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A Systematic Review and Meta-Analysis of the Adjuvant Therapeutic Effects of Vitamin D in Patients with Chronic Obstructive Pulmonary Disease

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ADMINISTRATIVE INFORMATION

Support - No support.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 September 2026 and was last updated on 10 September 2026.

INTRODUCTION

Review question / Objective Does vitamin D supplementation have an adjunctive therapeutic effect in patients with chronic obstructive pulmonary disease?.

Condition being studied Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. Given the ongoing challenges posed by population aging, the large numbers of smokers and those exposed to secondhand smoke, as well as indoor and outdoor air pollution, the situation regarding COPD prevention and control remains extremely serious.
In recent years, it has been discovered that vitamin D possesses immunomodulatory functions, and mounting evidence now indicates that vitamin D plays a critical role in both innate and adaptive immune responses to infection. Existing studies suggest that immunemediated inflammatory processes are pivotal in the persistence of pulmonary inflammation in COPD.
Vitamin D, an essential nutrient for the human body, is inexpensive and widely accessible; if its adjunctive therapeutic effects can be confirmed, it would offer significant health economic value.
As evidenced by the results of the aforementioned published randomized controlled trials, the efficacy of vitamin D supplementation as an adjunctive therapy for chronic obstructive pulmonary disease remains inconsistent. The observed heterogeneity in findings may be attributable to variations in sample size, baseline vitamin D levels, disease severity, disease stage, as well as differences in the dosing regimen, dose, and duration of vitamin D intervention; moreover, each study has its own limitations.
The results of systematic reviews and meta-analyses published over the past five years have also been inconsistent. Therefore, it is necessary to update the systematic review—incorporating literature up to 2026, strictly limiting the study design, and conducting subgroup analyses based on baseline vitamin D levels and dosage—to verify the adjunctive therapeutic effects of vitamin D in

chronic obstructive pulmonary disease and provide a theoretical basis for clinical practice.

METHODS

Search strategy Search method: The English database employs a combination of subject headings (MeSH/Emtree) with free-text terms and truncation symbols, while the Chinese database uses keyword and subject heading searches.
Search term:
Chinese:慢性阻塞性肺疾病、慢阻肺、COPD、COAD、肺气肿、慢性支气管炎、维生素D、25-羟维生素D、维生素D2、麦角钙化醇、胆钙化醇、阿法骨化醇、骨化二醇、骨化三醇、随机、对照、临床试验、随机对照试验。
English:Pulmonary Disease、Chronic Obstructive、COPD、Chronic Obstructive Pulmonary Disease、Chronic Obstructive Airway Disease/COAD、Chronic Obstructive Lung Disease、Emphysema、Chronic Bronchitis、Vitamin D、25-Hydroxyvitamin D、25(OH)D、vitamin D2、Ergocalciferol、vitamin D3、Cholecalciferol、Calcifediol、Alfacalcidol、Calcitriol、calcifediol、Randomized Controlled Trial、Controlled Clinical Trial、Randomised、Randomized、Randomly、Trial、Clinical Trial。.

Participant or population COPD patients with a definitive diagnosis (complying with GOLD or corresponding international/regional standards), with no restrictions on age, sex, disease duration, baseline vitamin D levels, sample size, and follow-up period.

Intervention In addition to conventional treatment, a vitamin D preparation was administered.

Comparator Received conventional treatment without vitamin D supplementation or received a placebo.

Study designs to be included A randomized controlled trial investigating vitamin D as an adjunctive therapy for COPD.

Eligibility criteria Duplicate publications; studies with incomplete data for which the authors could not be contacted; non-RCTs; crossover RCTs; and studies that included patients with other significant pulmonary conditions, such as asthma, bronchiectasis, or pulmonary fibrosis.

Information sources English Databases: PubMed/MEDLINE, Embase, Web of Science Core Collection, Cochrane Central Register of Controlled Trials (CENTRAL)
Chinese Databases: China National Knowledge Infrastructure (CNKI), Wanfang Data, and Chinese Scientific and Technical Journals Full-Text Database(VIP),Chinese Biomedical Literature Service System(SinoMed).
We will search for Google Scholar was used for supplementary searches, and the ClinicalTrials.gov registry was consulted to identify unpublished studies and mitigate publication bias.
Search period: from database inception to November 30, 2026.

Main outcome(s) Number and frequency of acute exacerbations, FEV1/FVC ratio, percentage of predicted FEV1, CAT score, mMRC score, SGRQ score, and 6-minute walk distance.

Data management Two researchers independently extracted data, including study characteristics, interventions, controls, and outcomes. The Cochrane Risk of Bias Tool was used to assess the quality of included studies.

Quality assessment / Risk of bias analysis The Cochrane Risk of Bias 2 (RoB 2) tool was used to assess the risk of bias across five domains—randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting—with results categorized into four levels: low risk, some concerns, high risk, or no information.

Strategy of data synthesis Using Stata 15.0 software.
Effect size selection: For dichotomous outcomes (e.g., rate of acute exacerbations), results are expressed as the relative risk (RR) with a 95% confidence interval; for continuous variables (e.g., FEV1, levels of inflammatory markers), results are presented as the mean difference (MD) when units are consistent, or as the standardized mean difference (SMD) when scales or units differ, along with the corresponding 95% confidence interval; for count data or incidence density (e.g., number or frequency of acute exacerbations), results are reported as events per patient-year or the incidence rate ratio (IRR), accompanied by a 95% confidence interval.
Publication bias assessment: Funnel plot analysis combined with Egger's regression test was used to evaluate publication bias (when the number of included studies was ≥10).
Heterogeneity testing: The chi-square test and the I^2 statistic were used. If I^2 0.1, a fixed-effects model was adopted; otherwise, a random-effects model was employed, followed by sensitivity analysis or

subgroup analysis to identify sources of heterogeneity.

Subgroup analysis Stratified by disease stage (stable phase vs. acute exacerbation phase)
Stratified by baseline 25(OH)D levels (50 nmol/L).
Stratified by dose (low dose vs. high dose).
Stratified by dosing frequency (daily administration vs. intermittent/large-dose bolus).
Disease severity stratification (GOLD classification) (mild vs. moderate vs. severe).
Follow-up duration was stratified (<6 months vs ≥6 months).

Sensitivity analysis Sensitivity analysis involved three approaches to assess the robustness of the results: sequentially excluding individual studies and re-combining the data, switching between fixed- and random-effects models, and including only studies with low risk of bias.

Country(ies) involved China.

Keywords COPD,Acute exacerbation,Meta-analysis,Supplementation, Systematic review, Vitamin D, FEV1,FEV1/FVC,CAT, mMRC, SGRQ,6MWD,RCT.

Contributions of each author
Author 1 - Wenning Liu - Conceived and designed the review; performed literature searches and data extraction; conducted data management and statistical analysis; interpreted the results; drafted the protocol;and writing the review.
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