# EFFECTS OF VITAMIN D ON RESPIRATORY FUNCTION AND IMMUNE STATUS FOR PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD): A SYSTEMATIC REVIEW

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***ABSTRACT***

***OBJECTIVES***

*To systematically review recent evidence on the effects of vitamin D on respiratory function and immune status in patients with COPD.*

***BACKGROUND***

*Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation, recurrent exacerbations, systemic inflammation, and impaired quality of life. Vitamin D has immunomodulatory and anti-inflammatory effects and has been investigated for its possible role in COPD progression and clinical outcomes.*

***METHODOLOGY***

*Eligible studies were identified through searches of PubMed, Web of Science, and Scopus. Search terms included vitamin D, COPD, respiratory function, inflammation, and immune status. Original human studies published between 2020 and 2025 were included. Eligible study designs included randomized controlled trials, cohort studies, case-control studies, longitudinal studies, and cross-sectional studies. Reviews, meta-analyses, pilot studies, case reports, case series, editorials, conference abstracts, and animal studies were excluded. Study selection was conducted according to PRISMA 2020 guidelines. Data were extracted narratively, and methodological quality was assessed using the Cochrane Risk of Bias 2 tool and Joanna Briggs Institute appraisal checklists.*

***RESULTS***

*A total of 512 records were identified, of which 18 original studies met the eligibility criteria for qualitative synthesis. Most studies showed that low serum 25-hydroxyvitamin D levels were associated with poorer lung function, greater symptom burden, increased risk of acute exacerbations, and higher inflammatory activity in COPD. Evidence from supplementation trials was inconsistent. Some studies reported improvement in exacerbation frequency and symptom scores, whereas others found no significant overall benefit.*

***CONCLUSION***

*Low vitamin D status appears to be associated with adverse respiratory and immune-inflammatory outcomes in patients with COPD. Current evidence does not support universal vitamin D supplementation for all COPD patients; however, assessment and correction of deficiency may be useful in selected high-risk or deficient patients. Further large, well-designed trials are needed to clarify the clinical relevance of vitamin D in COPD.*

***KEYWORDS:*** *Chronic Obstructive Pulmonary Disease, Vitamin D, Respiratory Function, Immune Status, Inflammation, Systematic Review*

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by persistent airflow limitation, progressive respiratory symptoms, recurrent exacerbations, and reduced functional capacity and quality of life.[1] In addition to pulmonary impairment, COPD is increasingly recognized as a systemic condition associated with chronic inflammation, oxidative stress, skeletal muscle dysfunction, and nutritional disturbances. These interacting mechanisms contribute to disease progression and may influence both respiratory outcomes and extrapulmonary complications.[2] Vitamin D is traditionally known for its role in calcium regulation and bone health. However, recent evidence indicates that it also plays an important role in immune regulation, inflammation control, and protection against respiratory infections.[3] Vitamin D receptors are present on several immune and respiratory cells. Vitamin D signaling may help regulate cytokine activity, oxidative stress, and susceptibility to infection. These effects are particularly relevant in COPD, where repeated infections and persistent airway inflammation contribute to disease severity and frequent exacerbations.[4,5] Many patients with COPD have low

serum vitamin D levels, and this deficiency has been associated with poorer lung function, greater symptom burden, more frequent exacerbations, and unfavorable clinical outcomes. However, the benefit of vitamin D supplementation in COPD remains uncertain, as clinical trials and review studies have reported inconsistent findings. Some studies suggest that supplementation may be more useful in patients with marked vitamin D deficiency or a high risk of exacerbations, while routine supplementation for all COPD patients is not consistently supported by current evidence.[4,6,7,8] Recent studies differ in their design, outcome measures, patient populations, and interpretation of respiratory and immune-related findings. Therefore, a focused review of recent evidence is needed. The objective of this systematic review was to evaluate the effects of vitamin D on respiratory function and immune status in patients with COPD by reviewing original studies published between 2020 and 2025.

## METHODOLOGY

This systematic review was conducted to evaluate the association of vitamin D status and supplementation with respiratory function and immune-related outcomes in patients with chronic obstructive pulmonary disease (COPD). Original human studies were reviewed and summarized to determine how serum vitamin D levels or vitamin D replacement were related to clinically relevant COPD outcomes. Because of differences in study design, population characteristics, vitamin D assessment, intervention protocols, and outcome measures, a meta-analysis was not performed. Therefore, the findings were synthesized narratively. A structured literature search was performed using three electronic databases: PubMed, Web of Science, and Scopus. The search was limited to articles published from 2020 to 2025 to include recent evidence. Search terms were developed according to the main concepts of the review and included "vitamin D," "25-hydroxyvitamin D," "chronic obstructive pulmonary disease," "COPD," "respiratory function," "lung function," "FEV1," "immune status," "inflammation," and "exacerbation." Boolean operators such as AND and OR were used to combine relevant terms. In addition, the reference lists of selected articles were manually reviewed to identify any eligible studies that may have been missed during database searching. Eligibility criteria were defined before screening. Studies were considered eligible if they were original human studies involving patients with COPD and assessed serum or plasma vitamin D levels, vitamin D deficiency, or vitamin D supplementation in relation to respiratory, clinical, immune, or inflammatory outcomes. Respiratory outcomes included lung function indices, respiratory symptoms, emphysema progression, disease severity, acute exacerbations, emergency visits, and other COPD-related clinical indicators. Immune and inflammatory outcomes included C-reactive protein, interleukins, inflammatory signaling pathways, vitamin D receptor-related findings, and T-lymphocyte parameters. The inclusion criteria comprised original human studies conducted on patients diagnosed with COPD, published between 2020 and 2025, that assessed serum or plasma vitamin D levels, vitamin D deficiency, or vitamin D supplementation, and that reported respiratory function, clinical respiratory outcomes, immune status, or inflammatory markers. Randomized controlled trials, cohort studies, case-control studies, longitudinal studies, prospective observational studies, and cross-sectional studies were included when full-text articles were available in English. The exclusion criteria included systematic reviews, meta-analyses, narrative reviews, pilot studies, case reports, case series, editorials, letters, conference abstracts, animal studies, and in vitro studies. Articles were also excluded if they did not include COPD patients, did not assess vitamin D status or supplementation, did not report respiratory or immune-related outcomes, or had insufficient data relevant to the review question. All records retrieved from the databases were imported into the screening process, and duplicate articles were removed. A total of 512 records were initially identified through database searching. After removing duplicates and other clearly ineligible articles, 408 records remained for title and abstract screening. Of these, 344 records were excluded during the initial screening phase. Sixty-four reports were sought, of which four could not be retrieved. Therefore, 60 full-text articles were assessed for eligibility. After full-text review, 42 articles were excluded because they had an ineligible study design, were review-type articles or case reports, or did not report outcomes relevant to the review question. Finally, 18 original studies fulfilled the eligibility criteria and were included in the qualitative synthesis. The study selection process was documented using a PRISMA 2020 flow diagram. Data were extracted using a structured data extraction form. The extracted information included author name, year of publication, country or study setting, study design, sample size, characteristics of the COPD population, type of vitamin D exposure or intervention, and the main respiratory, immune, and inflammatory outcomes. Additional information was also extracted regarding exacerbation frequency, lung function parameters, symptom scores, inflammatory markers, T-lymphocyte findings, and the effects of supplementation. The extracted data were organized into summary tables showing study

characteristics, respiratory outcomes, immune and inflammatory outcomes, and methodological quality. The methodological quality of the included studies was assessed according to study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 tool, while observational studies were assessed using the relevant Joanna Briggs Institute critical appraisal checklists. Each study was reviewed for possible sources of bias, including selection bias, confounding, measurement bias, lack of temporality, incomplete outcome reporting, and limited generalizability. The overall risk of bias was categorized as low, moderate, or high. A narrative synthesis approach was used for data analysis. Findings were grouped into the main themes of the review: general study characteristics, respiratory function and clinical respiratory outcomes, immune and inflammatory findings, and methodological quality. Particular attention was given to the consistency of associations between low vitamin D status and adverse COPD outcomes, as well as the direction of effect reported in vitamin D supplementation trials. Due to heterogeneity in study designs, outcome definitions, laboratory measures, and intervention protocols, quantitative pooling of results was considered inappropriate.

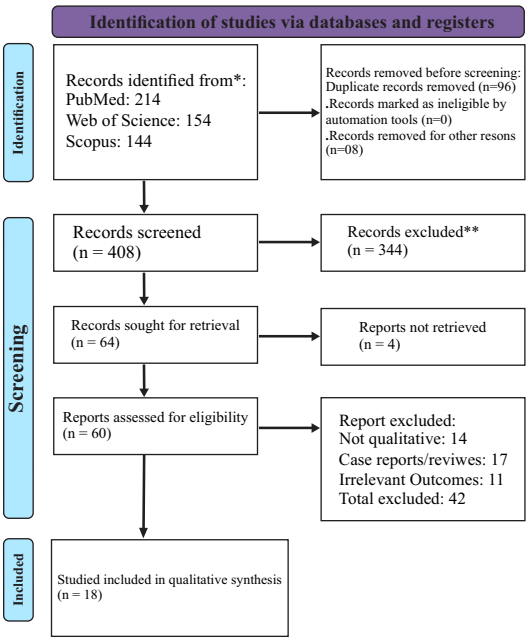


**Figure 1**: PRISMA-based study selection flow chart for the systematic review of vitamin D and COPD outcomes. The database search yielded 512 records. After removal of duplicates and other ineligible records, 408 articles proceeded to title and abstract screening. Full texts of 60 potentially relevant articles were assessed for eligibility. Finally, 18 original studies met the inclusion criteria and were included in the qualitative synthesis.

## RESULTS

Table 1 presents the main characteristics of the 18 original studies included in this systematic review. The included studies were published between 2020 and 2025 and were conducted in different countries, including the USA, Turkey, South Korea, Belgium, Germany, China, India, Spain, the Netherlands, South Africa, and Romania. Most studies were observational, including cross-sectional, cohort, longitudinal, and prospective designs. The review also included one case-control study and two randomized controlled trials. Sample sizes varied across studies, ranging from 65 patients in acute exacerbation settings to 1,876 COPD patients in secondary database analyses. Most studies assessed baseline serum or plasma 25-hydroxyvitamin D [25(OH)D] as the main exposure, while two randomized controlled trials evaluated the effect of vitamin D3 supplementation in vitamin D-deficient COPD patients. The main outcomes reported across the studies included lung function indices, respiratory symptom burden, emphysema progression, frequency of acute exacerbations, inflammatory markers, T-lymphocyte status, and all-cause mortality. Overall, the included studies showed that lower vitamin D levels were generally associated with poorer respiratory performance, increased inflammatory activity, and a higher risk of exacerbations in COPD. However, the evidence regarding the benefit of vitamin D supplementation was not fully consistent.

**Table 1: Characteristics of original studies included in the systematic review**

| Study | Country /setting | Study design | COPD population | Vitamin D exposure/intervention | Mainoutcomes reported | Key finding relevant to review |
|---|---|---|---|---|---|---|
| Burkes et al., 2020 [9] | USA, SPIROMICS cohort | Observational cohort analysis | Adults with COPD (SPIROMICS; n=1609) | Baseline serum 25 (OH) D | Lung function, prior exacerbations, longitudinal outcomes | Lower 25(OH)D was associated with worse lung function and with worse lung function and greater exacerbation burden |

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|---|---|---|---|---|---|---|
| Köktürk et al., 2020 [10] | Turkey, hospitalized patients | Cross-sectional observational study | Hospitalized COPD patients n=117 | Serum vitamin D status | Vitamin D deficiency prevalence, clinical severity profile | Vitamin D deficiency was highly prevalent in hospitalized COPD patients |
| Kim et al., 2020 [11] | South Korea | Longitudinal observational study | Male COPD patients (n=151) | Plasma 25(OH)D level | Emphysema severity/progression | Severe vitamin D deficiency was associated with empysema progression |
| Mathyssen et al., 2020 [12] | Belgium | Translational observational study | COPD airway tissue samples/patients | Vitamin D-related gene expression | Airway vitamin D pathway markers | COPD airways showed altered local vitamin D-related gene expression, supporting biological plausibilty for immune effects |
| Jorde et al., 2021 [13] | Germany | Cohort study | COPD cohort n=94 | Serum 25(OH)D | Disease severity, CRP, IL-6, prior FEV1 decline, exacerbations | Lower vitamin D was linked with greater disease severity, inflammation, and exacerbation re-lated outcomes |
| Fu et al., 2021 [14] | China | Observational study | Patients with COPD n=101 | Serum vitamin D status | Inflammatory markers | Low vitamin D status was associated with systemic inflammation in COPD |
| Lokesh et al., 2021 [15] | India | Case-control study | COPD patients and controls n=100 | Serum vitamin D deficiency | COPD presence and exacerbation status | Vitamin D deficiency was associated with COPD and with exacerbation risk |
| Calle Rubio et al., 2022 [16] | Spain, outpatient clinics | Cross-sectional study | High-risk COPD outpatient n=97 | Vitamin D testing/serum levels | High-risk COPD prevalence of deficiency. | Vitamin D deficiency/insufficiency was common in high-risk outpatient COPD populations. |
| Lee et al., 2022 [17] | South Korea | Cross-sectional study | Stable COPD patients n=329 | Serum vitamin D level | CAT score, respiratory symptoms | Vitamin D insufficiency/deficiency was associated with worse respiratory symptoms. |
| Rafiq et al., 2022 [18] | Netherlands | Randomized controlled trail | Vitamin D-deficient COPD patients n=115 | Vitamin D supplementation | Exacerbation rate, pulmonary function, muscle strength, inflammatory markers, Qol | Supplementation did not significantly reduce the overall exacerbation rate in deficient COPD patients |
| Wang et al., 2023 [19] | China | Cross-sectional study | Patients with acute exacerbation of COPD n=65 | Serum vitamin D and IL-1β | CAT score, inflammatory status | Lower vitamin D and higher IL-β corretaled with worse symptom burden in AECOPD |
| Kola et al., 2024 [20] | South Africa, tertiary hospital | Prospective cross-sectional study | COPD patients at Chris Hani Baragwanath Hospital n=76 | Serum vitamin D status | Deficiency prevalence and associated characteristics | Deficiency and insufficiency were common among COPD patients in this tert |

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|---|---|---|---|---|---|---|
| | | | | | | iary-care Africa an cohort |
| Jiang et al., 2024 [21] | USA, NHANES | Cohort analysis | COPD patients (n=1876) | Serum 25 (OH) D | All-cause mortality | Higher vitamin D levels were associated non linearly with lower all-cause mortality in COPD. |
| Lakra et al., 2025 [22] | India, tertiary care center | Randomized controlled trail | Stable COPD patients with hypovitaminosis D3 (n=100) | Vitamin D3 supplementation | Acute exacerbations, CAT score, emergency visits | Supplementation reduced acute exacerbations, improved CAT scores, and reduced emergency visits in deficient patients. |
| Jiang et al., 2025 [23] | China | Cross - sectional observational study | COPD patients | Serum vitamin D, inflammatory markers, T lymphocytes | COPD severity and acute exacerbation risk | Vitamin D, inflamatory markers, and T-cell parameters were correlated with severity and exacerbation risk |
| Zhou et al., 2025 [24] | China | Prospective observational study | COPD patients n=636 | Vitamin D deficiency categories | Risk of severe exacerbation | Marked vitamin D deficiency was associated with a greater likelihood of severe COPD exacerbations. |
| Han et al., 2025 [25] | USA, NHANES | Cross - sectional study | Commun-ity dwelling adults with COPD (n=1384) | Serum 25 (OH) D | FEV1 % predicted, FVC % predicted, airflow obstruction s | Higher vitamin D was associted with better lung fun |
| | | | | | severity | ction up to a threshold., inverse L-shaped relationship observed |
| Rus et al., 2025 [26] | Romania | Observational study | Patients with acute exacerbation of COPD n=105 | Serum vitamin D during AE during COPD | COPD severity, inflammtory profile | Lower vitamin D during exacerbation was associated with very severe COPD |

25(OH)D = 25-hydroxyvitamin D; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; CT = computed tomography; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; QoL = quality of life.

Table 2 summarizes the respiratory function and clinical respiratory outcomes reported in the included original studies. Most observational studies showed that low serum vitamin D levels were associated with poorer lung function, greater respiratory symptom burden, emphysema progression, and an increased risk of acute exacerbations in patients with COPD. However, the findings from vitamin D supplementation trials were not uniform. One randomized controlled trial reported no significant overall improvement in exacerbation rate or pulmonary function, whereas another trial showed reduced exacerbations, improved CAT scores, and fewer emergency visits among vitamin D-deficient COPD patients. These findings suggest that the respiratory benefit of supplementation may depend on baseline vitamin D status and patient risk profile.

**Table 2: Association of vitamin D with lung function and clinical respiratory outcomes in COPD.**

| Study | Respiratory Outcomes Assessed | Respiratory variables/Tools | Main Respiratory Finding | Overall Interpretation |
|---|---|---|---|---|
| Burkes et al., 2020 [9] | Lung function and exacerbation outcomes | FEV1, longitudinal lung function change, prior exacerbations | Lower 25 (OH)D was associated with worse cross-sectional and longitudinal lung function and increased odds of prior exacerbations | Negative association |

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|---|---|---|---|---|
| Kim et al., 2020 [11] | Emphysem a severity and progression | CT- assessed emphysema se verity/progres sion | Severe vitamin Deficiency wa s associated wi th emphyse ma progression in male COPD patients. | Negative association |
| Jorde et al., 2021 [13] | Disease severi ty, lung functi ion loss, exac erbation profil e | COPD severit y measures, pr ior FEV1 decl ine, exacerbati on | Lower vitamin D levels were linked with gre ater disease se verity, disease progression, and exacerbati on-related bur den | Negative association |
| Lokesh et al., 2021[15] | Exacerbation status | History of ac ute exacerbati on in previous year | Vitamin D- de ficient COPD patients were more likely to have previous-year exacerbat ions than non-deficint COPD patients. | Negative association |
| Lee et al., 2022 [17] | Respiratory symptom burden | CAT score, respiratory symptom assessment | Vitamin D insufficiency/d eficiency was associated with worse respirato ry symptoms in stable COP D. | Negative association |
| Rafiq et al., 2022 [18] | Exacerbation rate pulmonar y function, qu ality of life | Exacerbation rate, pulmona ry function tes ting, QoL mea sures | Vitamin D sup plementation did not signific antly reduce exacerbation rate overall and showed no clear overall pulmonary fun ction benifit | No significant overall benefit |
| Wang et al., 2023 [19] | Symptom severity during AECOPD | CAT score | Low vitamin D levels were associated with high CAT scores, sugges ting greater sy mptom burden during an acut e exacerbation. | Negative association |
| Lakra et al., 2025 [22] | Acute exacerb ations, symto m burden, em ergency visits | Acute exacerb ation frequenc y, CAT score, emergency visits | Vitamin D3 su pplementation decreased acut e exacerbation s, improved C AT score, and reduced emerg ency visits in d eficient patient | Positive eff ect of suppl ementation |
| Jiang et al., 2025 [23] | COPD severi ty and acute exacerbation risk | Clinical sev erity measur es, acute ex acerbation risk | Lower vitamin D was correlated with greater COP D severity and hig her risk of acute e xacerbation | Negative association |
| Zhou et al., 2025 [24] | Severe exacerbation risk | Severe vita min D defici ency categor ies, severe AECOPD risk | Patients with mar ked vitamin D def iciency showed a higher likelihood of experiencing severe COPD exa cerbations. | Negative association |
| Han et al., 2025 [25] | Pulmonary function and airflow limitation | FEV1% predicted, FVC% predicted, airflow obstruction severity | The relationship between serum 25 (OH)D and lung function was non linear, with a peak at higher levels of serum 25(OH)D. | Positive association |
| Rus et al., 2025 [26] | Severity duri ng acute exa cerbation | COPD sever ity during AECOPD | Lower vitamin D during acute exac erbation was asso ciated with very severe COPD. | Negative association |

25(OH)D = 25-hydroxyvitamin D; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; CT = computed tomography; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; QoL = quality of life.

Table 3 presents the immune and inflammatory outcomes reported in the included original studies. Overall, the evidence suggests that lower vitamin D levels in patients with COPD are associated with increased systemic or airway inflammation, altered vitamin D-related signaling, and poorer immune status. Several studies reported associations between low vitamin D levels and inflammatory markers, including CRP, IL-6, and IL-1β. One recent study also showed that vitamin D levels, inflammatory markers, and T-lymphocyte parameters were correlated with COPD severity and risk of acute exacerbation. However, the evidence remains limited, as vitamin D supplementation did not show a consistent anti-inflammatory benefit in all COPD patients with vitamin D deficiency.

**T able 3: Effects of vitamin D on immune status and inflammatory markers in patients with COPD.**

| Study | Immune/inflammatory outcomes assessed | Immune variables/ tools | Main immune-related finding | Over all interpretation |
|---|---|---|---|---|
| Mathysse n et al., 2020 [12] | Airway vitami n D pathway and local imm une-related bi | Vitamin D receptor (VDR), CYP27B1, | COPD airways showed altered local expressio n of vitamin D- | Altered airwa y vitamin D p athway |

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|---|---|---|---|---|
| | ology | CYP24A1 expression in airway tissue | related genes, supprting disturbed vitamin D signaling in the airway microenvironment | |
| Jorde et al., 2021 [13] | Systemic inflammation in relation to vitamin D status | Serum 25(OH)D, CRP, IL-6 | Lower serum vitamin D levels were associated with higher systemic inflammation and greater disease severity in COPD patients. | Negative association |
| Fu et al., 2021 [14] | Inflammatory signaling and vitamin D status | Serum vitamin D, inflammatory signaling markers, pulmonary VDR-related signaling | Low vitamin D status was inversely associated with inflammtory signaling, while pulmonary nuclear VDR expression was reduced in COPD. | Negative association |
| Rafiq et al., 2022 [18] | Inflammatory after supplementation | Vitamin D supplementation with inflammatory marker assessment | Vitamin D supplementation did not demonstrate a clear overall anti-inflammatory or clinical benefit across the full vitamin D-deficient COPD cohort | No significant overall benefit |
| Wang et al., 2023 [19] | Inflammatory status during acute exacerbation | Serum vitamin D, IL-1β, CAT score | Lower vitamin D levels and higher IL-1β were associated with greater symptom burden in AECOPD, sugdeting a link between deficiency and inflammatory activity. | Negative association |
| Jiang et al., 2025 [23] | Inflammation immune-cell status in COPD severity | Serum 25 (OH)D, inflammatory markers, T-lymphocyte subsets | Vitamin D levels, inflammatory markers, and T-lymphocyte parameters were correlated with COPD severity and risk of acute exacerbation | |
| Rus et al., 2025 [26] | Inflammatory profile during acute exacerbation | Serum 25 (OH)D, IL-6 | Lower vitamin D during acute exacerbation was associated with very severe COPD; IL-6 showed weaker predictive value than vitamin D | Negative association |

25(OH)D = 25-hydroxyvitamin D; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; CAT = COPD Assessment Test; CRP = C-reactive protein; CYP27B1 = 25-hydroxyvitamin D3-1α-hydroxylase; CYP24A1 = 24-hydroxylase; IL = interleukin; VDR = vitamin D receptor.

Overall, two studies were judged to have a low risk of bias, 12 studies a moderate risk, and 4 a high risk. The most frequent methodological limitations were residual confounding, cross-sectional study design, small sample size, and lack of temporal assessment between vitamin D status and COPD outcomes.

**Table 4: Quality appraisal of the included original studies**

| Author (year) | Study design | Appraisal tool | Main sources of bias | Summary risk of bias |
|---|---|---|---|---|
| Burkes et al., 2020 [9] | Observational cohort analysis | JBI Cohort Checklist | Residual confounding, baseline-only vitamin D measurement, observational design | Moderate |
| Köktürk et al., 2020 [10] | Cross-sectional observational study | JBI Analytical Cross-Sectional Checklist | Single-center hospitalized sample, no temporal relationship, possible selection bias | Moderate |
| Kim et al., 2020 [11] | Longitudinal observational study | JBI Chohort Checklist | Male-only population, residual conounding, possible follow-up bias possible | Moderate |

| | | | | |
|---|---|---|---|---|
| Mathyssen et al., 2020 [12] | Translational observational study | JBI Analytical Cross-Sectional Checklist | Selected airway tissue sample, limited generalizability, small mechanistic sample | High |
| Jorde et al., 2021 [13] | Cohort study | JBI Cohort Checklist | Small sample size, residual confounding, single-time vitamin D assessment | Moderate |
| Fu et al., 2021 [14] | Observational study | JBI Analytical Cross - Sectional Checklist | Cross-sectional design, uncertain control of confounders, of possible reverse causation | Moderate |
| Lokesh et al., 2021 [15] | Case-control study | JBI Case - Control Checklist | Selection bias, comparability of cases and controls, possible uncontrolled conoundi ng | Moderate |
| Calle Rubio et al., 2022 [16] | Cross - sectional study | JBI Analytical Cross - Sectional Checklist | Selected high - risk outpatient population, no temporality, possible measurement variation | Moderate |
| Lee et al., 2022 [17] | Cross - sectional study | JBI Analytical Cross - Sectional Checklist | Cross -sectional design, symptom - based outcome assessment, residual confounding | Moderate |
| Rafiq et al., 2022 [18] | Randomized controlled trail | Cochrane RoB 2 Tool | Minor concerns regarding subgroup responsiveness and reporting of some secondary outcomes | Low |
| Wang et al., 2023 [19] | Cross - sectional study | JBI Analytical Cross - Sectional Checklist | Small sample size, acute exacerbation setting, limited adjustment for confounders | High |
| Kola et al., 2024 m [20] | Prospective cross-sectional study | JBI Analytical Cross - Checklist | Single-center sample, modest sample size, no casual inference possible | Moderate |
| Jiang et al 2024 [21] | Cohort analysis | JBI Cohort Checklist | Secondary database analysis, residual confounding, nonlinear modeling assumptions | Moderate |
| Lakra et al., 2025 [22] | Randomized controlled trail | Cochrane RoB Tool | Limited reporting of allocation concealment/blinding, concealment/ single-center study | Moderate |
| Jiang et al., 2025 [23] | Single cross - sectional study | JBI Analytical Cross - Sectional Checklist | | Moderate |
| Zhou et al., 2025 [24] | Prospective observational study | JBI cohort Checklist | Observational design, residual confounding, vitamin D deficiency categories may vary. | Moderate |
| Han et al., 2025 [25] | Cross - sectional study | JBI Analytical Cross - Sectional Checklist | Secondary population dataset, no temporality, possible unmeasured confounders | Moderate |
| Rus et al., 2025 [26] | Observational study | JBI Analytical Cross - Sextional Checklist | Acute exacaerbation sample, single-center design, modest sample size | High |

Overall, 2 studies were judged to have low risk of bias, 12 to have moderate risk of bias, and 4 to have high risk of bias. The most frequent methodological limitations were residual confounding, cross-sectional design, small sample size, and lack of temporal assessment between vitamin D status and COPD outcomes.

## DISCUSSION

The present systematic review found a consistent association between low vitamin D status and poorer respiratory health in patients with COPD, including reduced lung function, greater symptom burden, higher exacerbation risk, and less favorable inflammatory profiles. This pattern is supported by recent studies showing that vitamin D deficiency is common among COPD patients and may be linked with clinical decline, reduced quality of life, and increased disease burden. Sun et al. and Fekete et al. also reported that vitamin D deficiency is frequently observed in COPD, although its causal role remains difficult to confirm, as most available studies are observational.[27,28] Regarding respiratory outcomes, this review found that lower 25-hydroxyvitamin D [25(OH)D] levels were generally associated with poorer FEV1, more severe respiratory symptoms, emphysema progression, and greater exacerbation burden. However, the results of supplementation trials were mixed. The Cochrane review published in 2024 reported that vitamin D supplementation had little or no overall effect on moderate or severe COPD exacerbations, lung function, mortality, or quality of life in the general COPD population.[4] Similarly, Hua et al. reported no significant reduction in exacerbations or improvement in FEV1 or FEV1/FVC among vitamin D-deficient COPD patients.[29] In contrast, Wang et al. found that supplementation improved pulmonary function and quality-of-life outcomes.[6] The Lung VITAL trial by Gold et al. also found no reduction in COPD exacerbations or improvement in lung function among adults who were not selected based on vitamin D deficiency.[30] These findings suggest that vitamin D

supplementation may not benefit all COPD patients equally and that its effect may depend on baseline vitamin D deficiency, disease phenotype, symptom severity, and the supplementation protocol. The immune and inflammatory findings of this review are biologically plausible and are supported by previous literature. In the included studies, low vitamin D levels were associated with higher CRP, IL-6, and IL-1β levels, altered airway vitamin D signaling, and unfavorable T-lymphocyte profiles. Valle et al. reported that vitamin D deficiency in COPD may contribute to inflammation, oxidative stress, mitochondrial dysfunction, and muscle impairment, while Sun et al. highlighted the possible immunomodulatory role of vitamin D.[27,31] Anitua et al. reported that vitamin D supplementation reduced the overall rate of respiratory infections, particularly when given daily, and Jolliffe et al. also found a small but significant reduction in acute respiratory infections in their 2021 meta-analysis.[3,8] However, the updated 2025 meta-analysis by Jolliffe et al. did not show a statistically significant reduction in acute respiratory infections in the overall population.[32] Similarly, Shah et al. reported that the protective effect against respiratory tract infection was more evident in selected populations rather than in all healthy adults.[33] This indicates that the immune-related benefit of vitamin D may be present but is likely modest and dependent on patient characteristics. A possible explanation for the variation across studies is that vitamin D may act more as a marker of clinical vulnerability and a targeted supportive treatment rather than as a universal therapy for COPD. Previous reviews have shown that the effect of vitamin D may vary according to baseline vitamin D concentration, dose, duration of supplementation, clinical setting, and whether the patient is stable or experiencing an exacerbation. The benefit appears more likely in patients with marked baseline deficiency or a high risk of exacerbation.[7] The 2024 consensus statement by Giustina et al. and the Endocrine Society evidence review by Shah et al. also support a more individualized approach to vitamin D testing and replacement, rather than routine supplementation in all patients without assessment.[5,33] These findings should be interpreted in light of the limitations of the available evidence. Most studies included in this review were observational, and several were cross-sectional with moderate risk of bias. Therefore, low vitamin D status may reflect reduced outdoor activity, malnutrition, chronic inflammation, frailty, or more severe COPD, rather than being an independent cause of worse outcomes. Recent nutritional reviews in COPD have also emphasized that systemic inflammation, poor dietary intake, muscle wasting, and micronutrient deficiencies often coexist, making it difficult to separate the independent effect of a single nutrient. Reviews by Fekete et al., Simon et al., and others support the need to interpret vitamin D findings within a broader nutritional and phenotype-based framework.[28,34,35] Overall, the current evidence supports screening and correcting vitamin D deficiency in high-risk COPD patients, while further well-designed, stratified randomized trials are needed to identify the subgroups most likely to benefit.

## CONCLUSIONS

Vitamin D deficiency appears to be an important factor associated with adverse outcomes in chronic obstructive pulmonary disease. The findings of this systematic review show that low vitamin D levels are generally linked with poorer respiratory function, increased exacerbation risk, and altered immune-inflammatory status. However, intervention studies have reported inconsistent results, and current evidence does not support universal vitamin D supplementation for all COPD patients. Assessment and correction of vitamin D deficiency may be useful in selected high-risk or deficient COPD patients as part of comprehensive clinical care. Future research should focus on adequately powered, well-stratified clinical trials to clarify the therapeutic value of vitamin D in specific COPD phenotypes and deficiency states.

## LIMITATIONS

This review has some limitations. Most of the included studies were observational, limiting causal inference. There was considerable heterogeneity in study design, population characteristics, vitamin D assessment methods, supplementation protocols, and reported outcomes. Several studies also had a moderate to high risk of bias due to residual confounding, small sample size, single-center design, and lack of temporal assessment. In addition, this review included studies published only between 2020 and 2025. Because of methodological and clinical heterogeneity across studies, a meta-analysis was not performed. Therefore, the findings should be interpreted with caution.

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*The authors accept responsibility for all aspects of the work and will ensure that any concerns regarding the accuracy or integrity of any part are properly investigated and resolved.*