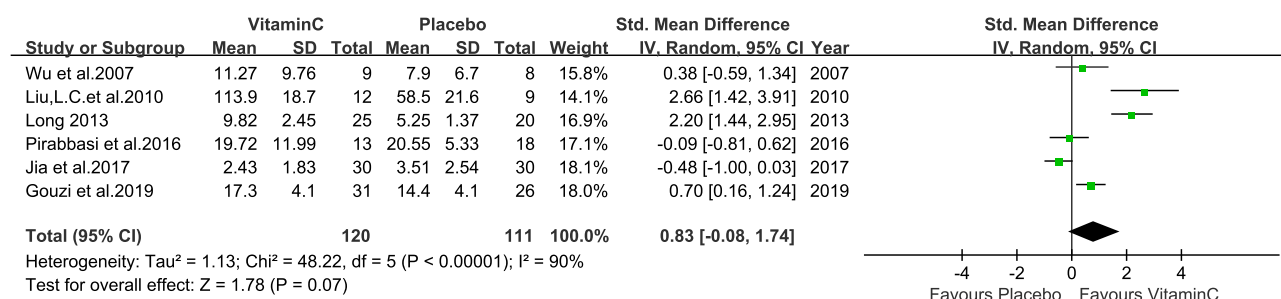
Four RCTs, including 185 patients<sup>14,22,23,27</sup> measured serum GSH levels, which were the major non-enzymatic antioxidants in the lung. The result from pooled data showed that serum GSH levels in vitamin C supplementation groups were higher than that of the placebo group (SMD:2.47, 95% CI: 1.06, 3.89,  $P=0.0006$ ), with significant heterogeneity among these studies ( $I^2=95\%$ ,  $P<0.00001$ ). The result is shown in Figure 8.

Included patients were divided into three subgroups based on the length of vitamin C supplementation: less than 3 month, 3 to 6 months, and over six months. And a subgroup analysis was conducted. As shown in Figure 8, in each subgroup, supplementation of vitamin C showed a trend to increase the GSH level in serum compared to supplementation with placebo. The difference was statistically significant.

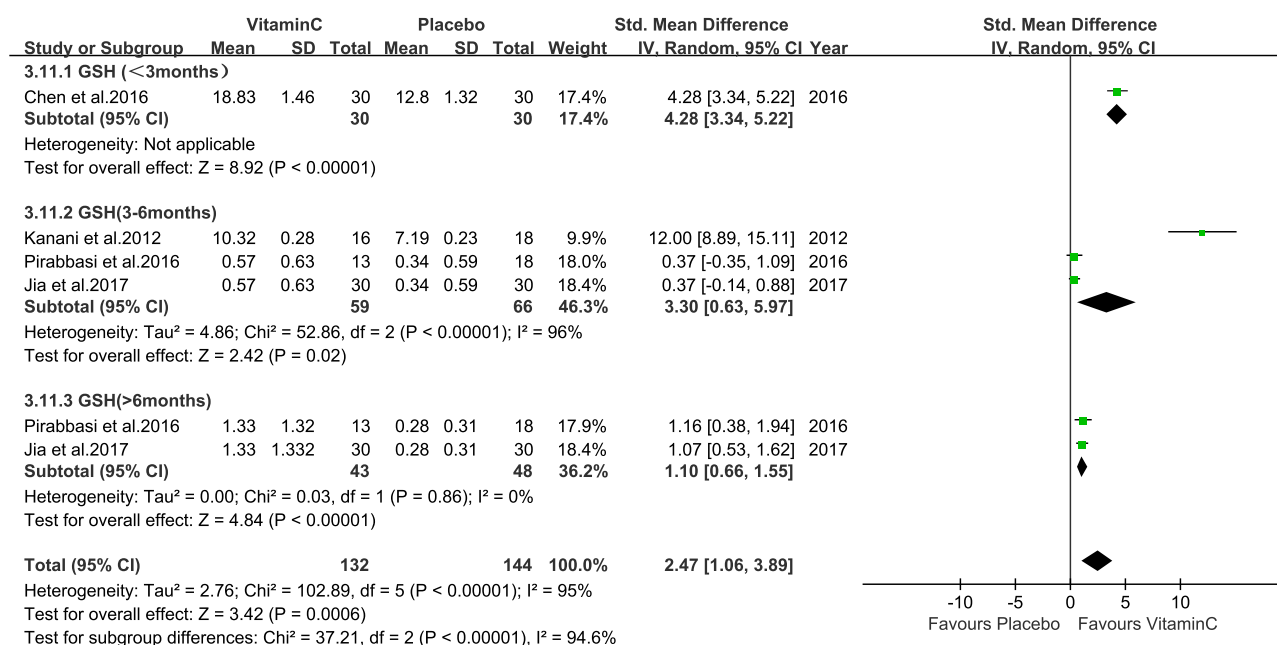
Sensitivity analysis results showed that the study conducted by Kanani et al<sup>14</sup> significantly influenced the results from the pooled data. In fact, in Kanani's study, both vitamin C and vitamin E were used to treat patients as antioxidation agents, which was different from other involved studies, where only vitamin C was used against oxidation. There were studies showing that vitamin E isoform  $\gamma$ -tocotrienol reduced cigarette smoke-induced airway inflammation and oxidative stress so vitamin E might possess the therapeutic potential to treat COPD.<sup>28</sup> However, no direct evidence supports the concept that vitamin E could increase the GSH level in serum. Thus, we decide that vitamin E combined with vitamin C in the treatment group may not be the source of heterogeneity in the present study and still keep Kanani's study included.

## Enzymatic Antioxidants of Lungs

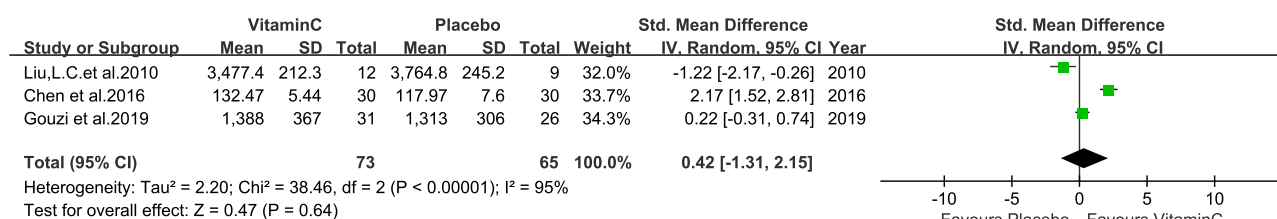
Three RCTs, including 138 patients<sup>13,15,22</sup> measured the level of serum SOD, which was the major enzymatic antioxidant in the lung. Overall, the result from the pooled data did not show a significant difference in terms of SOD level between the vitamin C group and placebo group (SMD: 0.42, 95% CI: -1.31, 2.15, 3 studies,  $P=0.64$ ). The result is shown in Figure 9. Sensitivity analyses showed that no individual study significantly influenced the result from the pooled data.



**Figure 7** Serum vitamin E level.



**Figure 8** GSH level in serum in COPD patients.



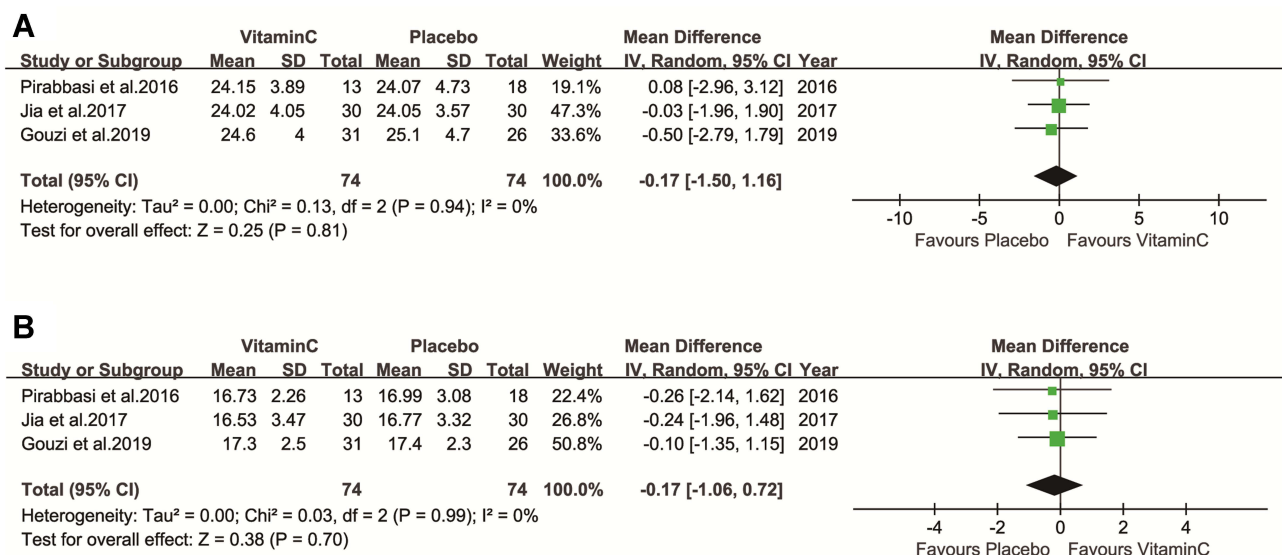
**Figure 9** Enzymatic antioxidants of lungs.

## Nutrition Levels

Three studies including 148 patients<sup>15,23,27</sup> reported changes in nutrition levels. The fixed effects model was used for the analysis of BMI (WMD: -0.17, 95% CI: -1.5, 1.16,  $P=0.81$ ) and FFMI (WMD: -0.17, 95% CI: -1.06, 0.72,  $P=0.70$ ). The results showed no significant improvement in BMI and FFMI by vitamin C treatment compared to placebo treatment. The results are shown in Figure 10.

## Discussion

Globally, more than 3 million people die from COPD every year, yet little progress in slowing the disease progression or reducing the mortality has been made.<sup>17</sup> Oxidative stress, a result of the oxidant/antioxidant imbalance, has been suggested to play a critical role in the pathogenesis of COPD.<sup>4-6</sup> An excess of oxidants may lead to the overexpression of pro-inflammatory genes, inactivation of antiproteases, and oxidative tissue injuries that lead to COPD.<sup>29</sup> Various factors, including smoking and air pollution, have been proved to be able to increase systemic oxidative stress in patients with COPD.<sup>30</sup> Overexposure to oxidants and/or decrease of antioxidants contribute to the development of COPD. One good example is smoking. In the over 4000 identified constituents of cigarette smoke, a large number of oxidants, especially different free radicals were found, which might be responsible for the extra oxidative stress in COPD patients who smoke.<sup>30,31</sup> Antioxidant supplementation may improve the symptoms of COPD.<sup>6</sup> Vitamin C is a well-known antioxidant supplementation. It has been shown that vitamin C supplementation were beneficial in COPD treatments by decreasing the damages caused by over oxidative stress.<sup>9</sup> Thus, we conducted the present meta-analysis to summarize



**Figure 10** Nutrition levels (A, B).

the effects of vitamin C administration in COPD patients, including pulmonary function, levels of serum antioxidant nutritional levels, to validate the function of vitamin C in treatment of COPD.

The results of the present meta-analysis showed that in COPD patients, vitamin C supplementation was significantly and positively correlated with the improvement of lung function, and higher levels of vitamin C and GSH in serum, but not other tested outcomes. Sensitivity analyses that excluded low-quality studies did not change these results. Through the subgroup analysis, we concluded that dose wisely, supplementation of more than 400 mg/day of vitamin C significantly improved lung function, while no significant change was found in patients supplemented with vitamin C less than 400 mg/day. We also conducted subgroup analysis based on the time of vitamin C supplementation, and the result showed vitamin C supplementation significantly increased the level of GSH in serum in all and each analyzed subgroup. No significant difference among the subgroups was found in terms of improvement of GSH levels in serum. All the evidence support that vitamin C intake provides a clinically meaningful benefit in COPD treatment.

## Lung Function Increase

The mechanism of vitamin C supplementation to improve lung function remains unclear.<sup>7-9</sup> Liu. et al have shown that vitamin C supplementation will enhance lung function and improves symptoms in COPD patients. Wu et al reported that the levels of dietary antioxidants, such as vitamin C, were positively correlated with lung function, but whether it was also beneficial in COPD treatment was unclear,<sup>6</sup> which was contrary to the results from several other studies.<sup>13,14,22,24,25</sup> Ansari et al showed that salbutamol and beclomethasone treatments in COPD patients showed noteworthy reductions in FEV1/FVC ratio, while a slight but non-significant drop was observed in FEV1/FVC ratio when vitamin C was added to standard therapy.<sup>26</sup> Our meta-analysis results indicate that supplementing vitamin C might improve lung function in COPD patients, which was consistent with other studies.<sup>32-35</sup> Such improvement might have many reasons. But the most important one might be its antioxidant property. Oxidative overload in COPD is quite common, mostly caused by hypoxia, and infection and plays a vital role in the impairment and remodeling of lung tissue. Vitamin C, as an antioxidant, has been widely used in many diseases sharing the same pathophysiologic characteristics as sepsis, ARDS, etc.<sup>36,37</sup> It has been well proven that vitamin C can effectively attenuate oxidative stress, for which it may slow down the remodeling of lung structure and furtherly the deterioration of lung function.<sup>38</sup> For instance, increased oxidative stress can lead to dysregulated antiproteases in lung tissue, which is the core of the pathogenesis of emphysema in COPD.<sup>39</sup> Moreover, molecularly, oxidative stress has been found to contribute to pulmonary fibrosis. A bunch of

studies show that imbalance between Reactive oxygen/nitrogen species (ROS/RNS), a sign of oxidative stress, leads to overexpression of some pro-fibrotic molecules, for example, TGF- $\beta$ .<sup>40</sup> Albeit there are several potential hypotheses that can explain the improving effect of vitamin C on lung function, there is still a lack of direct study focusing on their relationships. More attention is needed on this topic.

## Antioxidants in Serum

The underlying mechanisms by which the lung defends against possible oxidative challenges itself depend on two different types of antioxidants: non-enzymatic antioxidants, including glutathione, vitamin C and E, beta-carotene uric acid and enzymatic antioxidants such as superoxide dismutase, catalase and peroxidases.<sup>7</sup> Even for those people who smoke cigarettes, the DNA break induced by  $\text{H}_2\text{O}_2^-$  in the smoke was negatively correlated with the vitamin C level in serum, and the correlation was statistically significant.<sup>6</sup> Compared to those of nonsmokers, the levels of major plasma antioxidants (vitamin C, vitamin E and GSH) in smokers are decreased.<sup>14,41</sup> Superoxide dismutases (SODs) are a family of metalloenzymes that convert  $\text{O}^{2-}$  to  $\text{H}_2\text{O}_2$ . Catalase and glutathione peroxidase neutralize  $\text{H}_2\text{O}_2$  into water and oxygen.<sup>28,29,42</sup> Peh et al showed that inhibition of the activities of these three key antioxidant enzymes would increase oxidative stress, which contributed to the incidence of emphysema.<sup>28</sup> Vitamin C is a widely used antioxidant. In addition to its role as an enzyme cofactor, vitamin C is a critical, chain-breaking antioxidant in the aqueous phase.<sup>43</sup> Vitamin C can be rapidly depleted by electron spin resonance in the presence of increased free radical production in body fluids,<sup>44</sup> which is a part of the antioxidation process mediated by vitamin C. After being supplemented with vitamin C, the DNA break induced by  $\text{H}_2\text{O}_2$  was significantly decreased,<sup>6</sup> providing an appropriate environment to regenerate GSH radicals.<sup>45</sup>

The primary function of vitamin E is working as a chain-breaking antioxidant.<sup>46</sup> Vitamin C can facilitate the conversion of oxidized vitamin E into non-oxidized vitamin E to increase the serum concentration of non-oxidized vitamin.<sup>47,48</sup> Moreover, vitamin C demonstrated a synergistic effect with vitamin E in antioxidant activity.<sup>28</sup> Hanson. et al pointed out that increasing serum vitamin E was protective against COPD mortality.<sup>46,49</sup>

In the present study, a panel of antioxidants demonstrated a tendency of increased concentration in serum after being supplemented with vitamin C, but only the increase of serum vitamin C and GSH was statistically significant. Among all the studies, Liu et al showed a result about serum vitamin C and SOD that was opposite to the conclusions from other included studies.<sup>13</sup> However, in Liu et al study, the baseline vitamin C level in the vitamin C supplementation group was significantly lower than that of the control group. In addition, there were only 21 patients involved in their study, making it impossible to ignore the baseline difference in vitamin C between the two groups. Vitamin C could enhance the reuse of vitamin E, which could increase the activity of individual SOD molecules. Therefore, to keep the total SOD activity at a certain level, the total amount of SOD decreased.

In summary, vitamin C supplementation could improve the antioxidant capacity in serum, enhance the antioxidant ability in COPD patients and reduce the mortality rate of COPD.

## Nutritional Condition

Malnutrition is a problem that is often overlooked during the treatment of COPD.<sup>50</sup> About 20–50% of COPD patients suffer weight loss and protein and calorie malnutrition,<sup>27,50</sup> which contribute to the dysfunction of respiratory muscles, the severity of the disease, the progression of disability, and eventually the mortality of the disease.<sup>17,51</sup> Mete et al found that pulmonary function was significantly lower in those COPD patients with low BMI and malnutrition.<sup>50</sup> Similarly, the amount of fat-free body mass was also found significantly lower in COPD patients falling in a low BMI category and in patients who were at malnutrition risk or with malnutrition.<sup>50</sup> Decreased FFMI could lead to biologically negative consequences in COPD.<sup>52,53</sup> These indicated that total body mass and FFM are important prognostic factors in COPD. An imbalance of antioxidants may lead to systemic inflammation, which has been shown to damage bones and muscles, reduce ventilatory capacity, and reduce lung function.<sup>54,55</sup>

Meanwhile, oxidative stress is an important contributing factor in the pathogenesis of COPD and eventually results in poor respiratory function.<sup>27</sup> The limited gas exchange will lead to a sedentary lifestyle, which in turn results in the loss of appetite and nutrient deficiency through consumption of a low-antioxidant diet as feedback. The resulted malnutritional status would promote the disease progression and increase the oxidative stress in patients, which would further deteriorate the existing malnourishment in patients and increase the disease severity.<sup>54,56</sup> Multiple studies showed that

oxidative stress was indeed a deleterious factor leading to the dysfunction and atrophy of muscles in COPD patients.<sup>15,57</sup> Antioxidants play a key role in improving muscle endurance<sup>58</sup> and atrophy in COPD.<sup>59</sup> Although Gouzi et al pointed out that vitamin C failed to improve quadriceps endurance as a pulmonary rehabilitation supplementation, the improved quadriceps muscle strength, total protein in serum, and type I fiber proportion in vitamin C-treated patients demonstrated a trend toward improved muscle endurance.<sup>15</sup> A Cochrane systematic review found that low BMI and fat-free mass index (FFMI) conditions in the COPD population were related to a poor prognosis.<sup>60</sup> These findings are consistent with our results that vitamin C supplementation in COPD patients may improve their nutritional status.

## Advantages and Limitations

Our research has some advantages. It is the first systematic review and meta-analysis to evaluate the impact of vitamin C supplementation in COPD patients. Second, we conducted a subgroup analysis based on vitamin C intake dosage and found that vitamin C greater than 400 mg improved the symptoms in COPD patients. We also found that intake of vitamin C may contribute to the nutritional improvement in COPD by enhancing quadriceps muscle strength and total serum protein,<sup>15</sup> which remains to be confirmed. Based on these results, COPD patients may benefit from vitamin C, especially when given at a dose greater than 400 mg/day.

However, this meta-analysis and systematic review still have some limitations. Rabe et al classified COPD into two types: pink-puffer phenotype of COPD (are primarily affected by emphysema) and blue bloater phenotype of COPD (predominantly have chronic bronchitis) according to various clinical manifests.<sup>17</sup> In the present study, we did not analyze the data based on the type of COPD, which may contribute to the irrelevancy of vitamin C to the certain investigated outcomes in this study. Moreover, the relatively small number of included studies and the ethnicity of the patient population included in the study may introduce bias to the result of our meta-analysis.<sup>61,62</sup>

## Conclusion

In conclusion, we found that supplementing vitamin C to patients with COPD demonstrated vital clinical significance. It can promote lung function and serum antioxidant levels by decreasing oxidative damage to the lung. Meanwhile, we also found that vitamin C supplementation could increase the antioxidant level in serum, but not the nutritional level in COPD patients. These result needs to be further confirmed by large and well-designed prospective RCTs.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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