

# The association between vitamin D and COPD risk, severity, and exacerbation: an updated systematic review and meta-analysis

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**Background:** In recent years, the pleiotropic roles of vitamin D have been highlighted in various diseases. However, the association between serum vitamin D and COPD is not well studied. This updated systematic review and meta-analysis aimed to assess the relationship between vitamin D and the risk, severity, and exacerbation of COPD.

**Methods:** A systematic literature search was conducted in PubMed, Medline, EMBASE, Chinese National Knowledge Infrastructure, Wanfang, and Weipu databases. The pooled risk estimates were standardized mean difference (SMD) with 95% confidence interval (CI) for vitamin D levels and odds ratio (OR) with 95% CI for vitamin D deficiency. Meta-regression and subgroup analyses were performed on latitude, body mass index, and assay method.

**Results:** A total of 21 studies, including 4,818 COPD patients and 7,175 controls, were included. Meta-analysis showed that lower serum vitamin D levels were found in COPD patients than in controls (SMD:  $-0.69$ , 95% CI:  $-1.00$ ,  $-0.38$ ,  $P < 0.001$ ), especially in severe COPD (SMD:  $-0.87$ , 95% CI:  $-1.51$ ,  $-0.22$ ,  $P = 0.001$ ) and COPD exacerbation (SMD:  $-0.43$ , 95% CI:  $-0.70$ ,  $-0.15$ ,  $P = 0.002$ ). Vitamin D deficiency was associated with increased risk of COPD (OR: 1.77, 95% CI: 1.18, 2.64,  $P = 0.006$ ) and with COPD severity (OR: 2.83, 95% CI: 2.00, 4.00,  $P < 0.001$ ) but not with COPD exacerbation (OR: 1.17, 95% CI: 0.86, 1.59,  $P = 0.326$ ). Assay methods had significant influence on the heterogeneity of vitamin D deficiency and COPD risk.

**Conclusion:** Serum vitamin D levels were inversely associated with COPD risk, severity, and exacerbation. Vitamin D deficiency is associated with increased risk of COPD and severe COPD but not with COPD exacerbation. It is worth considering assay methods in the heterogeneity sources analysis of association between vitamin D deficiency and COPD.

**Keywords:** vitamin D, COPD, risk, severity, exacerbation, meta-analysis

## Introduction

COPD is the fourth leading cause of mortality worldwide,<sup>1</sup> posing a big threat to public health. This is a progressive disease characterized by persistent airflow limitation, as a consequence of chronic inflammation and structural changes.<sup>2</sup> COPD patients suffer from progressive reduction of lung function, loss of exercise capacity, frequent disease exacerbations, and development of extrapulmonary comorbidities (such as osteoporosis, infection, and cardiovascular disease).<sup>3</sup>

Vitamin D is traditionally known for its roles in bone health and homeostasis of calcium and phosphorus.<sup>4</sup> However, vitamin D is not just a vitamin. It is recognized as a pleiotropic prohormone with its receptor (vitamin D receptor [VDR]) ubiquitously distributed.<sup>5</sup> As an immunomodulatory effector, vitamin D can not only boost innate immune responses upon infection but also regulate adaptive immune responses.<sup>6</sup>

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Moreover, vitamin D is related to cell proliferation, cell differentiation, apoptosis, and intercellular adhesion.<sup>7</sup> The majority of vitamin D originates from skin with sunlight exposure, and the remaining can be obtained from diet or supplements.<sup>8</sup> Epidemiologic studies reported that vitamin D deficiency is a global and important health issue.<sup>9</sup> Vitamin D deficiency can underpin the etiology of broad range of diseases, including autoimmune diseases, allergy diseases, endocrine and metabolic disorders, cancer, infections, and cardiovascular disorders.<sup>10,11</sup>

With a focus on the association between COPD and vitamin D, evidence from some studies indicated a possible link between vitamin D and COPD.<sup>12–14</sup> However, the conclusion was not definite. Two meta-analyses on the roles of vitamin D in COPD have been conducted.<sup>15,16</sup> However, the studies did not include enough articles, did not extract correct data, pooled the levels of vitamin D from serum and plasma, included participants with vitamin D supplement, or did not analyze the sources of high heterogeneity. Therefore, we performed a further systematic review and meta-analysis to clarify the roles of vitamin D in COPD. In this study, the associations between circulating 25(OH)D levels and risk, severity, and exacerbations of COPD were addressed.

## Methods

### Bibliographic search

This meta-analysis was conducted in accordance with the statement of meta-analysis of observational studies in epidemiology.<sup>17</sup> Two investigators (MZ and TW) independently conducted a literature search in PubMed, Medline, EMBASE, Chinese National Knowledge Infrastructure, Wanfang, and Weipu databases for publications targeting vitamin D and COPD (up to September 15, 2015). The search terms were “vitamin D”, “cholecalciferol”, “D3”, “ergocalciferol”, “D2”, “hydroxycholecalciferols”, “25-hydroxyvitamin D2”, “dihydroxycholecalciferol” or “25(OH)D” in combination with “COPD”, “pulmonary emphysema”, “chronic obstructive pulmonary disease”, or “chronic bronchitis”. Additionally, the reference lists of retrieved articles and reviews on target topic were manually checked for potential eligible studies.

### Inclusion criteria and exclusion criteria

Two authors (MZ and TW) independently screened the titles and abstracts and further reviewed the full text for potentially eligible studies according to the following inclusion and exclusion criteria. The inclusion criteria were as follows: 1) cohort, case-control, or cross-section design; 2) analyzed the association between serum 25(OH)D and COPD; 3) the effect size and its 95% confidence interval (CI) were provided

or could be estimated; 4) high-quality study; and 5) reported in English or Chinese. The exclusion criteria were as follows: 1) reviews, case reports, conference abstracts, letters, or editorials; 2) cells or animal models; 3) involved individuals who had vitamin D supplement; and 4) the levels of vitamin D were quantified by 1,25(OH)2D only, other than 25(OH)D, as 25(OH)D was the best indicator of vitamin D status. For duplicate publications, the most complete one was included.

### Data extraction

The following information was extracted from the included studies: first author, year of publication, study design, country, latitude of the region, sample size, body mass index (BMI), assay method, serum vitamin D levels, and distribution of vitamin D deficiency. The quality of included studies was assessed by 9-star Newcastle–Ottawa Scale. The following three major study components were judged: selection (0–4 stars), comparability (0–2 stars), and exposure/outcome (0–3 stars). This meta-analysis included studies with  $\geq 6$  stars representing the better methodological quality. Any discrepancies were resolved by discussion or consulting a senior author. If necessary data were not offered, we mailed the corresponding author for details.

### Statistical analysis

For the continuous data, the standardized mean difference (SMD) and 95% CI were computed. For the dichotomous data, the odds ratio (OR) and 95% CI were calculated. Heterogeneity was assessed by the Cochran  $Q$  test and the  $I^2$  statistic. For the  $Q$  statistic,  $P < 0.10$  level indicated statistically significant heterogeneity. For the  $I^2$  statistic,  $I^2 > 50\%$  suggested substantial heterogeneity. When heterogeneity was confirmed, the results were pooled using random effects model; otherwise, the fixed effects model was used. To explore potential sources of heterogeneity, meta-regression analyses and subgroup analyses were used according to latitude (low latitude:  $0^\circ$ – $30^\circ$ , middle latitude:  $30^\circ$ – $60^\circ$ , and high latitude:  $60^\circ$ – $90^\circ$ ), BMI (normal: 18.5–24.99, overweight: 25.0–29.99, and obese:  $\geq 30.0$ ), and assay method (enzyme-linked immunosorbent assay (ELISA), immunoassay, liquid chromatography electrospray ionisation tandem mass spectrometry (LC-MS/MS), and electrochemiluminescence). Sensitivity analysis was applied by omitting single study in turn and recalculating the pooled estimates to test the robustness of the pooled estimate. Publication bias was assessed by funnel’s plot and Egger’s test. All statistical analyses were conducted using Stata 12.0 (StataCorp LP, College Station, TX, USA). A two-tailed  $P$ -value was considered statistically significant, unless explicitly stated.

## Results

### Study selection and study characteristics

The study selection process is presented in a flow chart (Figure 1). Briefly, a total of 528 related publications were identified based on the searching strategy, among which 166 were duplicates. After screening the titles and abstracts, 110 articles remained for full text review. Finally, 21 eligible articles<sup>18–38</sup> were included in this study. The characteristics of the included studies are shown in Table 1. The 21 articles were published from 2010 to 2015 covering 4,818 COPD patients and 7,175 controls. For vitamin D levels and COPD, 13 articles<sup>18,20,22,23,27–29,32–35,37,38</sup> were recruited. For vitamin D deficiency and COPD, 12 articles<sup>18–20,22,25,27,28,32,34,35,37,38</sup> were included. For vitamin D and COPD severity, nine articles<sup>18,20,23–26,30,33,35</sup> were used. For vitamin D and COPD exacerbation, seven articles<sup>20,21,26,31,32,36,38</sup> were identified.

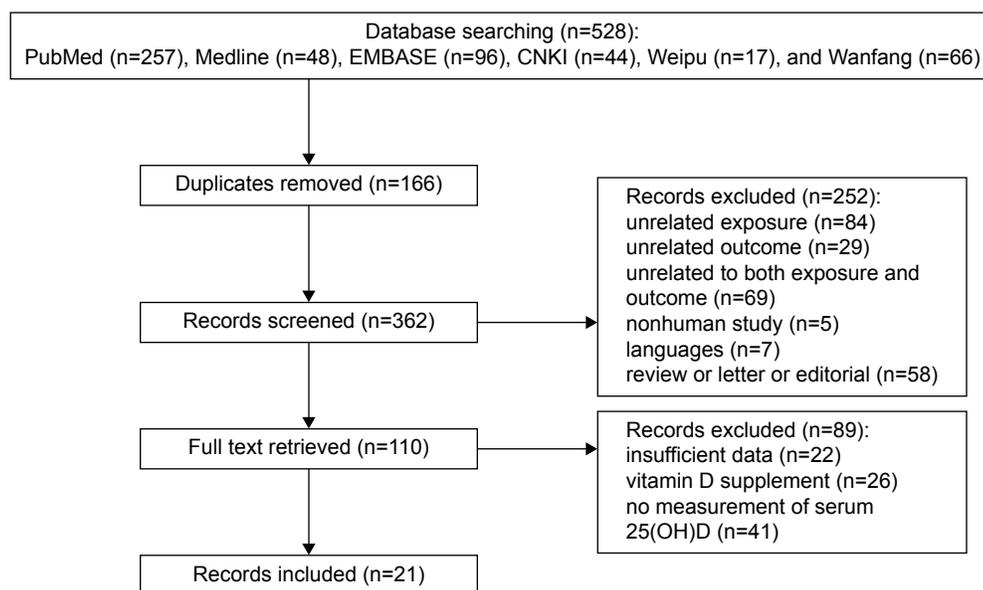
### Serum vitamin D levels in COPD patients

Thirteen studies<sup>18,20,22,23,27–29,32–35,37,38</sup> reported the levels of serum vitamin D in 1,981 COPD patients and 1,283 control subjects. The pooled effect sizes showed that the serum vitamin D levels in COPD patients were lower than the levels in control subjects (SMD:  $-0.69$ , 95% CI:  $-1.00$ ,  $-0.38$ ,  $P < 0.001$ ; Figure 2), with significant heterogeneity among these studies ( $I^2 = 94.0\%$ ,  $P < 0.001$ ). The regression analyses showed that latitude degree was a source of heterogeneity ( $R^2 = 25.21\%$ ,  $P = 0.061$ ). The latitude degree-special subgroup analyses showed that high heterogeneity remained and

subjects in low latitude region had lower serum vitamin D levels (SMD:  $-1.22$ , 95% CI:  $-2.08$ ,  $-0.36$ ,  $P = 0.005$ ) than subjects in middle latitude region (SMD:  $-0.43$ , 95% CI:  $-0.67$ ,  $-0.20$ ,  $P < 0.001$ ) and high latitude region (SMD:  $-0.02$ , 95% CI:  $-0.12$ ,  $0.16$ ,  $P = 0.781$ ). Sensitivity analyses showed that no individual study significantly influenced the pooled results. Publication bias was detected by Egger's test ( $P = 0.011$ ), but no missing studies were reported with the trim and fill method.

### Vitamin D deficiency and COPD risk

Twelve studies<sup>18–20,22,25,27,28,32,34,35,37,38</sup> reported the association between vitamin D deficiency and COPD in 3,224 COPD patients and 6,699 control subjects. Vitamin D deficiency was defined as serum 25(OH)D  $< 20$  ng/mL (50 nmol/L).<sup>39</sup> Significant heterogeneity was among the 12 studies ( $I^2 = 83\%$ ,  $P < 0.001$ ); thus, a random effect model was selected. Results showed that vitamin D deficiency patients had 77% higher odds of COPD compared with control subjects (OR: 1.77, 95% CI: 1.18, 2.64,  $P = 0.006$ ; Figure 3). To explore the sources of heterogeneity, meta-regression analyses were conducted. The results indicated that assay methods had significant influence on heterogeneity ( $R^2 = 69.36\%$ ,  $P = 0.001$ ). The subgroup analyses based on assay methods were carried out. Four studies applying immunoassay showed 116% higher odds of COPD in vitamin D deficiency patients compared with control subjects (OR: 2.16, 95% CI: 1.29, 3.63,  $P = 0.004$ ,  $I^2 = 13.7\%$ ,  $P = 0.324$ ). Meanwhile, four studies using ELISA



**Figure 1** Flow chart of study selection.

**Abbreviation:** CNKI, Chinese National Knowledge Infrastructure.

Table 1 Characteristics of included studies

Author	Year	Study design	Country, latitude degree	Sample size		BMI	Assay method	Serum 25(OH)D level (ng/mL)		Distribution of vitamin D deficiency (yes, %)	
				COPD	Control			COPD	Control	COPD	Control
Janssens et al <sup>18</sup>	2010	Case-control	Belgium, middle latitude	262	152	25-30	RIA	All: 19.9±8.2; I (70) 22.4; II (87) 20.35; III (75) 18.8; and IV (30) 16.0	24.6±8.7	All: 136 (51.91); I: 27 (38.57); II: 41 (47.13); III: 45 (60.00); and IV 23 (76.67)	47 (30.92)
Duckers et al <sup>19</sup>	2011	Case-control	UK, middle latitude	30	15	25-30	Immunoassay	Geometric mean (SD) 11.4 (1.9)	16.1 (1.4)	24 (80.00)	9 (60.00)
Persson et al <sup>20</sup>	2012	Case-control	Western Norway, high latitude	433	325	<25	LC-MS/MS	All: 25.2±10.0; II (199) 28.1±9.8; III (182) 22.7±9.3; IV (52) 21.6±10.0; AECOPD (359) 25.4±9.9; and SCOPD (74) 23.7±10.5	25.0±9.5	143 (33.03)	110 (33.85)
Quint et al <sup>21</sup>	2012	Cohort	UK, middle latitude	58	-	25-30	Immunoassay	AECOPD (58) 13.34±15.79 and SCOPD (58) 14.50±18.27	-	-	-
Zhou et al <sup>22</sup>	2012	Case-control	People's Republic of China, middle latitude	193	181	<25	ELISA	12.86±4.3	14.34±4.97	182 (94.3)	156 (86.19)
Zhang et al <sup>18</sup>	2012	Case-control	People's Republic of China, low latitude	74	30	<25	ELISA	-	-	AECOPD: 19 (52.78) and SCOPD: 15 (39.47)	5 (16.67)
Berg et al <sup>23</sup>	2013	Case-control	USA, middle latitude	348	150	25-30	LC-MS/MS	All: 22.9±11.99; II (116) 24.6±11.9; III (116) 21.9±11.9; and IV (116) 22.2±12.1	26.7±11.93	-	-
Holmgaard et al <sup>24</sup>	2013	Cohort	Denmark, middle latitude	462	-	<25	LC-MS/MS	All: 21.35±14.92; II (118) 21.96±14.53; III (239) 21.08±14.38; and IV (105) 21.96±16.14	-	-	-
Huang et al <sup>22</sup>	2013	Case-control	People's Republic of China, low latitude	90	38	NA	ELISA	All: 27.74±18.72; AECOPD (46) 21.56±14.03; and SCOPD (44) 34.21±20.87	76.44±53.26	AECOPD: 24 (52.17) and SCOPD: 16 (36.36)	6 (15.79)
Tan et al <sup>35</sup>	2013	Case-control	People's Republic of China, middle latitude	104	100	<25	ELISA	23.58±8.51	27.62±6.59	39 (37.50)	16 (16.00)
Zhang et al <sup>21</sup>	2014	Case-control	People's Republic of China, low latitude	78	30	<25	ELISA	AECOPD (38) 22.72±13.10 and SCOPD (40) 34.35±21.82	71.62±5.53	-	-
Lee et al <sup>25</sup>	2014	Case-control	USA, middle latitude	1,869	5,877	25-30	NA	-	-	All: 689 (38.69); I: 403 (44.93); and II-IV: 286 (32.35)	1,813 (32.04)
Puhan et al <sup>26</sup>	2014	Cohort	Switzerland and the Netherlands, middle latitude	356	-	NA	Immunoassay	II (234) 15.5±8.6; III (87) 15.5±9.7; and IV (35) 15.4±8.6	-	RR (95% CI): 1.01 (0.77-1.57)	-
Wang et al <sup>27</sup>	2014	Case-control	People's Republic of China, low latitude	50	50	<25	Immunoassay	13.6±5.7	13.0±5.7	44 (88.00)	45 (90.00)

Lu et al <sup>33</sup>	2014	Case-control	People's Republic of China, low latitude	126	50	NA	ELISA	All: 20.9±4.2; I (58) 22.2±3.4; II (39) 22.4±3.8; III (25) 16.5±1.9; and IV (4) 14.3±3.5	27.9±5.5	-	-
Lu et al <sup>34</sup>	2014	Case-control	People's Republic of China, middle latitude	56	30	NA	ELISA	28.41±18.34	65.43±33.62	19 (33.93)	3 (10.00)
Ye et al <sup>36</sup>	2014	Cohort	People's Republic of China, low latitude	62	-	NA	Immunoassay	AECOPD (62) 15.24±6.39 and SCOPD (62) 18.99±4.68	-	-	-
Heidari et al <sup>28</sup>	2015	Case-control	Iran, middle latitude	90	100	NA	ECL	25±7.92	23±30.17	14 (15.56)	46 (46.00)
Said and Abd-Elinaem <sup>37</sup>	2015	Case-control	Egypt, low latitude	61	20	<25	Immunoassay	33.53±19.33	44.4±9.1	10 (16.39)	0 (0)
Yumrutepe et al <sup>29</sup>	2015	Cross-sectional	Turkey, middle latitude	90	57	25-30	RIA	14.5±11.06	16.8±10	-	-
Persson et al <sup>30</sup>	2015	Cohort	Western Norway, high latitude	426	-	NA	LC-MS/MS	-	-	II: 39 (19.70); III: 76 (42.56); and IV: 27 (55.10)	-

Note: The COPD severity is based on the GOLD classification.

Abbreviations: AECOPD, acute exacerbation COPD; BMI, body mass index; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; LC-MS/MS, liquid chromatography electrospray ionization tandem mass spectrometry; NA, not available; RIA, radioimmunoassay; RR, relative risk; SCOPD, stable COPD.

showed 240% higher odds of COPD in vitamin D deficiency patients compared with control subjects (OR: 3.40, 95% CI: 2.30, 5.01,  $P<0.001$ ,  $I^2=0\%$ ,  $P=0.90$ ). Sensitivity analyses showed no excessive change in summarized results. Neither Begg's test ( $P=0.837$ ) nor Egger's test ( $P=0.324$ ) indicated publication bias.

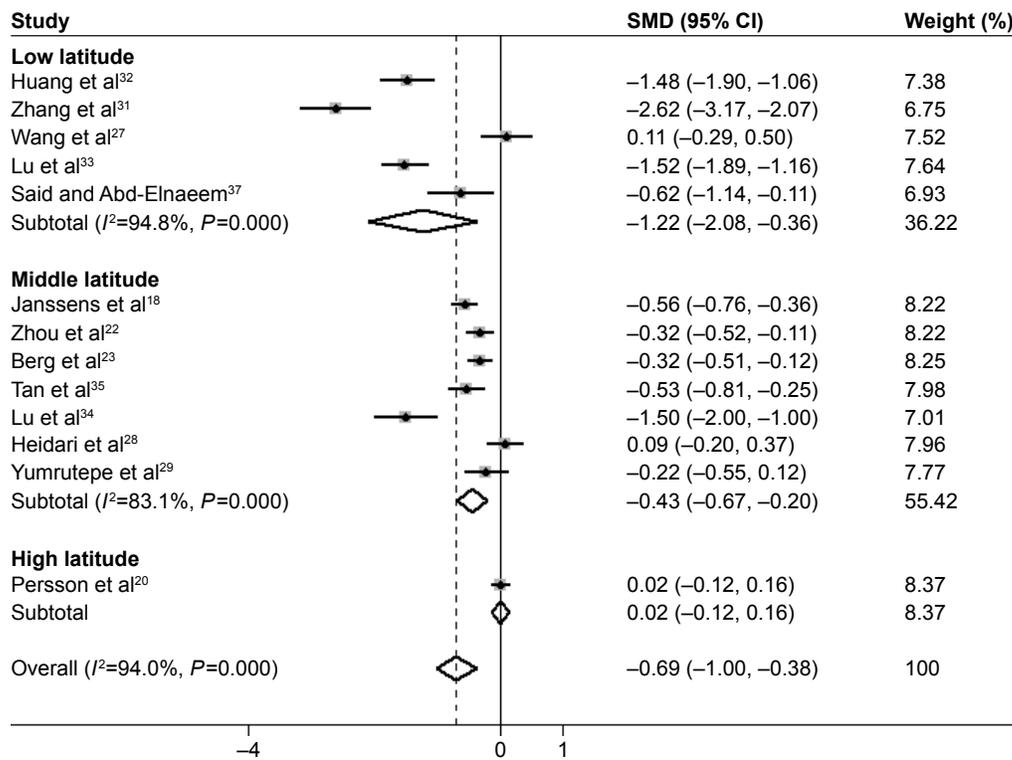
## Vitamin D and COPD severity

Seven studies<sup>18,20,23,24,26,33,35</sup> (2,091 COPD patients) investigated the association between serum vitamin D levels and COPD severity. All studies defined COPD severity based on the Global Initiative for Obstructive Lung Disease (GOLD) classification. Meta-analysis was conducted to analyze the vitamin D levels between mild-moderate (GOLD 1 and 2) COPD and severe-very severe (GOLD 3 and 4) COPD. Severe-very severe COPD patients had lower serum vitamin D levels compared to mild-moderate COPD patients (SMD:  $-0.87$ , 95% CI:  $-1.51$ ,  $-0.22$ ,  $P=0.001$ ; Figure 4). However, high degree of heterogeneity was assessed ( $I^2=97.6\%$ ,  $P<0.001$ ). The subgroup analyses based on latitude, BMI, and assay method showed that there was only a slight drop in the heterogeneity, which was still high. Sensitivity analyses showed that overall results were not obviously altered by individual studies. Begg's test ( $P=0.293$ ), as well as Egger's test ( $P=0.251$ ), did not indicate evidence of publication bias.

Only three studies<sup>18,25,30</sup> reported the vitamin D deficiency by COPD severity. Two of the studies reported the vitamin D deficiency status in mild (GOLD 1) COPD patients and moderate-very severe (GOLD 2-4) COPD patients. And another two provided the vitamin D deficiency status in moderate (GOLD 2) COPD patients and severe-very severe (GOLD 3-4) COPD patients. No association was found between vitamin D deficiency and moderate-very severe COPD compared to mild COPD (OR: 1.08, 95% CI: 0.31, 3.74,  $P=0.908$ ,  $I^2=94.4\%$ ,  $P<0.001$ ). However, meta-analysis reported that vitamin D deficiency patients had higher risk of severe-very severe COPD than moderate COPD (OR: 2.83, 95% CI: 2.00, 4.00,  $P<0.001$ ,  $I^2=42.3\%$ ,  $P=0.188$ ). The sensitivity analyses and publication bias analyses were not conducted for the limited amount of studies.

## Vitamin D and COPD exacerbation

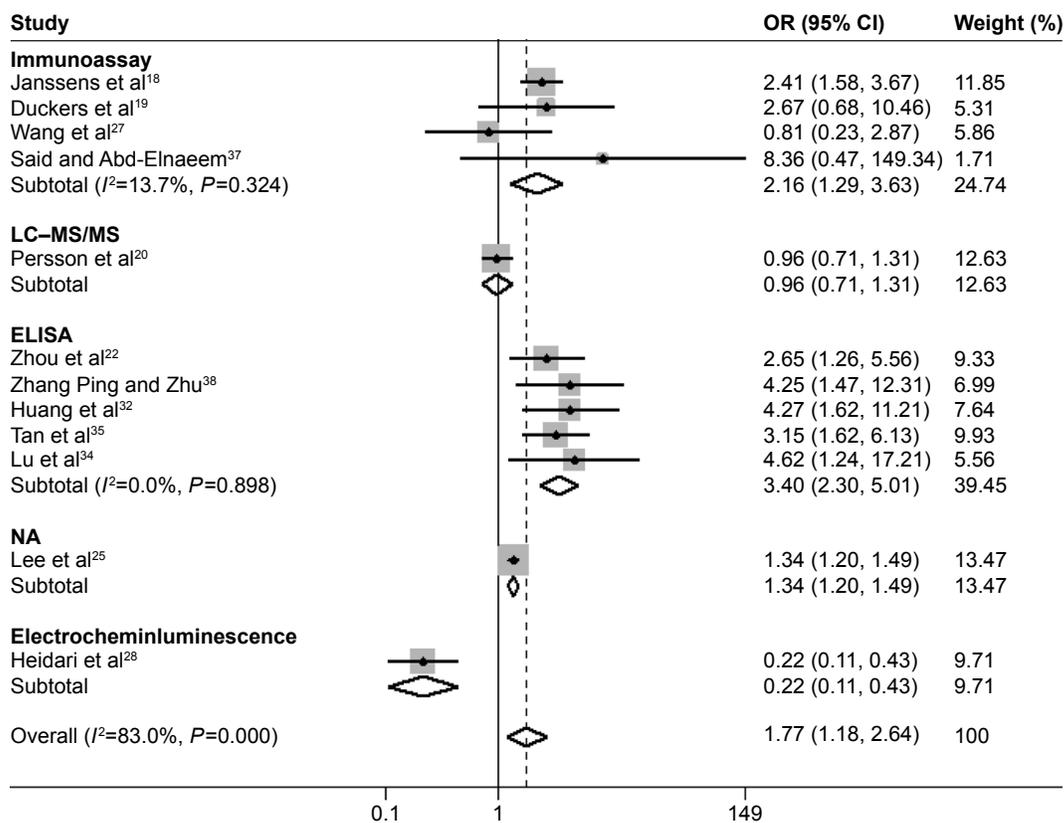
Five studies,<sup>20,21,31,32,36</sup> including 278 acute exacerbation COPD (AECOPD) patients and 563 stable COPD patients, were under meta-analysis. AECOPD was defined as worsening or new symptoms from stable state and requiring additional treatment.<sup>40</sup> Combined by the random effect model, the pooled results reported that AECOPD patients had lower



**Figure 2** Meta-analysis of serum vitamin D levels in COPD patients compared with controls.

**Note:** Stratified analysis based on latitude degree.

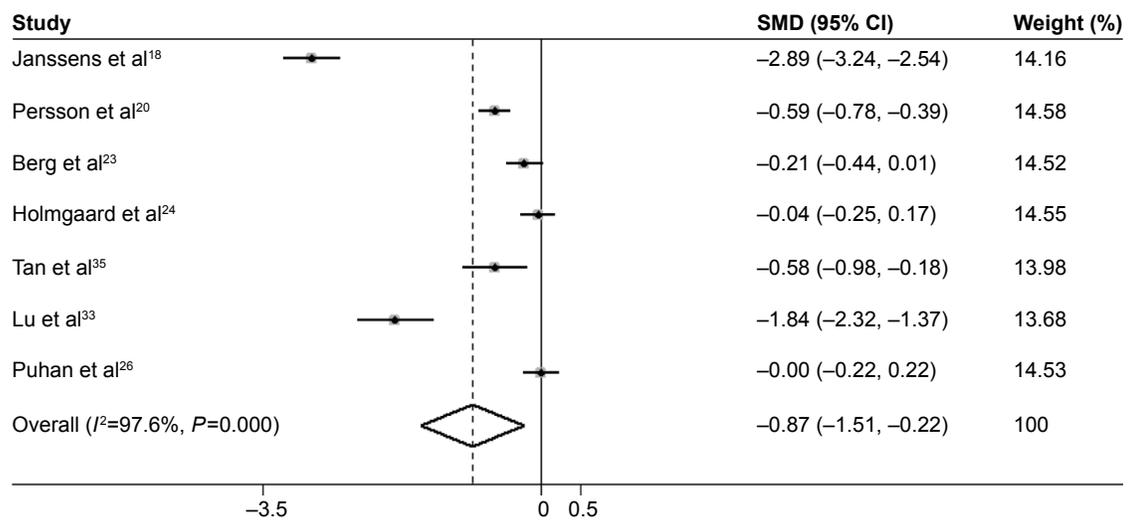
**Abbreviations:** SMD, standardized mean difference; CI, confidence interval.



**Figure 3** Meta-analysis of vitamin D deficiency in COPD patients compared with controls.

**Note:** Stratified analysis based on assay methods.

**Abbreviations:** OR, odds ratio; CI, confidence interval; LC-MS/MS, liquid chromatography electrospray ionization tandem mass spectrometry; ELISA, enzyme-linked immunosorbent assay; NA, not available.



**Figure 4** Meta-analysis of serum vitamin D levels in severe–very severe COPD patients compared with mild–moderate COPD patients.  
**Abbreviations:** SMD, standardized mean difference; CI, confidence interval.

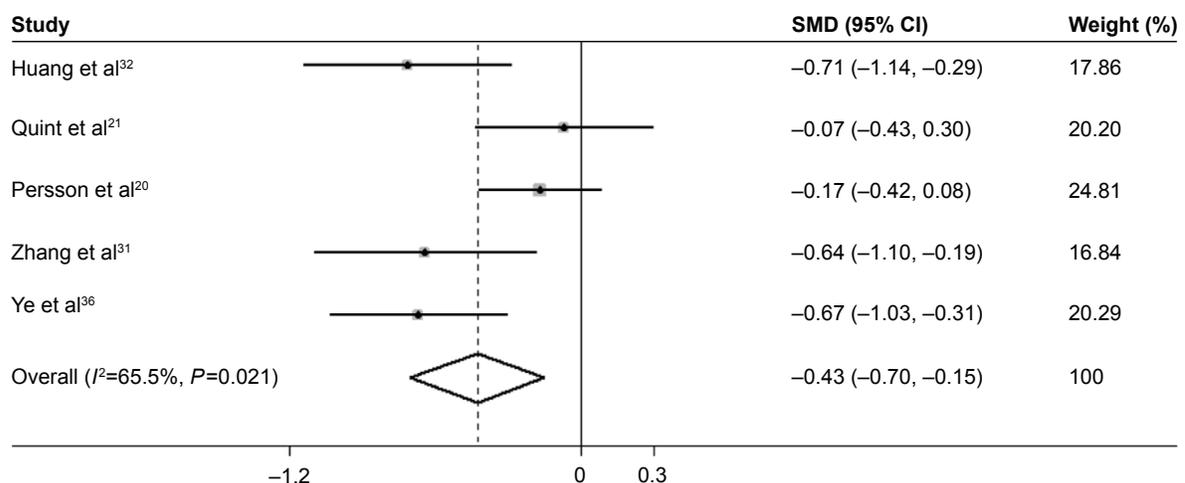
levels of serum vitamin D compared to stable COPD patients (SMD:  $-0.43$ , 95% CI:  $-0.70$ ,  $-0.15$ ,  $P=0.002$ ,  $I^2=65.5\%$ ,  $P=0.021$ ; Figure 5). The sensitivity analyses indicated consistency of overall results. No publication bias was detected (Begg's test:  $P=0.806$ , Egger's test:  $P=0.426$ ).

For the association between vitamin D deficiency and COPD exacerbation, only three studies<sup>26,32,38</sup> were included. No significant association was detected between vitamin D deficiency and COPD exacerbation (OR: 1.17, 95% CI: 0.86, 1.59,  $P=0.326$ ,  $I^2=23.2\%$ ,  $P=0.272$ ). The sensitivity analyses and publication bias analyses were not conducted for the limited amount of studies.

## Discussion

The roles of vitamin D in COPD have been highlighted in recent years. Vitamin D plays a role in the pathogenesis of

COPD via several biological processes.<sup>41</sup> Previously, two meta-analyses were conducted to assess the association between vitamin D and COPD. Zhang et al<sup>15</sup> just included two studies, and no statistical significance was found in the analysis. Zhu et al<sup>16</sup> conducted a meta-analysis of 18 studies. The analysis showed that the serum levels of 25(OH) D were lower in COPD patients and vitamin D deficiency was associated with COPD severity rather than COPD risk. However, the vitamin D levels in the included studies were measured either in serum or in plasma. And participants with vitamin D supplement were included. Furthermore, the high source of heterogeneity was not analyzed. To explore more accurately the association between vitamin D and COPD, current studies including 21 studies were conducted on the vitamin D roles in COPD risk, severity, and exacerbation. Serum vitamin D levels were inversely associated with COPD



**Figure 5** Meta-analysis of serum vitamin D levels in AECOPD patients compared with stable COPD patients.  
**Abbreviations:** AECOPD, acute exacerbation COPD; SMD, standardized mean difference; CI, confidence interval.

risk, severity, and exacerbation. Vitamin D deficiency was associated with increased risk of COPD and severe COPD. Furthermore, assay methods is the sources of high heterogeneity in the analysis of association between vitamin D deficiency and COPD risk. There was no enough evidence to support the association between vitamin D deficiency and COPD exacerbation.

This meta-analysis found certain evidence for the association between low serum vitamin D levels and COPD. It may be due to the reduction in outdoor activity inducing the absence of sun exposure, reduced dermal vitamin D synthesis due to aging skin and smoking, increased vitamin D catabolism by glucocorticoids, and lower vitamin D storage capacity in COPD patients.<sup>42</sup> The latitude degree-special subgroup analysis showed a tendency toward lower serum vitamin D levels in lower latitude degree region with high heterogeneity. This result ran counter to the traditional theory in which lower latitude degree region gains more sun exposure, thus more vitamin D synthesis. The point of Kimlin et al could account for this discrepancy. They suggested that latitude did not influence vitamin D levels for the majority of the year and only has a affect in the coldest months of year.<sup>43</sup> The season variation, as a confusion factor, may impact the overall results.

This meta-analysis demonstrated that subjects with vitamin D deficiency had an increased risk of COPD. Vitamin D deficiency is prevalent in the elderly with atrophic skin reducing vitamin D production and inadequate outdoor activity, insufficient diet intake, decreased intestinal absorption, as well as hydroxylation in the liver and kidneys.<sup>44</sup> The majority of COPD patients are elderly people.<sup>45</sup> Thus, the proportion of vitamin D deficiency comorbid COPD was large, especially in the elderly. Besides, many chronic disease such as cardiovascular diseases which are usually co-morbid COPD relate to vitamin D deficiency. Maybe, vitamin D deficiency and COPD could mutually promote bridging by those co-morbid chronic diseases.<sup>11,14</sup>

Several biological mechanisms may explain the contribution of vitamin D deficiency to COPD. First, vitamin D acts as a potent inhibitor in either innate or adaptive immune response via activation of VDR.<sup>46</sup> VDR is expressed in various types of inflammatory and structural cells. Vitamin D deficiency fails to restrain the maturation of dendritic cell and macrophage by regulating the major histocompatibility complex class II molecules,<sup>47</sup> decrease the production of proinflammatory cytokines and chemokines,<sup>48</sup> promote monocyte and neutrophil recruitment depending on NFκB-mediated pathway,<sup>49</sup> and shift Th1 T-cell toward

Th2 and regulatory T-cell.<sup>50,51</sup> The dysregulated immune-inflammatory response leads to the development of chronic inflammation and lung structural destruction, which in turn, promotes the onset and progress of COPD. Second, vitamin D can upregulate the expression of antimicrobial peptides in response to infections.<sup>52,53</sup> Vitamin D deficiency increases the susceptibility to respiratory infections, which in turn, contributes to airway colonization and chronic inflammation. Third, vitamin D deficiency has an effect on airway smooth muscle by regulating the expression of genes related to cell proliferation, glucocorticoid response, and smooth muscle contraction.<sup>54</sup> In addition, vitamin D deficiency contributes to the remodeling of airway smooth muscle and lung tissue by inducing fibroblast proliferation, promoting collagen synthesis, and increasing levels of matrix metalloproteinase.<sup>55</sup> Fourth, vitamin D is associated with the metabolism of bone and muscle. Vitamin D deficiency plays a role in the development of osteoporosis and skeletal muscle weakness, indicating the loss of lung function.<sup>56,57</sup>

Vitamin D deficiency was defined as serum 25(OH) D <20 ng/mL (50 nmol/L) in this meta-analysis and in the included studies. Due to the various sensitivities and accuracies of different assay methods, interassay and interlaboratory variations in vitamin D measurements can contribute to the heterogeneity of vitamin D deficiency and COPD.<sup>58,59</sup> Thus, it is optimal that cut-point data are assayed by special assay method. In this study, we performed meta-regression and subgroup analyses on assay method to remove the influence of assay methods on heterogeneity. Substantial drop in heterogeneity was found. This result supported the point that assay method factor can affect vitamin D measurement and should be taken into account in vitamin D deficiency-related analysis. The present study indicates that the serum vitamin D levels were inversely associated with the severity of COPD and severe COPD was more likely to develop in individuals who suffered vitamin D deficiency. Severe COPD patients suffer more disabling pulmonary function, poor nutritional status, comorbid cardiovascular diseases, rib fractures and psychological distress, are an economic and society burden, and have impaired quality of life.<sup>60,61</sup> They are more likely to stay indoors, have longer smoking history,<sup>62</sup> be anorectic,<sup>63</sup> and take oral glucocorticoids, which reduces the levels of vitamin D. Vitamin D deficiency contributes to severe COPD by magnifying inflammation, enhancing structural changes, decreasing lung function, and allowing microbe infection.

The present study suggests that COPD patients with exacerbation had lower levels of vitamin D than stable COPD patients. A higher risk of COPD exacerbation

in vitamin D deficiency patients was observed but not statistically significant. Exacerbations are mainly triggered by microorganism infections leading to an amplified inflammation. Vitamin D benefits the anti-inflammation effects by activating monocytes and macrophages, inducing antimicrobial peptides as well as enhancing the chemotactic and phagocytic capacity of inflammatory cells. Low levels of vitamin D are unable to upregulate the innate immune defense system and reduce pathogen load and colonization. The consequence is frequent exacerbations with worse airway flow and even dyspnea. The association between vitamin D deficiency and COPD exacerbation is controversial. Puhan et al<sup>26</sup> reported a trend that severe vitamin D deficiency patients were susceptible to exacerbations without statistically significant association. Martineau et al<sup>64</sup> suggested that vitamin D supplementation protected against moderate or severe exacerbation in COPD patients with vitamin D deficiency. However, the study by Lehouck et al<sup>65</sup> held inconsistent results that vitamin D supplementation had no effect on the rate of COPD exacerbations. A study exploring the effect of vitamin D supplementation on the incidence of exacerbations in vitamin D deficiency comorbid COPD patients is in progress.<sup>66</sup> Maybe, it can broaden our knowledge of vitamin D and COPD exacerbation.

The limitations of this study should be acknowledged. First, many of the included studies were case-control or cross-sectional. The nature of study design resulted in the identification of association but not causality link. The evidence just addressed the association between abnormal levels of vitamin D and COPD. However, it was still not clear whether abnormal level of vitamin D was a consequence of COPD or a contributor to COPD. Hence, further prospective, longitudinal, and well-designed cohort studies are needed. Second, potential confounders, such as sunlight exposure, seasonal variation, and diet intake, can affect vitamin D status. However, insufficient information regarding these factors in included studies limited the adjustment of the results. Statistical heterogeneity was still assessed, even with stratified analyses based on latitude degree, assay method, and BMI. Thus, the potential confounders may be the source of heterogeneity. Third, the limited number of eligible studies on the association between vitamin D and COPD severity as well as COPD exacerbations confined the analyses.

## Conclusion

This meta-analysis suggests that, as compared to controls, serum vitamin D levels were lower in patients with

COPD, severe COPD, and COPD exacerbation. Vitamin D deficiency is associated with increased risk of COPD and severe COPD but not COPD exacerbation. The results provided an improved understanding of the roles of vitamin D in COPD development and progression. Further prospective, large, and well-designed studies are needed to confirm the results. Awareness of association between vitamin D and COPD risk, severity, and exacerbation in clinical practice may benefit disease outcomes.

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## Disclosure

The authors report no conflicts of interest in this work.

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