Original Article

The efficacy of vitamin D therapy for patients with COPD: a meta-analysis of randomized controlled trials

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Background: Many studies have demonstrated that vitamin D has clinical benefits when used to treat patients with chronic obstructive pulmonary disease (COPD). However, most of these studies have insufficient samples or inconsistent results. The aim of this meta-analysis was to evaluate the effects of vitamin D therapy in patients with COPD.

Methods: We performed an electronic literature search of the databases PubMed, China National Knowledge Internet (CNKI), Embase, Web of Science and Wanfang Data. Meta-analysis was carried out by Review Manager Version 5.3 (Revman 5.3), and standardized mean difference (SMD) and mean difference (MD) were used to assess the efficacy of vitamin D therapy in patients with COPD.

Results: A total of 25 articles involving 2,670 participants were included in this study. The overall results showed a statistical significance of vitamin D therapy in patients with COPD on forced expiratory volume in 1 second (FEV1) (SMD: 1.21, 95% CI: 0.76–1.66, P<0.01), FEV1/FVC (SMD: 1.07, 95% CI: 0.56–1.58, P<0.01), Exacerbations (SMD: 0.39, 95% CI: 0.23–0.64, P<0.01), Sputum volume (SMD: −6.02, 95% CI: −8.25 to −3.79, P<0.01), 6-minute walk distance (6MWD) (MD: 8.82, 95% CI: 1.67–15.98, P=0.02) and COPD assessment test (CAT) score (SMD: −1.19, 95% CI: −1.74 to −0.63, P<0.01).

Conclusions: Our analysis indicated that vitamin D used in patients with COPD could improve the lung function (FEV1, FEV1/FVC), 6MWD and reduce acute exacerbation, sputum volume and CAT score.

Keywords: Chronic obstructive pulmonary disease (COPD); vitamin D; meta-analysis

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Introduction

Chronic obstructive pulmonary disease (COPD), one of the top ten leading causes of death worldwide (1), is characterized by progressive and persistent airflow obstruction accompanied by an enhanced chronic inflammatory response and is mainly caused by environmental exposure to smoke and smoking (2). COPD, which is not only treatable, but preventable, represents an important public health challenge. The majority of COPD cases (85%) are smoking-related (3). Exposure to tobacco smoke causes changes in pulmonary function by impeding growth, decreasing peak function and accelerating age-related decline (4). Although lots of drugs, such as theophylline, long-acting beta2-agonists (LABA), inhaled corticosteroids (ICS), can effectively manage COPD, the disease remains the fourth leading cause of mortality in the world (5) and is projected to be the third leading cause of death by 2020. Currently, vitamin D is regarded as a sort of medicine which can play an important role for COPD patients and has certain related systemic effects (6). Furthermore, due to its effects on gene regulation, vitamin

D has protective effects against pulmonary diseases (7).

Vitamin D, a form of fat-soluble steroid hormone with biological functions and receptors in various organs, exerts powerful effects on the human body (8,9). These effects are seen particularly in the myometrium and tumor tissue (10). In humans, vitamin D is mostly produced through endogenous cutaneous synthesis of pre-vitamin D3. This synthesis is derived from 7-dehydrocholesterol via exposure to ultraviolet radiation (11). Fatty fish and fish liver oils are the best sources of vitamin D, and beef liver, cheese, and egg yolks also have small amounts of the vitamin (12,13). Vitamin D in these foods is mainly in the form of vitamin D3 (14). Vitamin D is widely known for its functions in calcium and bone metabolism. However, studies in recent decades have suggested that vitamin D has a far broader range of physiological functions and is related to the existence of vitamin D receptors (VDR) on the cells of these tissues, with effects on muscle function and the immune system (15). These functions could have clinical implications for COPD patients. Notably, many COPD patients experience vitamin D deficiency, with the content of vitamin D being closely associated with lung function, inflammatory factors and prognosis (3). Moreover, increased rates of exacerbation and hospitalization in COPD patients are attributed to vitamin D deficiency (16,17). Recent meta-analyses have concluded that vitamin D deficiency is directly related to the severity of a patient's COPD and, therefore, acute exacerbation may be prevented with vitamin D supplementation (18-20). Some studies have suggested that prognosis for COPD patients who are suffering from respiratory tract infections may improve through correction of their serum vitamin D level (21).

Although the clinical value of vitamin D supplementation in the treatment of COPD has been demonstrated in many studies, several of these had insufficient samples or inconsistent results. To provide accurate evidence for clinical research, we conducted a meta-analysis to investigate whether vitamin D can improve COPD assessment test (CAT) score, sputum, acute exacerbation, 6-minute walk distance (6MWD), or lung function, such as FEV1 and FEV1/FVC, in COPD patients.

Methods

Inclusion criteria

(I) The study should have been conducted as a randomized controlled trial (RCT);
(II) Patients must be diagnosed as COPD according to the Guidelines for the Diagnosis and Treatment of COPD;
(III) The study should explore the relationship between vitamin D and COPD;
(IV) Observational index: FEV1, FEVI/FVC, acute exacerbation, sputum, 6MWD, CAT score.

Exclusion criteria

(I) The study's results were affected by a small sample size;
(II) The study included non-compliant patients or people who had been deficient in vitamin d since childhood;
(III) The study failed to follow the principles of a randomized-controlled trial (rct);
(IV) References clearly did not meet the eligibility criteria;
(V) The Jadad score was less than two.

Search methods

We executed a comprehensive search of the electronic databases PubMed, China National Knowledge Internet (CNKI), Embase, Web of Science and Wanfang Data. Searches were conducted using key words including 'vitamin D', 'sputum', 'CAT', 'lung function, '6-minute walking distance', 'exacerbation' and 'chronic obstructive pulmonary disease'. There were no language restrictions.

Study selection and data extraction

Two independent authors browsed for studies of relevance based on their titles and abstracts. The authors then read the full texts of the potentially relevant studies, applying the inclusion and exclusion criteria. When disagreements arose, a consensus was reached through discussion or re-evaluation by the third author. As shown in *Tables 1* and *2*, the content for inclusion was: first author, publication year, sample size of experimental and control group, study type, and outcome indicators.

Quality appraisal

The Cochrane Collaboration tool was used to assess the included studies. Two independent authors evaluated the quality of each study. Divergences were decided by a senior author. The quality evaluation of the literature considered five biases: selection bias, withdraw bias, performance bias, publication bias, and other bias. Moreover, the methodology quality assessment used by the Jadad score in each study

Table 1 Characteristics of included studies in the present meta-analysis

First author	Year	Country	Ethnicity	Age (year)	Sample size (n)	Jadad score
				Experiment/control	Experiment/control	
Shi Rui	2012	China	Asian	65.23±11.6/65.23±11.6	36/36	3
Lehouck An	2012	Belgium	Caucasian	68±9/68±9	91/91	3
Zhang Tianwei	2014	China	Asian	66.42±7.20/66.38±7.15	175/175	2
Tang Lixin	2014	China	Asian	64.5±11.3/64.5±11.3	30/30	5
He Yeying	2014	China	Asian	60.5±5.5/60.5±5.5	62/58	4
Zhang Han	2015	China	Asian	71±10/73±9	60/60	4
Zendedel Abolfazl	2015	Iran	Asian	48.5±9.2/48.5±9.2	44/44	3
Qu Xia	2015	China	Asian	49.8±8.54/49.8±8.54	37/37	3
Chang Caihong	2015	China	Asian	59.3±1.2/56.7±0.8	40/40	3
Gu Haiting	2015	China	Asian	65.95±7.56/60.13±3.46	86/86	4
Du Zhenying	2015	China	Asian	60.8±11.9/63.1±12.6	29/29	5
Sanjari (Calcitriol)	2016	Iran	Asian	55.6±10.4/58.4±9.5	39/42	4
Li Yong	2016	China	Asian	65.72±4.98/65.60±4.91	50/50	3
Sanjari (Vitamin D)	2016	Iran	Asian	55.8±9.5 /58.4±9.5	39/42	4
Feng Congrui	2017	China	Asian	76.73±5.92/74.33±6.43	20/20	3
Khan Dur Muhammad	2017	Pakistan	Asian	46.28±8.83/46.28±8.83	60/60	5
Wang Yuehua	2017	China	Asian	69.95±3.05/67.77±4.34	50/50	3
Rafiq Rachida	2017	Dutch	Caucasian	64±3/61±4	24/24	3
Hornikx Miek	2012	Belgium	Caucasian	67±8/69±6	15/16	4
Van de Bool Coby	2017	Netherland	Caucasian	62.8±1.3/62.2±1.3	38/35	4
Gu Wenchao	2015	China	Asian	65.37±6.23/65.13±7.03	30/30	3
Ma Yinbo	2014	China	Asian	48.36±6.02/48.36±6.02	146/146	4
Zhang Wei	2015	China	Asian	45.3±3.4/45.2±3.2	100/100	3
Wu Yunping	2015	China	Asian	53.6±7.4/54.1±9.3	44/45	5
Tan Zhixiong	2016	China	Asian	53.9±7.8/54.3±8.6	53/53	3
Alavi Foumani Ali	2019	Iran	Asian	67.9±7.9 /68.4±7.8	32/31	5

should have been more than two.

Statistical analysis

Meta-analysis was carried out by Review Manager Version 5.3 (Revman 5.3). We used standardized mean difference (SMD) and mean difference (MD) to assess the efficacy of vitamin D therapy in patients with COPD. There was a statistically significant difference when $P<0.05$. The I^2 statistic was used to evaluate heterogeneity of the included studies. In the absence of significant heterogeneity, we used a fixed-effect model ($P\geq 0.05$, $I^2\leq 50\%$), otherwise a random-effect model was adopted.

Results

Study characteristics

Searches of the PubMed, CNKI, Embase, Web of Science

Table 2 Characteristics and Investigated indexes of included studies in the present meta-analysis

First author	Year	Antibiotic and dose	Duration of therapy	Investigated indexes
Shi Rui	2012	Alfacalcidol 0.5 μg QD	3 months	FEV1
Lehouck An	2012	Vitamin D 400 to 880 IU QD	1 year	FEV1, FEV1/ FVC
Zhang Tianwei	2014	Calcitriol 0.25 μg QD	3 months	FEV1, FEV1/ FVC
Tang Lixin	2014	Alfacalcidol 0.5 μg QD	2 months	FEV1, FEV1/FVC
He Yeying	2014	Vitamin D3 30 U QD + Calcitriol 0.25 μg QD	3 months	FEV1, sputum, exacerbations
Zhang Han	2015	Alfacalcidol 0.5 μg QD	6 months	FEV1, FEV1/FVC
Zendedel Abolfazl	2015	100,000 IU of oral vitamin D per month	6 months	FEV1, exacerbations
Qu Xia	2015	Vitamin D3 0.25 μg + vitamin A 5,000 IU QD	3 months	FEV1, FEV1/FVC, exacerbations
Chang Caihong	2015	Vitamin D3 125 IU QD	4 month	FEV1, 6MWD
Gu Haiting	2015	Alfacalcidol 0.25 μg QD	6 months	FEV1, FEV1/ FVC, exacerbations
Du Zhenying	2015	Vitamin D 2 g BID	2 months	FEV1, FEV1/ FVC
Sanjari (Calcitriol)	2016	Calcitriol 0.25 μg QD	6 months	FEV1, FEV1/ FVC
Li Yong	2016	Alfacalcidol 400 U QD	2 months	FEV1, FEV1/ FVC, exacerbations
Sanjari (Vitamin D)	2016	Vitamin D 50,000 IU QD	6 months	FEV1, FEV1/ FVC
Feng Congrui	2017	Calcitriol 0.25 μg QD	8 weeks	FEV1, FEV1/FVC
Khan Dur Muhammad	2017	Vitamin D 2,000 IU QD	6 months	Exacerbation, FEV1
Wang Yuehua	2017	Alfacalcidol 0.25 μg QD	1 year	FEV1, FEV1/FVC
Rafiq Rachida	2017	Vitamin D3 1,200 IU QD	6 months	FEV1, FEV1/ FVC, exacerbations, 6MWD
Hornikx Miek	2012	Colecalciferol 100,000 IU per month	3 months	6MWD
Van de Bool Coby	2017	Vitamin D 0.5 QD	4 months	6MWD
Gu Wenchao	2015	Liquid calcium + vitamin D 1,000 IU QD	1 year	6MWD CAT
MA Yinbo	2014	Vitamin D 300,000 IU QD + Calcitriol 0.25 μg QD	2 months	Sputum CAT
Zhang Wei	2015	Vitamin D3 300,000 IU + Calcitriol 0.25 μg QD	3 months	Sputum
Wu Yunping	2015	Vitamin D3 100,000 IU BIW	2 months	CAT
Tan Zhixiong	2016	Vitamin D3 100,000 IU BIW	2 months	CAT
Alavi Foumani Ali	2019	Vitamin D3 50,000 IU QW	6 months	FEV1, FEV1/FVC, CAT, exacerbations

QD, quaque day; BID, bis in day; BIW, bis in week; QW, quaque week; FEV1, forced expiratory volume in 1 second; 6MWD, 6-minute walking distance; CAT, COPD assessment test.

and WanFang Data databases returned 232 potentially relevant records. After their titles or abstracts were read, 190 of these records were excluded. The remaining 42 studies were read and the inclusion and exclusion criteria were applied. From these studies: 5 articles were non-RCTs, 4 articles had observational indexes not related to this meta-analysis, 3 articles did not provide the date required for this meta-analysis, 3 articles were excluded because of insufficient sample sizes, and 2 articles were duplicates. Finally, 26 studies of 25 articles (22-45), with a total of 2,670 participants (of which 1,355 were in the experiment group and 1,315 were in the control group) were included in this

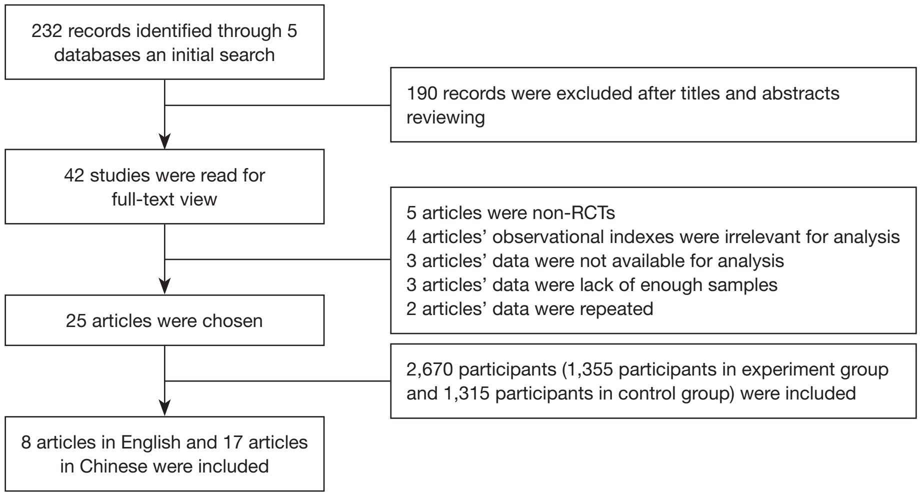

Figure 1 The flow diagram of included and excluded studies. RCT, randomized controlled trial.

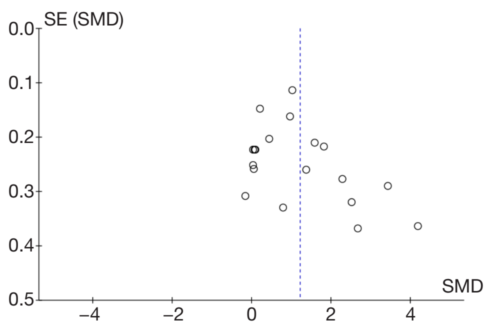

Figure 2 Funnel plot for the assessment of publication bias in this study.

meta-analysis. As shown in *Figure 1*, 8 articles were written in English (22-29) and 17 were written in Chinese (30-46).

Methodological quality of included studies

The 26 included studies were assessed using the Cochrane Collaboration tool. The quality of each study was evaluated by 2 independent reviewers. Differences were resolved by the third reviewer.

Publication bias

Funnel plots were used to assess the publication bias of the included studies. Both Egger's regression test and Begg's test were conducted. The Begg's funnel plot appeared to have a symmetrical shape. No evident publication bias was found in the eligible studies through this analysis (P=0.606 for Egger's regression test, and P=0.315 for Begg's test) (*Figure 2*).

Meta-analysis results

FEV1

We collected 19 studies (involving 2,004 patients) from 18 articles which reported the effects of vitamin D supplementation on FEV1 in the experimental group in comparison with the control group (22-26,29-39,42,43). We used a random effects model to assess SMD when the I^2 test showed heterogeneity (I^2=95%, P<0.01). The results showed a statistically significant difference between the FEV1 of the patients treated with vitamin D supplementation and those treated without. (SMD: 1.21, 95% CI: 0.76–1.66, P<0.01) (*Figure 3*).

FEV1/FVC

Thirteen studies (involving 1,524 patients from 12 studies] compared FEV1/FVC in the experimental group after vitamin D supplementation with that of the control group (22,25,26,29-36,38,39). Overall, the results demonstrated that vitamin D in patients with COPD had a statistical significance in FEV1/FVC (SMD: 1.07, 95% CI: 0.56–1.58, P<0.01), according to a random effects model (I^2=95%, P<0.01) (*Figure 4*).

Acute exacerbation

Six articles (involving 539 patients: 272 in the experimental group, and 267 in the control group) showed acute

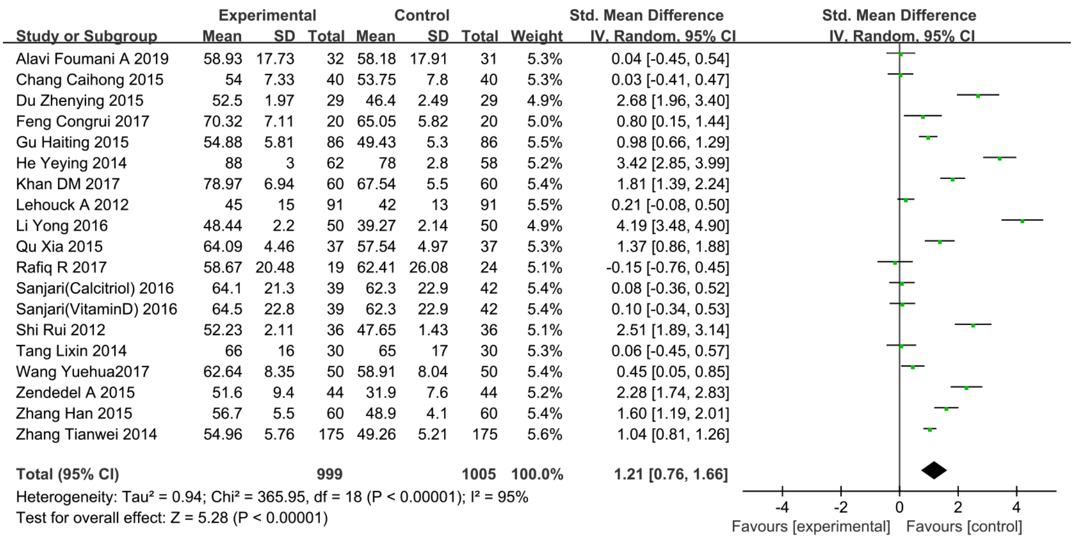

Figure 3 Meta-analysis of vitamin D used in patients with COPD on FEV1 using a random effects model. COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second.

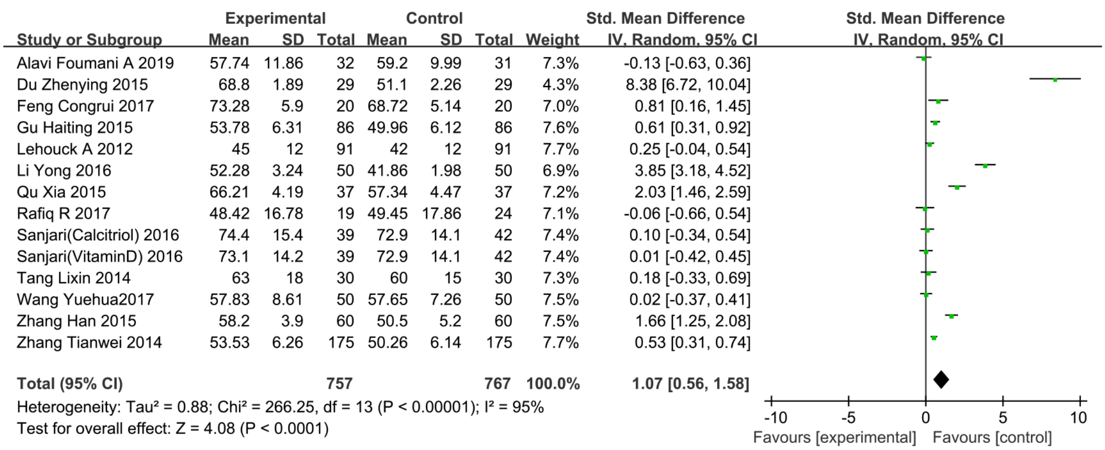

Figure 4 Meta-analysis of vitamin D used in patients with COPD on FEV1/FVC using a random effects model. COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second.

exacerbation in the experimental group after vitamin D supplementation, in comparison with the control group (22-24,30-31,42). Overall, the frequency of acute exacerbation in the experimental group was less than in the control group (SMD: 0.39, 95% CI: 0.23–0.64, P<0.01). As the results showed no heterogeneity, we chose a fixed effects model (I^2=0%, P=0.68) (*Figure 5*).

Sputum

In total, 3 articles (involving 612 patients: 308 in the experimental group, and 304 in the control group) showed the effects of vitamin D supplementation on sputum (41-43). The results revealed that sputum in COPD patients with vitamin D supplementation decreased significantly when compared to the control group (SMD: −6.02, 95% CI: −8.25 to −3.79, P<0.01). We used a random effects model to integrate the data (I^2=97%, P<0.01) (*Figure 6*).

6MWD

Five articles (involving 287 patients: 142 in the experimental

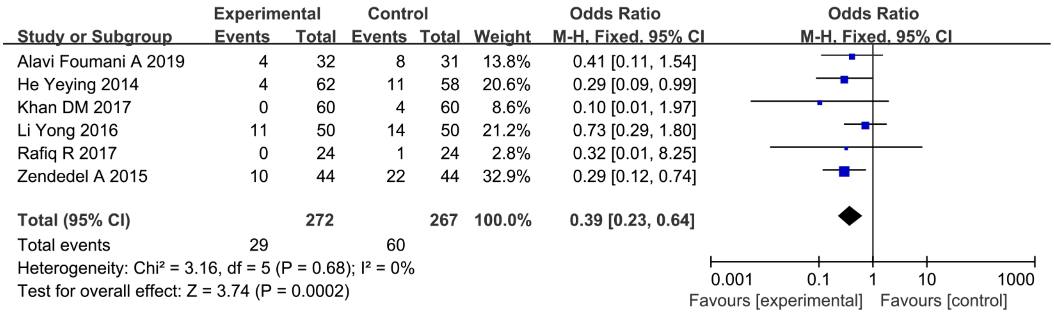

Figure 5 Meta-analysis, using a random effects model, of the effects of vitamin D on sputum in patients with COPD. COPD, chronic obstructive pulmonary disease.

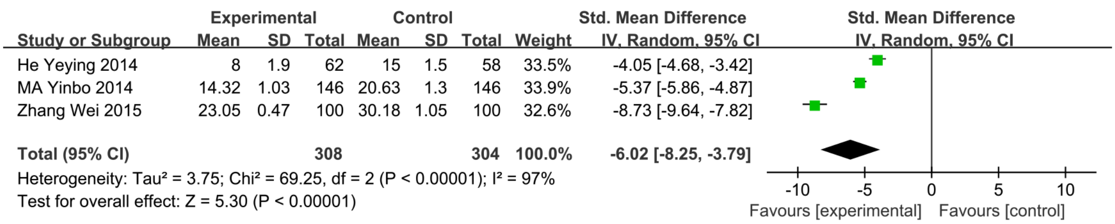

Figure 6 Meta-analysis, using a fixed effects model, of the effects of vitamin D on acute exacerbation when used in patients with COPD. COPD, chronic obstructive pulmonary disease.

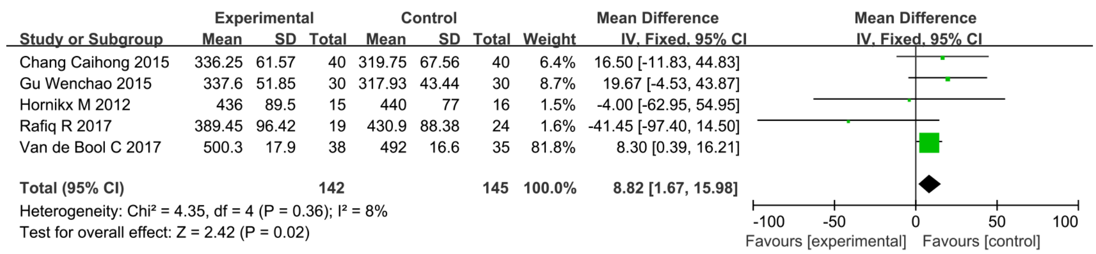

Figure 7 Meta-analysis, using a fixed effects model, of the effects of vitamin D on 6MWD in patients with COPD. 6MWD, 6-minute walk distance; COPD, chronic obstructive pulmonary disease.

group, and 145 in the control group) showed the effects of vitamin D supplementation on the 6-minute walk distance in the experimental group in comparison with the control group (22,27,28,36,40). Due to the absence of significant heterogeneity, we used a fixed effects model (I^2=8%, P=0.36). The results indicated a statistically significant difference between the 6MWD of patients treated with vitamin D supplementation and those treated without (MD: 8.82, 95% CI: 1.67–15.98, P=0.02) (*Figure 7*).

CAT score

Five studies (involving 610 patients: 305 in the experimental group and 305 in the control group), included the COPD assessment test (CAT) score (30,40,41,44,45). Overall, the results demonstrated that there is a statistically significant difference in CAT between those COPD patients treated with vitamin D supplementation and those treated without (SMD: −1.19, 95% CI: −1.74 to −0.63, P<0.01). Because of the significant heterogeneity (I^2=88%, P<0.01, we used a random effects model to examine the SMD (*Figure 8*).

Discussion

Vitamin D, one of the fat-soluble vitamins, is found in

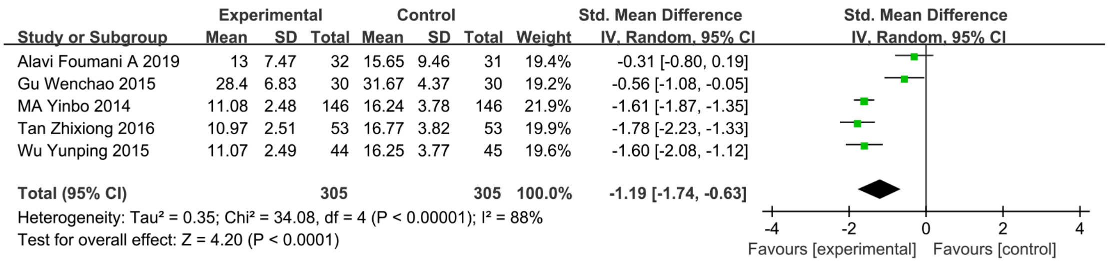

Figure 8 Meta-analysis, using a random effects model, of the effects of vitamin D on CAT score of patients with COPD. CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease.

two compounds: ergocalciferol (D2) and cholecalciferol (D3). Vitamin D plays a crucial role in bone and mineral metabolism (46) as, by functioning as a negative regulator of the renin–angiotensin–aldosterone system (RAAS), it modulates myocardial extracellular matrix turnover. Thus, vitamin D deficiency can cause the deterioration of heart function and accelerate myocardial remodeling (47). Vitamin D insufficiency is a factor in other conditions, sometimes leading to rickets, osteoporosis and osteomalacia, as well as other bone-related disorders (46). Recently, an increasing number of studies have suggested that vitamin D has a far broader range of physiological functions, which might have clinical implications for COPD patients (22).

Recently, there has been a growing desire to investigate the role of vitamin D in the treatment of respiratory diseases, including asthma and chronic obstructive pulmonary disease (COPD). Some hopeful reports on the possible application of vitamin D as a treatment for asthma have been published (48). Vitamin D, which plays an essential function in the pathogenesis of asthma, reduces the production of inflammatory cytokines via T-helper type-9 lymphocytes, such as interleukin-5 (IL-5), IL-9, and IL-13 (49). Further links between vitamin D and COPD have also been highlighted. Some experimental studies have suggested that the role of vitamin D in the growth and development of COPD can not be ignored. The existence of vitamin D in alveolar type II cells can enhance surfactant synthesis and regulate epithelial-mesenchymal interactions (49). Furthermore, there is a molecular relationship between smoking and vitamin D signaling. Cigarette smoke extracts inhibit VDR translocation in human alveolar epithelial cells, which leads to downregulation of local vitamin D signaling, resulting in deficiency in the control of proinflammatory processes in the airways of COPD patients (50).

In 2017, Rafiq *et al.* reported that there were no differences in 6-minute walk test results, handgrip strength, pulmonary function, exacerbation rate, or quality of life between COPD patients in the vitamin D group and the placebo group. Taking vitamin D increases the serum 25(OH)D levels (22). Unfortunately, one study alone may have insufficient power to support or suppose the use of vitamin D in COPD patients. Some contributing factors are as follows: (I) the article was a pilot trial, and the major limitation of this study was the small sample size, which only included 50 participants; (II) the study excluded participants aged >70 years, which could have led to a lower mean age of the study population; (III) the study also excluded patients with severe vitamin D deficiency (15 nmol/L), which might have affected the outcomes, as a potential effect of vitamin D supplementation was expected to be stronger in vitamin D-deficient COPD patients. In 2017, Khan *et al.* also revealed the relationship between the vitamin D and COPD patients (24). In this study, the results demonstrated that prolonged vitamin D use in patients with COPD could reduce the frequency of acute exacerbation and improve FEV1, FVC; however, it couldn't alleviate dyspnea, sputum volume, or sputum purulence. Khan *et al.* showed that the dose of vitamin D used to treat COPD patients and the baseline serum vitamin D levels in patients might lead to contradictory results. Furthermore, more studies regarding vitamin D therapy for COPD patients have been emerging (36,41,42). However, their results have been inconclusive due to factors including sample size, participation, the dose of vitamin D, and course of treatment.. Therefore, we enforced a comprehensive meta-analysis to evaluate the effects of vitamin D supplementation in patients with COPD.

In our meta-analysis, we found that vitamin D used in patients with COPD can improve lung function (FEV1, FEV1/FVC), 6MWD and reduce the acute exacerbation, sputum, and CAT score. The pathogenesis of COPD mainly includes inflammation, oxidative stress, and pulmonary protease-antiprotease imbalance. A number of articles have reported the relationship between vitamin D and the pathogenesis of COPD. Some previous experimental studies have suggested that the existence of vitamin D in alveolar type II cells promotes surfactant synthesis and regulates epithelial-mesenchymal interactions. Our report (51,52) proved that vitamin D could decrease oxidative stress and particulate matter-induced IL-6 response, and that vitamin D sufficiency was probably beneficial in protecting against pollution-associated diseases related to the induction of airway and systemic inflammation. Smoking was the most important element which led to airway inflammation. The study demonstrated the relationship between smoking and vitamin D signaling (50). Cigarette smoke extracts inhibit VDR translocation in human alveolar epithelial cells and result in downregulation of local vitamin D signaling, which causes deficiency in controlling proinflammatory processes in the airways of COPD patients. This means that by supplying vitamin D to COPD patients, their symptoms could be improved.

At present, theophylline, long-acting beta2-agonists (LABA), inhaled corticosteroids (ICS) are the most commonly used drugs to treat patients with COPD. The main function mechanisms of these drugs is to eliminate inflammation and to relax the bronchial tube to decrease airway resistance. Interestingly, vitamin D sufficiency is perhaps beneficial in protecting against airway and systemic inflammation diseases. Many studies have considered that vitamin D supplementation can improve COPD symptoms. According to previous studies and our meta-analysis, we also could put forward a hypothesis that vitamin D could increase the serum concentration of the previously mentioned drugs and improve patients' lung function. In this meta-analysis, the included 25 articles did not respectively observe all indexes which we discussed in our study. Different articles might draw different conclusions due to the dose of vitamin D used, the method of administering vitamin D and individual differences, including age, gender and race. However, by analyzing the 25 articles, we can arrive at a general conclusion that, when used in patients with COPD, vitamin D can improve some indexes. The follow points may explain the validity of this conclusion: (I) the articles we chose came from different countries and contained a mass of samples; (II) for differences in the methods of application, dosage and courses of treatment of vitamin D, we carried out a unified and detailed analysis; (III) the 25 articles were chosen in accordance with strict inclusion criteria and exclusion criteria.

However, there were still some limitations of the present meta-analysis when explaining aggregated results. Firstly, each of the included individuals had a different environment and their jobs were not classified, and we lacked sufficient data to perform subgroup analysis to reduce the influence of individual differences. Secondly, several inevitable problems existed within the included studies, such as sample size, age and gender of research objects, and differences in inclusion and exclusion criteria which could cause bias. Thirdly, the articles were published at different periods in time and may be limited by current medical conditions, which could also have affected our results. In this meta-analysis, no subgroup analysis was conducted to factor in the range in vitamin D dosage. Furthermore, the degree of COPD and the baseline level of 25(OH)D in serum each had an impact on the efficiency of vitamin D used in COPD patients and were not addressed. Despite these limitations, we were able to select more articles according to our inclusion criteria to increase sample size to control bias and could confirm results through well designed studies with large sample sizes. We were also able to minimize bias throughout the entire process by creating a detailed protocol, selecting articles independently, and using statistical analysis and data selection. We, therefore, have full confidence in the reliability of our results.

Conclusions

Overall, the results of this meta-analysis showed that treatment with vitamin D may improve the lung function of COPD patients (FEV1, FEV1/FVC), 6MWD and reduce the frequency of acute exacerbation, sputum, and CAT score.

Acknowledgments

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was reviewed by the experts of the hospital ethics committee and was approved as complying with the requirements and guidelines of research.

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