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Vitamin D does not improve lung function decline in COPD: a meta-analysis

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Abstract. – OBJECTIVE: Vitamin D deficiency plays an important role in chronic obstructive pulmonary disease (COPD). However, the effects of vitamin D supplementation on lung function decline in COPD were inconsistently reported and a meta-analysis is thus needed.

MATERIALS AND METHODS: Eligible cohort and randomized controlled trials (RCTs) were searched from databases including PubMed, Embase, and Web of Science. Pooled standardized mean difference (SMD) with 95% confidence interval (CI) was calculated in a random or fixed effects model.

RESULTS: Eight studies reaching the inclusion criteria and involving 687 COPD patients were included. Pooled effect size showed vitamin D treatment resulted in no significant improvements in FEV_1 (SMD: 0.38, 95% CI: -0.13 to 0.88, p= 0.144), FVC (SMD: 0.55, 95% CI: -0.49 to 1.58, p=0.299), and FEV_1/FVC (SMD: 0.00, 95% CI: -0.27-0.27, p=0.995) in COPD patients. Subgroup analysis revealed neither short-term (<6 months) (SMD: 0.10, 95% CI: -0.17 to 0.37, p=0.479) nor long-term (≥6 months) (SMD: 0.52, 95% CI: -0.23 to 1.27, p=0.172) vitamin D exposure could significantly benefit lung function decline in COPD.

CONCLUSIONS: This meta-analysis shows neither short-term nor long-term additional supplementation of vitamin D can benefit the lung function decline in COPD. Moreover, large scale RCTs focusing on COPD smokers with low level of vitamin D should be considered.

Key Words:
Chronic obstructive pulmonary disease, Lung function, Meta-analysis, Vitamin D.

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease that is characterized by persistent airflow limitation owing to chronic inflammatory response to cigarette smoke and other noxious particles or gases, which eventually results in progressive lung function decline and increasing exacerbation frequency[1]. However, to our knowledge, no effective intervention on lung function decline in COPD is available now. It is well-known that vitamin D and its active form (vitamin D3 or cholecalciferol) are beneficial for skeletal health, which plays an important role in prevention and treatment of osteoporosis[2,3]. Moreover, vitamin D sufficiency, defined as the serum level of the stable metabolite 25(OH) D, is necessary for regulating immune-inflammatory responses to infections with its receptor[4,5]. In COPD, low level of vitamin D leads to more severe exacerbation, which is thought to be a result of an impaired innate response to pathogens and other stimuli, such as cigarette smoke, followed by an excessive adaptive immune response with increased inflammatory cytokines and airway inflammation[6,7]. Recently, some studies[8-12] have shown low serum 25(OH)D concentration is related to poor lung function and severity of COPD. However, regarding the benefits of vitamin D supplementation on lung function decline in COPD, some researches indicated the positive results[13,14], while others reported the negative conclusions[15-20].

Meta-analysis has been considered to be a useful mean to pool the independent statistical powers and thus achieve a quantitative understanding of inconsistent results. Therefore, to our knowledge, we performed a meta-analysis for the first time to draw a pooled conclusion on the effect of vitamin D on lung function decline in COPD.

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Materials and Methods

Search Strategy

To identify all published clinical trials related to vitamin D and COPD, the literature search was performed using the databases including PubMed, Embase, and Web of Science, up to May 2018, with the following terms: 1) vitamin D, vitD, vitamin D3, or cholecalciferol; 2) COPD, chronic obstructive pulmonary disease, chronic obstructive airway disease, or chronic airway disease. Additionally, the reference lists of the retrieved articles were manually checked for potentially eligible studies.

Data Extraction

Two investigators (Fangying Chen and Min Xiao) independently selected the studies according to inclusion and exclusion criteria. Cohort and randomized controlled trials (RCTs) reporting the data of lung function of COPD patients exposed to vitamin D will be included, regardless of use the blind methods or not. Exclusion criteria were: (1) subjects with COPD and asthma overlap (ACO); (2) *in vitro* studies; (3) duplicated reports; (4) no data for extraction; (5) meeting abstracts. Publication time and language were unlimited. Unpublished data were not considered. Any disagreement was resolved in the presence of another investigator (Bing Ling) before reaching a consensus.

Quality Assessment

To assess the quality of the eligible studies, two independent assessors (Min Xiao and Bing Ling) scored the studies according to the Newcastle-Ottawa Scale (NOS) for cohort studies and Jadad Scale for randomized controlled studies. The 9-point NOS contains three items: selection (0-4), comparability (0-2), and exposure (0-3). The 5-point Jadad Scale also contains three items: randomization (0-2), blinding (0-2), and withdrawals/dropouts (0-1). Studies that scored over 7 points on the NOS or over 3 points on the Jadad Scale were deemed to be of high quality. Any disagreement was resolved via a discussion with a third assessor (Lin Liu) until a consensus was reached.

Statistical Analysis

Continuous variables were presented as standardized mean differences (SMDs) with 95% confidence intervals (CIs). Pooled SMD with 95% CI was calculated and $p<0.05$ indicated statistical significance. Heterogeneity was detected by the Q-test. Thus, meta-analysis was done with the random-effects model with heterogeneity ($p<0.1$ for the Q-test), or the fixed-effects model without heterogeneity ($p\geq0.1$ for the Q-test). Sensitivity analysis was checked using the leave-one-out method. Funnel plots with the Begg's rank correlation test and Egger's linear regression test was performed to assess the publication bias ($p<0.05$). All the statistical analyses were conducted by Stata 12.0 (Stata Corp LP, College Station, TX, USA).

Results

Description of Studies

Based on the search strategies, 126 studies were collected according to the search terms. After screening the titles, abstracts, and articles, only eight studies matched the inclusion criteria. The eight included articles were published from 2012 to 2017 covering 687 COPD patients and carried out in Belgium, Iran, Egypt, Pakistan, and the Netherlands[11-18]. The process of literature screening was presented in Figure 1. The main characteristics of the included eight studies in this meta-analysis were shown in Table I.

Quantitative Synthesized Results

Pooled effect size showed no significant improvements in forced expiratory volume in 1 second (FEV_1) (SMD: 0.38, 95% CI: -0.13 to 0.88, $p=0.144$) (Figure 2), forced vital capacity (FVC) (SMD: 0.55, 95% CI: -0.49 to 1.58, $p=0.299$) (Figure 3) and FEV_1/FVC (SMD: 0.00, 95% CI: -0.27-0.27, $p=0.995$) (Figure 4) in COPD patients after vitamin D supplementation treatment. In subgroup analysis, neither shot-term (<6 months) (SMD: 0.10, 95% CI: -0.17 to 0.37, $p=0.479$) nor long-term (≥6 months) (SMD: 0.52, 95% CI: -0.23 to 1.27, $p=0.172$), there were no benefits to lung function decline after vitamin D treatment (Figure 2).

Heterogeneity and Sensitivity and Publication Bias

Significant heterogeneity was observed among included studies in the meta-analysis. In the subgroup analysis, no significant heterogeneity was revealed in the short-term exposure subgroup ($p=0.879$) (Figure 2). Further, the leave-one-out sensitivity analysis was performed to explore the

Table I. Clinical features of included studies. NR=not reported; M=male; F=female; VitD=vitamin D; 25(OH)D=25-hydroxyvitamin D; FEV_1=forced expiratory volume in one second; FVC=forced vital capacity; pred=predicted; NOS=New-castle-Ottawa Scale; JAD=Jadad Scale; Δ: alterations of lung function between before and after treatment with vitD.

Reference	Country	Study design	Subjects	Gender (M/F)	Age (years)	Smoking (pack-years)	Intervention	Combined Therapy	Follow-up	Lung function test		Quality Score	
										VitD	Placebo/Baseline	NOS	JAD
Lehouck et al[15] 2012	Belgium	randomized double-blind prospective placebo-controlled	182 moderate to severe COPD (25(OH)D=20±12 nmol/L)	145/37	68±9 (VitD) 68±8 (placebo)	51±23 (VitD) 53±32 (placebo)	oral VitD 100 000 IU every 4 weeks	long-acting anticho-linergic, short-acting bronchodilators, Steroids	1 year	FEV_1%pred 1.2±0.5	FEV_1%pred 1.2±0.5		7
Rezk et al[18] 2015	Egypt	cohort	30 severe COPD (25(OH)D< 20 ng/ml)	26/4	66.7±8.5	48±8.1	oral $VitD_3$ 50,000 IU once weekly (8w) + 800 IU daily	NR	1 year	FEV_1%pred 38.98±6.50 FVC%pred 63.03±4.79	FEV_1%pred 38.27±6.32 FVC%pred 60.53±4.36	6	
Said et al[19] 2015	Egypt	cohort	31 stable COPD (25(OH) D=20.4±6.6 ng/mL)	23/8	61.1	21±4.5	VitD 200,000 IU monthly intramuscular injection	NR	6 months	FEV_1%pred 33.5±17.2 FVC%pred 56.4±15.6	FEV_1%pred 32.4±14.1 FVC%pred 55.9±10.4	7	
Moosavi et al[16] 2015	Iran	cohort	24 mild to severe COPD (25(OH) D=13±4 ng/mL)	20/4	62±12	NR	VitD 300,000 or 600,000IU intramus-cular injection+oral 50000 IU weekly	NR	12 weeks	FEV_1%pred 52±17 FVC%pred 69±20	FEV_1%pred 52±17 FVC%pred 67±17	7	
Zendedel et al[14] 2014	Iran	randomized double-blind prospective placebo-controlled	88 severe and very severe COPD	60/28	year<45, n=2 year45-60, n=15 year>60, n=27	NR	oral VitD 100,000 IU per month	routine treatment	6 months	ΔFEV_1%pred 17±12.7	ΔFEV_1%pred -2.5±19		6
Sanjari et al[20] 2016	Iran	randomized double-blind prospective placebo-controlled	81 moderate to severe COPD	57/24	55.8±9.5 (VitD) 58.4±9.5 (placebo)	NR	oral VitD 50000 IU daily	NR	7 days	ΔFEV_1%pred 17.8±27.6 ΔFEV_1/FVC% 4.9±22	Δ: FEV_1%pred 15.6±37 ΔFEV_1/FVC% 2.7±22		7
Sanjari et al[20] 2016	Iran	randomized double-blind prospective placebo-controlled	81 moderate to severe COPD	63/18	55.6±10.4 (calcitriol) 58.4±9.5 (placebo)	NR	oral calcitriol 0.25 µg daily	NR	7 days	ΔFEV_1%pred 46.3±17.5 ΔFEV_1/FVC% 5.3±22	ΔFEV_1%pred 62.3±22.9 ΔFEV_1/ FVC% 2.7±22		7
Khan et al[13] 2017	Pakistan	cohort	120 AECOPD	78/42	46.28±8.83	NR	oral VitD 2000 IU daily	routine treatment	6 months	FEV_1%pred 78.97±6.94 FVC%pred 91.34±5.52	FEV_1%pred 67.54±5.50 FVC%pred 77.83±5.49	3	
Rafiq et al[17] 2017	Netherlands	randomized double-blind placebo-controlled	50 COPD	26/24	61[58-66] 64[61-66]	30.9±18.5 (VitD) 29.6±6.7 (placebo)	$VitD_3$ 1200 IU daily	calcium intake of at least 1,000 mg per day	6 months	ΔFEV_1%pred 0.21±4.25 ΔFVC%pred 0.81±5.52 ΔFEV_1/FVC% -0.34±3.02	ΔFEV_1%pred 3.46±8.05 ΔFVC%pred 3.86±8.31 ΔFEV_1/FVC% 0.99±4.38		7

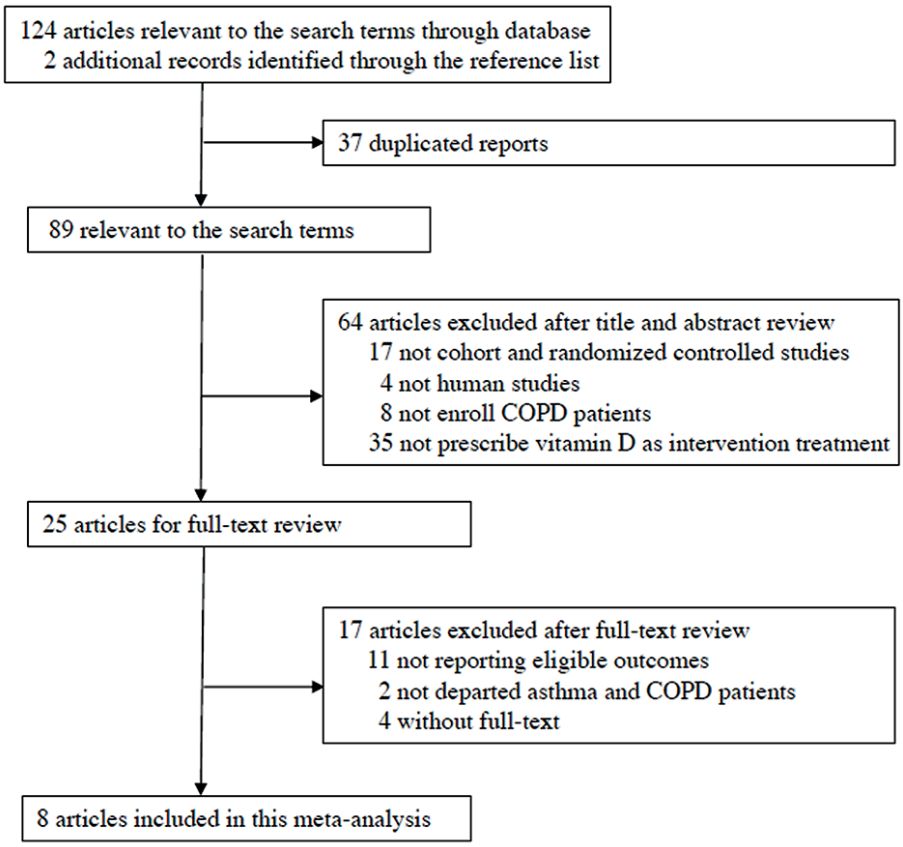

Figure 1. Follow diagram of search process.

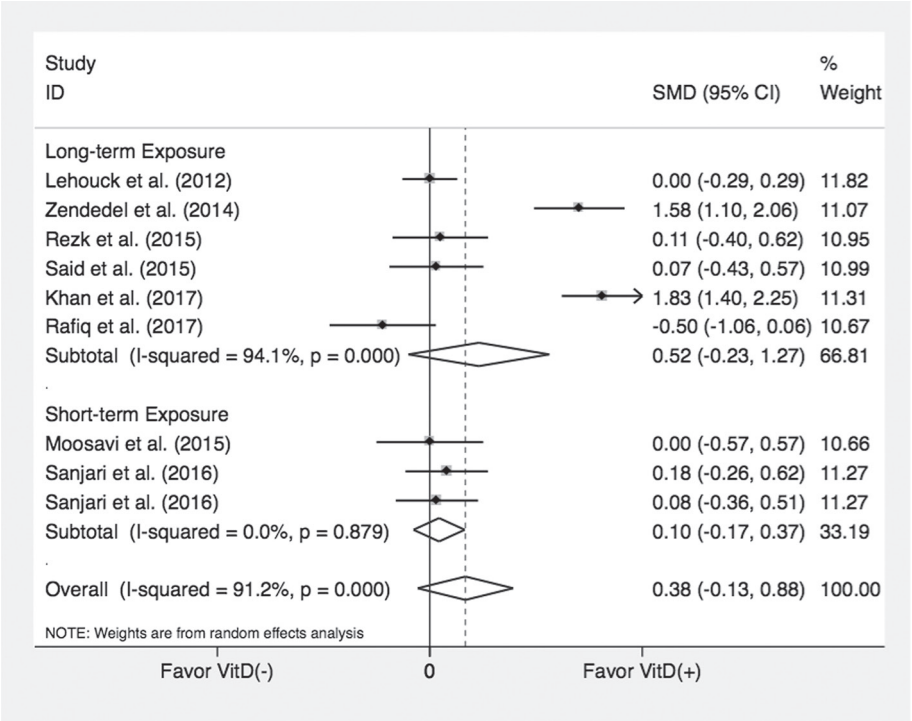

Figure 2. Forest plots of SMD with 95% CI for the effect of vitamin D on FEV_1 in COPD patients.

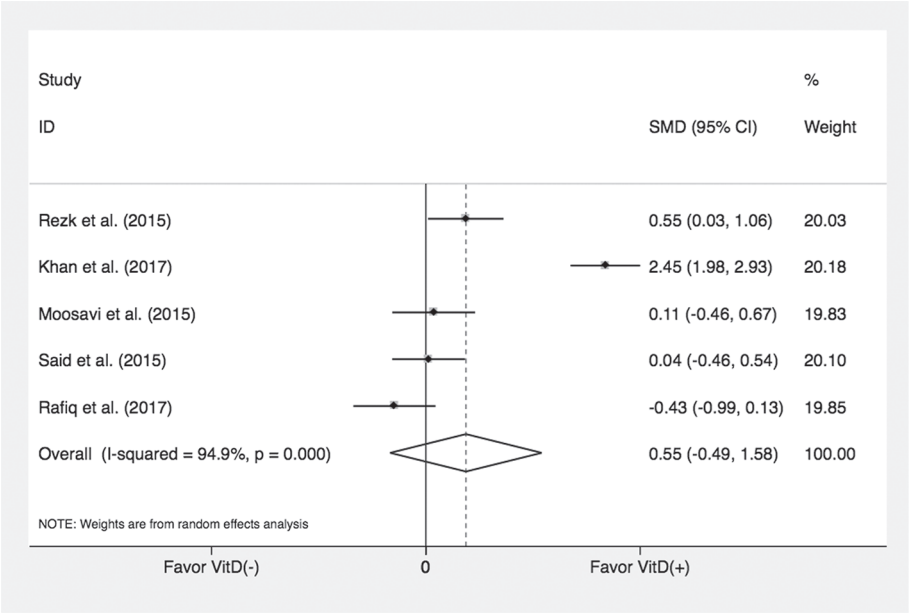

Figure 3. Forest plots of SMD with 95% CI for the effect of vitamin D on FVC in COPD patients.

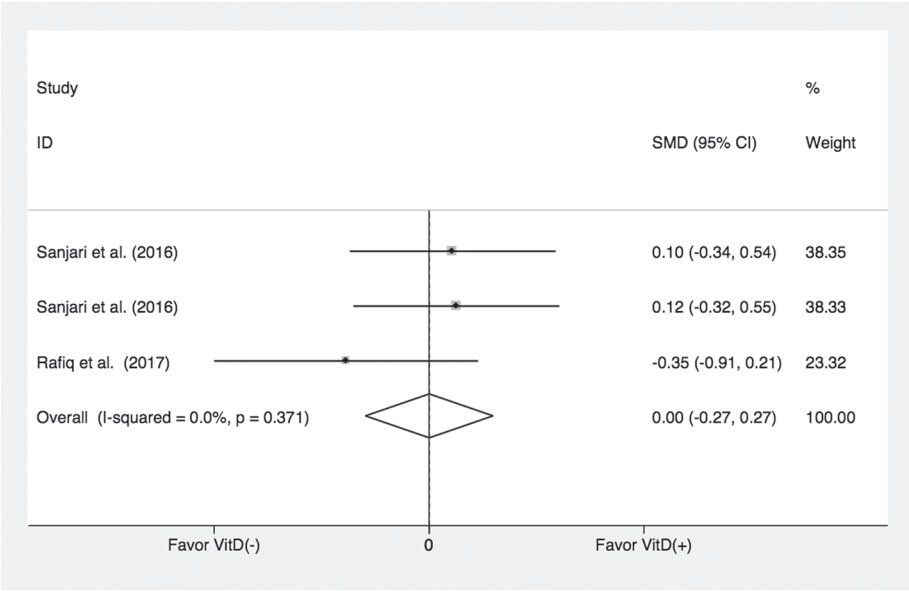

Figure 4. Forest plots of SMD with 95% CI for the effect of vitamin D on FEV_1/FVC in COPD patients.

possible causes of heterogeneity on the pooled results. No significant alterations in pooled results were demonstrated after the removal of all included studies one by one (Figure 5). Begg's rank correlation test (p=0.602) and Egger's linear regression test (p=0.899) indicated no publication bias in this meta-analysis (Figure 6).

Discussion

In this meta-analysis, no significant improvements in FEV_1, FVC, and FEV_1/FVC in COPD were revealed after vitamin D treatment. Moreover, neither short-term (<6 months) nor long-term (≥6 months) exposure with vitamin D could

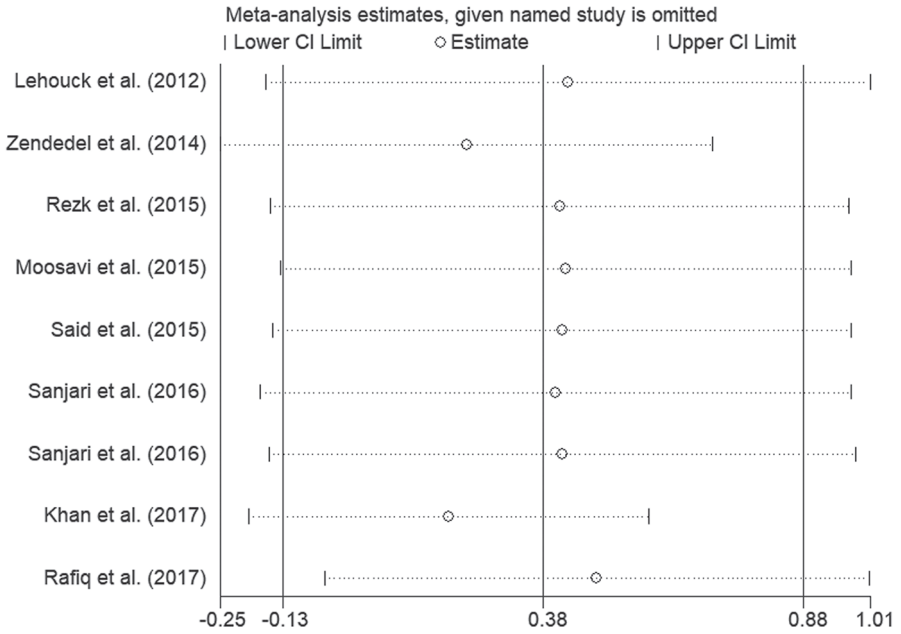

Figure 5. The leave-one-out sensitivity analysis for the effect of vitamin D on FEV_1 in COPD patients.

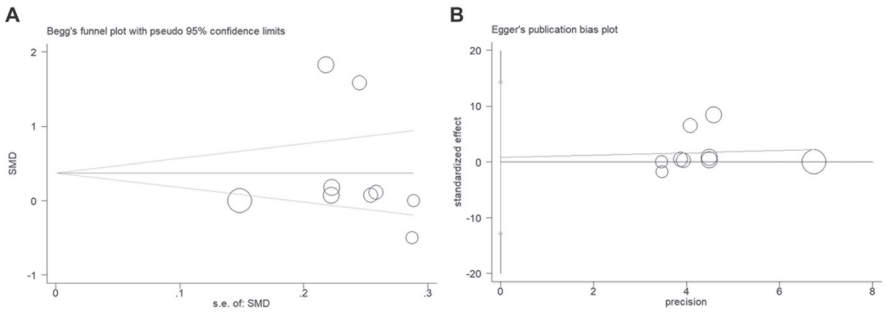

Figure 6. Begg's (**A**) and Egger's (**B**) funnel plots for evaluation of publication bias for the effect of vitamin D on FEV_1 in COPD patients.

significantly improve lung function decline in COPD.

COPD patients are at risk for vitamin D deficiency[7,12,21], with the indication of the more 25(OH)D deficiency, the poor lung function with more severity of COPD[8,10,22]. Previously Hornikx et al[23] demonstrated that vitamin D supplementation might enhance inspiratory muscle strength and improve maximal oxygen uptake in COPD. However, not all COPD patients, but the subgroup of ever-smoking[24], especially severe subjects with 25(OH)D deficiency[14,25], might benefit from vitamin D supplementation. Although no significant results were revealed in this meta-analysis, the included studies by Zendedel et al[14] and Khan et al[13] indicated vitamin D intake could significantly improve FEV_1 in COPD, which is probably owing to two potential reasons: (i) low serum level of 25(OH)D at baseline[13,14], (ii) advanced COPD subjects with a majority of smokers[14].

However, when applying the results in the present study, limitations should be taken into account as follows: first, only eight studies with 687 COPD subjects were included. The small sample size might weaken the statistic power of the pooled results. Second, the pooled estimates in this meta-analysis were not based on adjustment by potential confounded factors, such as age, gender, smoking history, nationality, combined therapies, the baseline level of 25(OH)D, dose and administration of vitamin D, etc., which might influence the stringency of the pooled results.

Conclusions

This meta-analysis cautiously suggests neither short-term nor long-term exposure of vitamin D can improve lung function decline in COPD. However, large scale randomized controlled trials are warranted, which would aim at COPD smokers with low circulating level of vitamin D.

Acknowledgements

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Conflicts of interest

The authors declare no conflicts of interest.

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