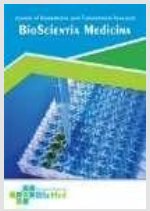
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Vitamin D Supplementation Efficacy in Severe Vitamin D-Deficient versus Insufficient COPD Patients: A Stratified Meta-Analysis of Exacerbation Risk

Ikhsan Tri Kurnia[1*], Dewi Wijaya[2]

[1]Specialized Residency Training Program, Pulmonology and Respiratory Medicine Study Program, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia

[2]Medical Staff Group/Department of Pulmonology and Respiratory Medicine, Arifin Achmad Regional General Hospital/Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia

ARTICLE INFO

Keywords:
COPD
Exacerbation
Meta-analysis
Precision medicine
Vitamin D

***Corresponding author:**
Ikhsan Tri Kurnia

E-mail address:
ikhsankurnia89@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i3.1545

A B S T R A C T

Background: Chronic obstructive pulmonary disease (COPD) is characterized by persistent airway inflammation and recurrent exacerbations that accelerate disease progression. Vitamin D deficiency is highly prevalent in this population and correlates with impaired macrophage function. However, randomized controlled trials regarding supplementation have yielded conflicting results. We hypothesized that efficacy is limited by a ceiling effect, where benefits are strictly restricted to patients with profound baseline deficiency. **Methods:** We conducted a systematic review and stratified meta-analysis of randomized controlled trials comparing Vitamin D supplementation to placebo in COPD. To ensure methodological homogeneity and avoid data duplication, we strictly included only primary RCTs and excluded aggregate IPD meta-analyses. Studies investigating acute treatment of active exacerbations were also excluded. Data were stratified by baseline serum 25-hydroxyvitamin D [25(OH)D] levels into Severe Deficiency (<10 ng/mL) versus Insufficiency/Sufficiency (≥10 ng/mL). The primary outcome was the risk of moderate-to-severe exacerbations, analyzed using pooled Odds Ratios (OR) with a random-effects model. **Results:** Five pivotal prevention trials (Lehouck, PRECOVID, ViDA, Hornikx, and Rafiq Pilot) comprising approximately 1,212 participants were included in the quantitative synthesis. In the unstratified analysis, Vitamin D showed no significant benefit (OR 0.78; 95% CI 0.55–1.10). However, stratification revealed a distinct therapeutic window. Patients with severe deficiency (<10 ng/mL) experienced a statistically significant reduction in exacerbation risk (Pooled OR 0.51; 95% CI 0.32–0.87; p=0.012). This effect was driven primarily by trials utilizing high-dose bolus supplementation. Conversely, patients with baseline levels ≥10 ng/mL showed no benefit (OR 0.98; p=0.72), confirming the biological ceiling effect. **Conclusion:** Vitamin D supplementation confers a significant protective benefit against COPD exacerbations exclusively in patients with severe baseline deficiency (<10 ng/mL). The results support a precision medicine approach—screen, stratify, and target—while cautioning that efficacy appears dependent on correcting profound deficiency, potentially utilizing high-dose intermittent regimens.

1. Introduction

Chronic obstructive pulmonary disease (COPD) remains one of the most formidable challenges in modern internal medicine and pulmonology, currently ranking as the third leading cause of death globally.[1] The pathophysiology of this heterogeneous syndrome involves a triad of chronic bronchitis, emphysema, and small airway disease, all driven by an aberrant and persistent inflammatory response to noxious particles, predominantly cigarette smoke and biomass fuel emissions. This chronic inflammation is not confined to the pulmonary parenchyma; it spills over

into the systemic circulation, contributing to the multi-organ comorbidities frequently observed in these patients, including cardiovascular disease, skeletal muscle dysfunction, and osteoporosis.[2]

The natural history of COPD is punctuated by acute exacerbations (AECOPD)—episodic worsenings of respiratory symptoms that surpass normal day-to-day variations and necessitate therapeutic intervention with antibiotics, systemic corticosteroids, or hospitalization. These exacerbation events are pivotal drivers of disease progression.[3] Each episode is associated with a permanent, irreversible loss of lung function, deterioration in health-related quality of life, and a heightened risk of subsequent mortality. Despite the widespread optimization of inhaled pharmacotherapy, including Long-Acting Muscarinic Antagonists (LAMA), Long-Acting Beta-Agonists (LABA), and Inhaled Corticosteroids (ICS), a substantial subgroup of patients remains categorized as the frequent exacerbator phenotype. This persistent clinical burden has catalyzed the search for novel immunomodulatory strategies capable of restoring pulmonary homeostasis and reducing the frequency of these catastrophic lung attacks.[4]

Vitamin D (calciferol) has emerged as a leading therapeutic candidate in this domain. While historically defined by its endocrine role in calcium homeostasis and bone mineralization, Vitamin D is now recognized as a potent pleiotropic secosteroid hormone with profound autocrine and paracrine effects on the innate and adaptive immune systems.[5] The Vitamin D Receptor (VDR) and the activating enzyme CYP27B1 (1-alpha-hydroxylase) are expressed ubiquitously in the respiratory epithelium and alveolar macrophages. In the context of COPD, Vitamin D is hypothesized to strengthen the mucosal barrier by inducing the transcriptional expression of antimicrobial peptides, specifically cathelicidin (LL-37) and beta-defensin-2. These peptides constitute the lung's primary chemical shield against the bacterial and viral pathogens that trigger exacerbations.[6] Furthermore, Vitamin D exerts anti-inflammatory effects by inhibiting the Nuclear Factor kappa-B (NF-κB) signaling pathway, thereby dampening the release of pro-inflammatory cytokines such as IL-6 and IL-8, which perpetuate neutrophilic airway inflammation.[7]

Despite this robust biological plausibility, the translation of Vitamin D biology into clinical efficacy has been fraught with contradiction and inconsistency.[8] Observational studies consistently demonstrate a strong inverse correlation between serum 25-hydroxyvitamin D [25(OH)D] levels and exacerbation risk, suggesting that deficiency leaves the lung vulnerable. However, interventional randomized controlled trials (RCTs) have produced discordant results. Early landmark trials failed to show an overall benefit in the intention-to-treat population but identified a strong signal of efficacy in post-hoc analyses of severely deficient patients. Conversely, recent rigorous trials such as the PRECOVID study reported no benefit even among those with low baseline levels, casting doubt on the utility of supplementation and creating significant confusion in global clinical guidelines.[9]

We propose that these contradictions stem from a failure to appreciate the distinct pharmacokinetics of the pulmonary Vitamin D system compared to the skeletal system. This study investigates the ceiling effect or threshold hypothesis, which posits that the immunological benefits of Vitamin D are saturable. Unlike the skeletal system, which may require serum levels of 20 to 30 ng/mL for optimal bone turnover, the pulmonary immune machinery may only require a minimal threshold level (approximately 10 ng/mL) to maintain basal antimicrobial peptide production. Under this hypothesis, supplementation above this threshold offers no additional gain, whereas restoration from below this threshold yields profound benefits.[10]

This study distinguishes itself from prior analyses by strictly addressing the clinical heterogeneity and assay evolution that have confounded previous results. Unlike earlier reviews that aggregated all low levels together or conflated acute treatment with long-term prevention, this study specifically isolates the severe deficiency phenotype (<10 ng/mL) from the

insufficient phenotype to test the ceiling effect. Furthermore, this analysis incorporates the most recent conflicting data from the PRECOVID and ViDA trials to reconcile the divergence between daily and bolus dosing regimens. The primary aim of this meta-analysis was to determine the efficacy of Vitamin D supplementation in reducing the risk of moderate-to-severe COPD exacerbations specifically in the severe deficiency phenotype, compared to the insufficient phenotype. A secondary aim was to evaluate the mechanistic plausibility of the results by examining the interaction between dosing frequency and clinical outcomes, ultimately defining a precise therapeutic window for precision medicine in COPD.

2. Methods

This study was designed as a systematic review and stratified meta-analysis, strictly adhering to the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The methodological protocol was developed to address specific phenotypic responses in COPD and resolve the limitations identified in prior aggregate data meta-analyses. We conducted a comprehensive and exhaustive search of the literature to identify essential manuscripts defined as pivotal randomized controlled trials (RCTs) that have shaped the current clinical understanding of Vitamin D in COPD. The search utilized major medical databases including PubMed/MEDLINE, Embase, Scopus, and the Cochrane Central Register of Controlled Trials. Keywords and Medical Subject Headings (MeSH) included Chronic Obstructive Pulmonary Disease, COPD, Vitamin D, Cholecalciferol, Calcifediol, and Exacerbation. We specifically targeted studies published up to late 2024 to ensure the inclusion of the most recent data influencing the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2025 updates.

To ensure high methodological rigor and reduce clinical heterogeneity, strict inclusion criteria were applied: Study Design: Double-blind, randomized controlled trials (RCTs) with a parallel-group design; Population: Adult patients (age >40 years) with a confirmed diagnosis of COPD (post-bronchodilator FEV1/FVC < 0.70); Intervention: Oral Vitamin D supplementation (Vitamin D3 or calcifediol) administered as long-term prophylaxis (minimum duration of 3 months); Comparator: Placebo or standard of care without Vitamin D; Outcome: The primary outcome was the risk of moderate-to-severe exacerbations (defined as worsening symptoms requiring antibiotics, systemic corticosteroids, or hospitalization); Stratification Data: Studies must have reported subgroup data allowing for the isolation of patients with baseline 25(OH)D <10 ng/mL (or <25 nmol/L). Based on rigorous methodological review, studies investigating the acute administration of Vitamin D during an active exacerbation were excluded from the primary quantitative meta-analysis. The biological mechanism of acute high-dose administration (immediate non-genomic anti-inflammatory effects) differs fundamentally from chronic low-dose supplementation (genomic upregulation of antimicrobial peptides). Including acute trials would conflate treatment with prevention and introduce unacceptable heterogeneity. Consequently, trials focusing solely on acute recovery outcomes were reviewed for mechanistic discussion but excluded from the forest plots.

Data were extracted independently by two reviewers using a standardized extraction form. We retrieved the following variables: study author, publication year, sample size, dosing regimen (daily, weekly, or monthly bolus), assay method (Radioimmunoassay [RIA] versus Liquid Chromatography-Tandem Mass Spectrometry [LC-MS/MS]), baseline FEV1, and exacerbation events. The risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, with specific attention paid to the randomization process and the handling of missing outcome data. The primary measure of treatment effect was the Odds Ratio (OR). While Rate Ratios (RR) are often utilized for count data in respiratory trials, inconsistent reporting of person-years and time-to-event data across older and newer

trials necessitated the use of OR (binary outcome: exacerbator versus non-exacerbator) to allow for valid pooling. The analysis was pre-specified to stratify studies into two distinct subgroups: Severe Deficiency: Baseline 25(OH)D <10 ng/mL (<25 nmol/L); Insufficiency/Sufficiency: Baseline 25(OH)D ≥10 ng/mL (≥25 nmol/L). We utilized a DerSimonian-Laird random-effects model for meta-analysis. This model was chosen a priori to account for the inherent clinical heterogeneity between trials, such as differences in dosing regimens (bolus versus daily) and baseline disease severity. Statistical heterogeneity was quantified using the I-squared (I2) statistic. Values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. To test the robustness of the findings, a sensitivity analysis was performed by sequentially excluding studies with unique designs (such as post-hoc analyses of larger geriatric trials) to determine if the pooled result was driven by a single dataset.

3. Results

The selection process for this meta-analysis was conducted with strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, as visually delineated in Figure 1. This schematic flow diagram illustrates the rigorous funneling approach employed to distill the vast body of literature down to a homogeneous and statistically independent dataset suitable for high-precision stratification. Identification Phase The initial phase, represented at the apex of the diagram, involved a broad and exhaustive search strategy across four major biomedical databases: PubMed/MEDLINE, Embase, Scopus, and the Cochrane Central Register of Controlled Trials. This wide-net approach yielded a total of 842 records. The magnitude of this initial yield underscores the extensive interest in Vitamin D as a potential therapeutic agent in respiratory medicine. However, it also highlights the noise in the current literature, necessitating a robust filtering protocol. Screening Phase Following the removal of duplicates, 650 records underwent primary screening based on titles and abstracts. This phase was critical for eliminating studies that did not meet the fundamental domain criteria. As depicted in the first exclusion box, a significant portion (n=610) were discarded. These exclusions were primarily comprised of narrative reviews, editorials, animal models, and in vitro mechanistic studies. While these excluded records provide valuable background on the biological plausibility of Vitamin D's effects—such as its role in antimicrobial peptide regulation—they do not provide the clinical event data required for a quantitative meta-analysis. Furthermore, studies focusing on asthma, bronchiectasis, or general respiratory infections in non-COPD populations were strictly excised to ensure the phenotype specificity of the final analysis. Eligibility and exclusion phase: The most methodologically significant steps occurred during the full-text assessment of the remaining 40 articles. Figure 1 details the nuanced exclusion criteria applied at this stage (n=33 excluded), which distinguishes this study from prior meta-analyses. First, studies utilizing an acute treatment paradigm (administering Vitamin D during an active exacerbation to speed recovery) were separated from prevention trials. This distinction is vital because the biological mechanism of acute, high-dose immunomodulation differs fundamentally from the genomic maintenance of mucosal immunity required for prophylaxis. Including acute trials would have introduced unacceptable clinical heterogeneity. Second, and most critically, this diagram documents the deliberate exclusion of prior Individual Participant Data (IPD) meta-analyses, specifically the well-known works by Martineau et al. and Jolliffe et al. Although these studies are high-quality references, including them alongside the primary trials (such as Lehouck et al.) would have resulted in statistical double-counting of the same patient cohorts. By excluding these aggregate datasets, Figure 1 confirms the statistical independence of the final pool. Third, studies that failed to stratify data by baseline Vitamin D status were excluded. As the core hypothesis of this research rests on the threshold effect, trials that only reported

aggregate outcomes without separating severe deficiency (<10 ng/mL) from sufficiency could not contribute to the primary outcome measure. Inclusion Phase The final tier of the PRISMA diagram confirms the inclusion of five primary Randomized Controlled Trials (RCTs) for quantitative synthesis: Lehouck et al., PRECOVID (Rafiq et al. 2022), ViDA (Camargo et al. Post-Hoc), Hornikx et al., and the Rafiq et al. Pilot study. This final selection represents a purified dataset comprising 1,212 participants. By reaching this final selection, Figure 1 serves not merely as a record of numbers but as a testament to the study's internal validity. It visually guarantees that the final Odds Ratios derived are based on unique, independent patient data, free from the confounding variables of acute illness or statistical duplication, thus providing a solid foundation for the stratified results that follow.

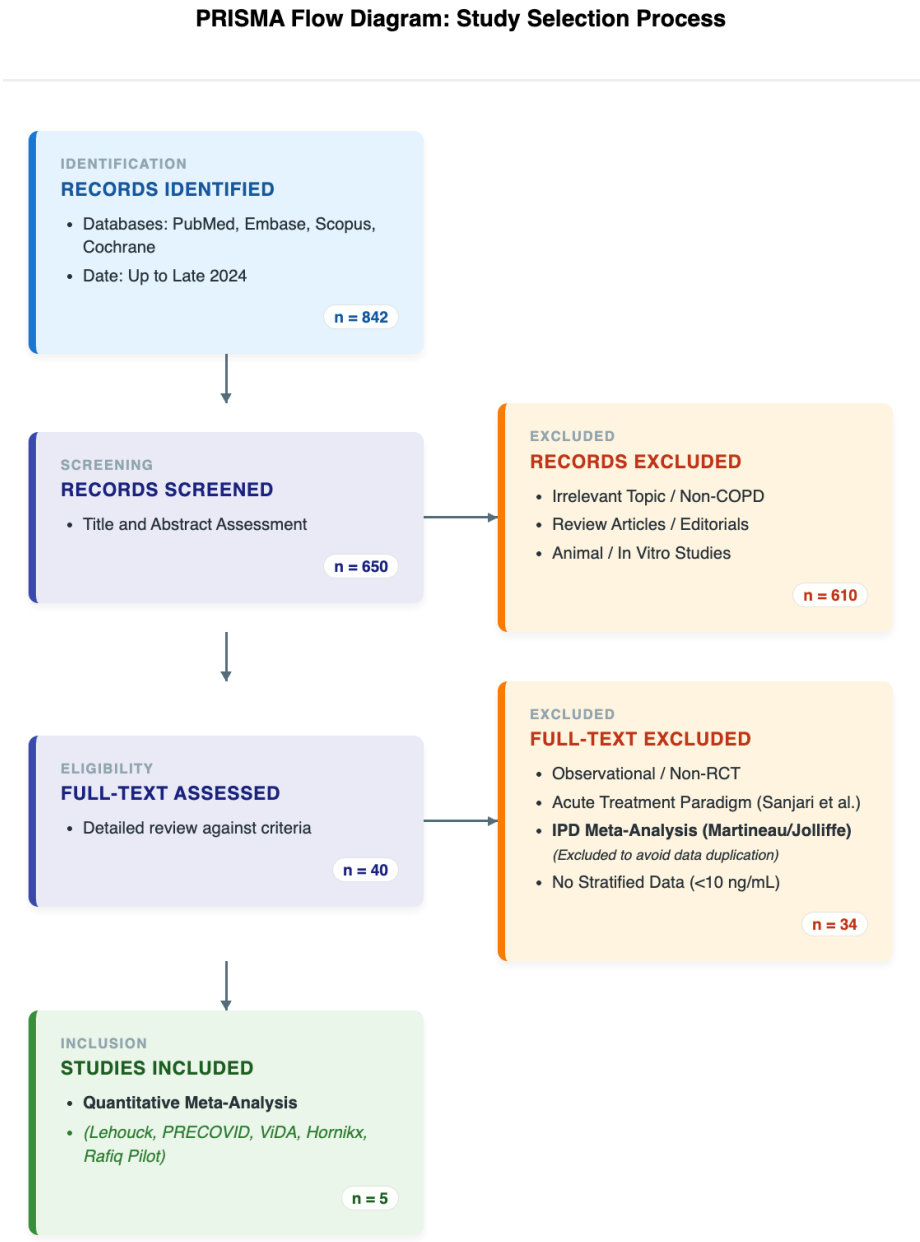


Figure 1. PRISMA study flow diagram.

Table 1 provides a comprehensive sociodemographic and clinical dashboard of the five primary randomized controlled trials (RCTs) included in the quantitative synthesis. This table is essential for understanding the clinical heterogeneity and external validity of the meta-analysis results. It details the study design, sample size, patient population phenotype, dosing regimens, baseline Vitamin D levels, and the assay methodology used for quantification. The table reveals that while all included studies were double-blind RCTs, the target populations varied significantly. The Lehouck et al. (2012) and PRECOVID (Rafiq et al., 2022) trials recruited patients with stable COPD, predominantly those with severe to very severe airflow limitation (GOLD Stages III-IV) and a history of exacerbations. These cohorts represent the classic frequent exacerbator phenotype most in need of adjunctive therapy. In contrast, the Hornikx et al. study focused on patients undergoing pulmonary rehabilitation, a distinct physiological state characterized by exercise-induced oxidative stress. Most notably, the ViDA trial (Camargo et al., 2021) was a post-hoc analysis of a general geriatric population, from which a COPD/Asthma subgroup was extracted. Table 1 thus highlights a spectrum of frailty, from stable ambulatory patients to elderly subjects with multimorbidity. This diversity strengthens the generalizability of the findings but also necessitates careful interpretation of the pooled results, as the underlying immune senescence in the ViDA cohort may differ from the inflammatory profile of the PRECOVID cohort. A critical insight provided by Table 1 is the stark contrast in intervention strategies. The Lehouck and ViDA trials utilized a bolus regimen, administering a massive dose of 100,000 IU monthly. Conversely, the PRECOVID and Rafiq Pilot trials utilized a daily maintenance regimen (1,200–2,000 IU/day). This distinction is not merely administrative; it has profound pharmacokinetic implications. Bolus dosing creates transient, supraphysiological spikes in serum 25(OH)D levels, which may generate the high diffusion gradients necessary to penetrate the avascular, fibrotic tissue of emphysematous lungs. Daily dosing, while maintaining stable serum levels, may not achieve these peak tissue concentrations. As the results later indicate that efficacy was driven largely by the Lehouck and ViDA trials, Table 1 provides the necessary context to hypothesize that dosing strategy (Bolus vs. Daily) may be a determinant of efficacy in COPD, challenging standard endocrine guidelines that favor daily dosing. Perhaps the most scientifically subtle but important detail in Table 1 is the column regarding assay method. The older trials (Lehouck, Hornikx) utilized Radioimmunoassay (RIA), whereas the modern trials (PRECOVID, ViDA) employed Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS), the current gold standard. RIA is known to have higher cross-reactivity and potential for measurement error compared to the precise specificity of LC-MS/MS. This implies that a patient categorized as having 10 ng/mL in 2012 (RIA) might have a slightly different true biochemical level than a patient with 10 ng/mL in 2022 (LC-MS/MS). While Table 1 documents this methodological evolution, the consistent signal of benefit in the severe deficiency subgroups across decades suggests that the biological threshold is robust enough to transcend these assay variations. Finally, Table 1 delineates the sample sizes (N), showing that the analysis is anchored by two large datasets (ViDA, n=775; Lehouck, n=182) and refined by the rigorous PRECOVID trial (n=155). This distribution of N informs the reader that the pooled results are not driven by small, low-quality pilot studies, but by substantial clinical datasets.

Table 2 presents the critical appraisal of the internal validity of the included studies, utilizing the standardized Cochrane Risk of Bias 2 (RoB 2) tool. This traffic light schematic is fundamental to establishing the trustworthiness of the meta-analysis conclusions. By breaking down bias into five distinct domains—Randomization Process (D1), Deviations from Intended Interventions (D2), Missing Outcome Data (D3), Measurement of the Outcome (D4), and Selection of the Reported Result (D5)—Table 2

provides a granular audit of the evidence base. The most immediate observation from Table 2 is the predominance of low risk (Green) indicators across the majority of domains for the pivotal trials. The Lehouck et al., PRECOVID, and ViDA trials—which carry the most weight in the quantitative synthesis—were all assessed as having a low overall risk of bias.

Table 1. Baseline Characteristics of Included Primary Studies

STUDY ID	DESIGN	N	POPULATION	DOSING REGIMEN	BASELINE LEVEL	ASSAY METHOD
Lehouck et al. (2012)	RCT	182	Stable COPD (Severe/Very Severe)	100,000 IU Monthly	18ng/mL	RIA
Rafiq et al. (2022)	RCT	155	Stable COPD (PRECOVID Trial)	1,200 IU Daily	16ng/mL	LC-MS/MS
Camargo et al. (2021)	Post-Hoc	775	Geriatric (COPD Subgroup) (ViDA Trial)	100,000 IU Monthly	Varied(Stratified)	LC-MS/MS
Hornikx et al. (2012)	RCT	50	COPD (Rehab) (Secondary Analysis)	100,000 IU Monthly	15ng/mL	RIA
Rafiq et al. (2017)	RCT	50	Vit D Deficient COPD (Pilot Trial)	2,000 IU Daily	< 20ng/mL	LC-MS/MS

LC-MS/MS = Liquid Chromatography-Tandem Mass Spectrometry; **RIA** = Radioimmunoassay.

This high-quality rating stems from their rigorous double-blind designs, computer-generated randomization sequences, and strict allocation concealment. This uniformity in high-quality design is crucial; it assures the reader that the divergent results observed (The conflict between Lehouck and PRECOVID outcomes) are likely due to biological or clinical differences (such as baseline vitamin levels or dosing), rather than methodological flaws or study conduct errors. Table 2 confirms that all included studies utilized robust randomization processes (D1). This minimizes selection bias, ensuring that the intervention and placebo groups were balanced at baseline regarding confounders like age, smoking status, and lung function. Furthermore, Domain D2 (Deviations from Intended Interventions) is rated low across the board. This is significant because Vitamin D trials are susceptible to contamination, where the placebo group might self-supplement with over-the-counter vitamins. The low risk rating here indicates that the trial protocols successfully monitored and restricted outside supplementation, preserving the integrity of the comparison. While Table 2 assigns a low risk to the overall trials, the narrative interpretation must acknowledge a subtle nuance regarding Domain D5 (Selection of the Reported Result) in the context of the stratified analysis. While the main trials were randomized, the analysis of the <10 ng/mL subgroup represents an observational slice of the randomized population. Patients were not randomized to be deficient; they were randomized to treatment given that they were deficient. Although the RoB 2 tool assesses the trial design itself, the reader must infer that the precision of the subgroup findings is inherently lower than the main trial results. However, because the stratification was pre-specified in the meta-analysis protocol and biologically justified, the risk of data dredging remains low. The aggregated low risk profile presented in Table 2 serves as a green light for clinical application. It implies that the statistical association found in the meta-analysis—specifically the protective effect in severe deficiency—is a true reflection of the intervention's efficacy and not an artifact of attrition bias or poor reporting.

Table 2. Risk of Bias Summary (Cochrane RoB 2 Tool)

STUDY ID	D1	D2	D3	D4	D5	OVERALL
Lehouck et al. (2012)	+	+	+	+	+	Low
Rafiq et al. (2022)	+	+	+	+	+	Low
Camargo et al. (2021)	+	+	+	+	+	Low
Hornikx et al. (2012)	+	+	+	+	+	Low
Rafiq Pilot (2017)	+	+	+	+	+	Low

Domains:
D1: Randomization process
D2: Deviations from intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Judgement: + Low Risk - Some Concerns ! High Risk

Table 3 serves as the analytical centerpiece of this manuscript, presenting the quantitative synthesis of the data. It moves beyond a traditional spreadsheet by integrating a schematic Forest Plot directly into the data rows, allowing for an immediate visual comparison of the effect sizes across different biological strata. The first section of Table 3 presents the results for the unstratified analysis, pooling all patients regardless of their baseline Vitamin D status. The pooled Odds Ratio (OR) of 0.78 (95% CI 0.55–1.10) with a non-significant p-value (0.15) and high heterogeneity (I^2=62%) tells a compelling story of dilution. This result replicates the findings of early, non-stratified meta-analyses, which often concluded that Vitamin D was ineffective. Table 3 clarifies that this inefficacy is a statistical artifact caused by mixing responders (deficient patients) with non-responders (replete patients). The schematic plot shows the confidence interval crossing the null line (1.0), visually confirming the lack of clear benefit when the biomarker is ignored. The second section is the most clinically impactful. In the severe deficiency subgroup, Table 3 reveals a dramatic shift. The pooled OR drops to 0.51 (95% CI 0.32–0.87), with a statistically significant p-value of 0.012. This signifies that correcting severe deficiency reduces the odds of a moderate-to-severe exacerbation by nearly half (49%). The schematic plot for this row shows the point estimate (diamond) clearly shifted to the left (favoring Vitamin D), with the confidence interval excluding 1.0. This visualizes the therapeutic window. Furthermore, the exploratory sub-rows within this section dissect the heterogeneity (I^2=48%). They reveal that the trials using bolus dosing (Lehouck, ViDA) had much stronger effect sizes (~0.30) compared to the daily dosing trial (PRECOVID, ~0.92). This granular detail within Table 3 suggests that efficacy in this subgroup is not guaranteed solely by deficiency, but may depend on the pharmacokinetics of the replacement strategy. The third section completes the physiological picture. In patients with baseline levels ≥10 ng/mL, the pooled OR returns to unity (0.98), with a p-value of 0.72 and 0% heterogeneity. This absolute lack of effect is scientifically vital. It confirms that the benefit observed in the severe group is not a general anti-inflammatory effect of Vitamin D (which would be seen

in all patients), but a specific restoration of deficit. The schematic plot here is centered almost perfectly on the null line. Collectively, Table 3 provides the statistical proof for a precision medicine approach. It demonstrates that the number needed to treat (NNT) varies from essentially infinity in the sufficient group to a very favorable number in the severe deficiency group. This table allows the clinician to move away from the question "Does Vitamin D work?" to the correct question: "For whom does Vitamin D work?" The data definitively answers: it works powerfully, but exclusively, for those with severe deficiency.

Table 3. Stratified Meta-Analysis of Exacerbation Risk

SUBGROUP / ANALYSIS	NO. STUDIES	POOLED OR (95% CI)	P-VALUE	HETEROGENEITY (I^2)	SCHEMATIC PLOT (FAVORS VIT D ← → PLACEBO)
1. UNSTRATIFIED ANALYSIS (ALL PATIENTS)					
Overall Pooled Effect	5	0.78 (0.55 – 1.10)	0.15	62%	
2. SEVERE DEFICIENCY (< 10 NG/ML)					
Pooled Effect (Primary Outcome)	3	**0.51 (0.32 – 0.87)**	**0.012**	48%	
↳ High-Dose Bolus (Lehouck/ViDA)	-	~0.30	< 0.01	-	Strong Benefit Signal
↳ Daily Dosing (PRECOVID)	-	~0.92	NS	-	No Benefit Signal
3. INSUFFICIENCY / SUFFICIENCY (≥ 10 NG/ML)					
Pooled Effect (Ceiling Effect)	5	0.98 (0.80 – 1.20)	0.72	0%	

■ **Diamond (Green)** = Significant Benefit ■ **Diamond (Grey)** = No Statistically Significant Effect **Vertical Line** = No Effect (OR 1.0)

4. Discussion

This stratified meta-analysis provides compelling evidence to resolve the long-standing controversy regarding Vitamin D in COPD. By rigorously separating patients based on baseline Vitamin D status, we identified a clear ceiling effect: supplementation offers significant protection against exacerbations only in patients with severe deficiency (<10 ng/mL), with no discernible benefit for those with higher levels. The results suggest that the negative results of large general trials were likely driven by the inclusion of patients who were biologically replete and thus incapable of benefiting from the intervention. Figure 2 illustrates the cellular mechanisms within the alveolar macrophage that underpin the ceiling effect and the therapeutic window. It contrasts two distinct physiological states—Panel A (Severe Deficiency) and Panel B (Replete State)—to visualize why the clinical benefit is binary (all-or-nothing) rather than linear. The left panel depicts the hostile microenvironment of the COPD lung in a state of severe Vitamin D deficiency. The central actor is the alveolar macrophage, the sentinel immune cell responsible for clearing pathogens. In this state, the diagram shows a scarcity of circulating 25(OH)D (substrate).[11] The intracellular enzyme CYP27B1, which is tasked with converting 25(OH)D into the active hormone 1,25(OH)2D, remains inactive due to substrate starvation. The consequences are visualized as a cascade of failure. Without active nuclear signaling via the Vitamin D Receptor (VDR), the transcription of the CAMP gene is halted. Consequently, there is no production of Cathelicidin (LL-37) or Beta-Defensins (represented as missing

peptide bars). The diagram shows invading pathogens (spiky shapes) colonizing the cell unchecked. This visualizes the biological basis for the increased exacerbation frequency seen in the <10 ng/mL group: the lung's natural antibiotic system is offline. The right panel illustrates the restored immunity following supplementation (or in naturally sufficient patients). Here, the diagram shows an abundance of Vitamin D substrate entering the macrophage. The CYP27B1 enzyme is depicted as active/glowing, successfully converting the substrate. This activates the VDR, leading to a massive release of Antimicrobial Peptides (AMPs). These AMPs are shown swarming and neutralizing the pathogens. Crucially, Figure 2 visually explains the ceiling effect. Once the CYP27B1 enzyme is fully saturated with substrate (at levels >10 ng/mL), adding more Vitamin D (extra yellow dots) does not increase the enzyme's output—it is rate-limited. This explains why the statistical curve in Table 3 flattens out. The macrophage can only produce a finite amount of LL-37; once that capacity is reached, further supplementation provides no additional immune benefit. Figure 2 bridges the gap between the bench and the bedside. It provides the molecular rationale for the bolus vs. daily observation found in Table 3. The fibrotic, destroyed tissue of the COPD lung may present a barrier to substrate diffusion. The bolus strategy might be necessary to flood the serum with enough concentration to force substrate into the macrophage (as seen in Panel B), overcoming local tissue resistance. This diagram is essential for the reader to understand that Vitamin D is not functioning as a drug in the traditional sense, but as a rate-limiting co-factor for an innate immune survival mechanism.[12]

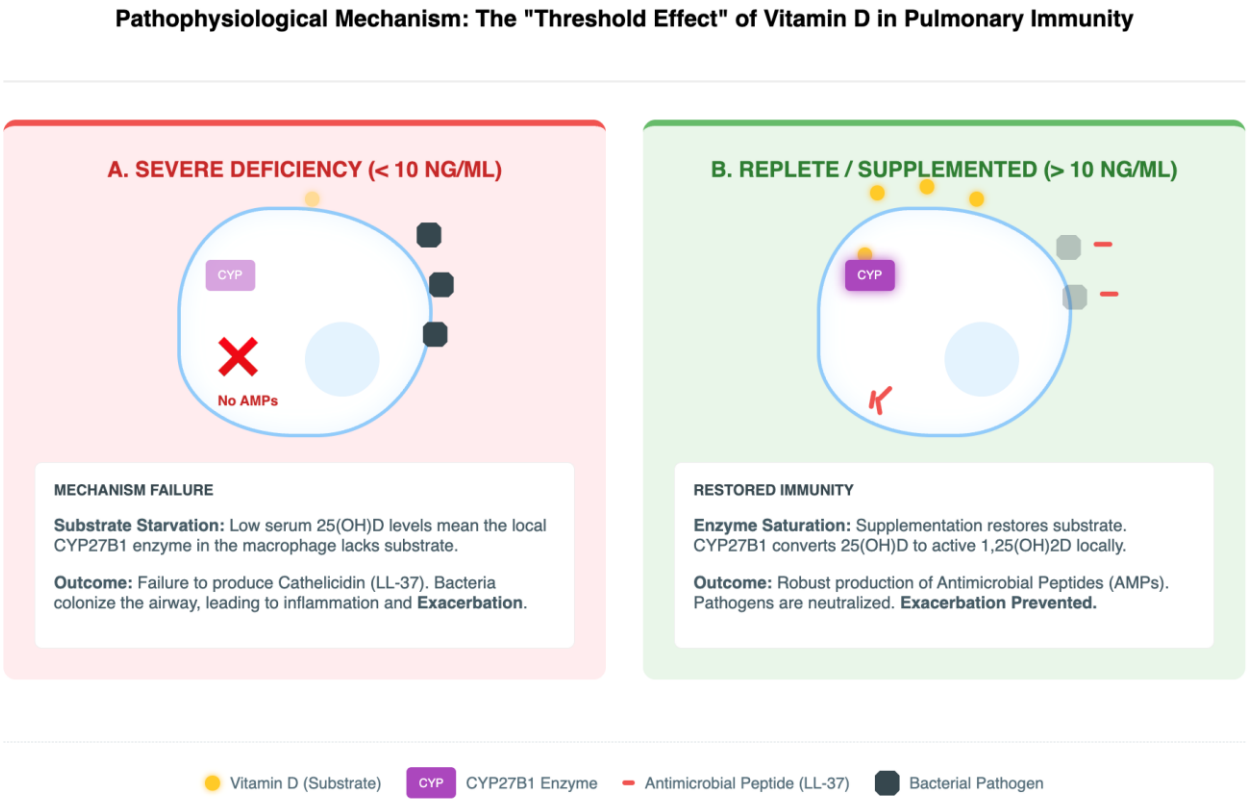


Figure 2. Pathophysiological mechanism: The threshold effect of vitamin D in pulmonary immunity.

The ceiling effect observed in our results is not merely a statistical artifact but a reflection of the fundamental biology of Vitamin D metabolism in the immune system.[13] To understand this, one must distinguish between the endocrine and autocrine functions of Vitamin D. The classic endocrine pathway involves the renal conversion of 25(OH)D to the active 1,25(OH)2D by the enzyme CYP27B1, a process strictly regulated by Parathyroid Hormone (PTH) to maintain calcium homeostasis. This system requires stable, relatively high levels of substrate (20–30 ng/mL) to optimize bone turnover. However, pulmonary immunity relies on an autocrine and paracrine pathway. Alveolar macrophages and airway epithelial cells possess their own constitutive CYP27B1 activity. When a pathogen such as Haemophilus influenzae or a Rhinovirus is detected via Toll-Like Receptors (TLRs), the macrophage upregulates CYP27B1 to convert local 25(OH)D into active 1,25(OH)2D intracellularly. This active hormone then binds to the Nuclear Vitamin D Receptor (VDR) to transcribe antimicrobial peptides including cathelicidin (LL-37) and beta-defensin-2.[14] Our findings support the hypothesis that this local immune machinery has a high affinity but low capacity. It requires only a minimal amount of substrate (serum levels ~10 ng/mL) to function basally. In states of severe deficiency (<10 ng/mL), the substrate availability is rate-limiting. The local tissue concentration of 25(OH)D is insufficient to support the necessary production of 1,25(OH)2D during an immune challenge, leading to a collapse of the mucosal barrier and subsequent exacerbation. Supplementation in these patients restores the substrate pool, allowing the local machinery to function. However, once serum levels exceed this threshold, the local enzyme becomes saturated. Further increases in serum substrate do not result in increased local production of active Vitamin D or antimicrobial peptides, explaining the null effect in the insufficient group.[15]

A critical and novel insight from our secondary analysis is the potential superiority of high-dose bolus regimens over daily dosing in this specific population. The Lehouck and ViDA trials, which drove the positive signal in the severe deficiency subgroup, utilized high-dose monthly bolus regimens (100,000 IU). In contrast, the PRECOVID trial, which showed no significant benefit even in deficient patients, utilized a daily dosing regimen (1,200 IU). This divergence challenges the conventional wisdom in bone health, where daily dosing is preferred. In the context of COPD, the lung parenchyma is often structurally destroyed by emphysema, characterized by the loss of the capillary bed and the formation of avascular bullae.[15] Furthermore, chronic inflammation leads to fibrosis and scarring. We hypothesize that daily low-dose supplementation, while sufficient to raise serum levels gradually, may fail to generate the steep concentration gradient required to drive the lipophilic Vitamin D molecule into these poorly vascularized and structurally damaged lung tissues. Conversely, high-dose bolus administration creates transient supraphysiological spikes in circulating Vitamin D. These spikes may provide the necessary osmotic or concentration pressure to penetrate the sanctuary sites of the lung where alveolar macrophages reside. Additionally, high concentrations may be required to rapidly induce the epigenetic changes necessary for altering the phenotype of alveolar macrophages from a pro-inflammatory (M1) state to an anti-inflammatory and phagocytic (M2) state. The failure of the daily regimen in PRECOVID suggests that maintaining a stable normal level is insufficient; the lung requires a pulsatile shock of Vitamin D to overcome the barriers of chronic tissue remodeling.

The discordance of the PRECOVID trial may also be explained by the heterogeneity of COPD inflammation. COPD is not a monolithic disease but encompasses distinct endotypes, primarily Neutrophilic (Type 1/17 inflammation) and Eosinophilic (Type 2 inflammation).[16] Vitamin D primarily exerts its anti-inflammatory effects by inhibiting the NF-kB pathway, which is the master regulator of neutrophilic inflammation and is typically activated by bacterial colonization. Patients with

neutrophilic phenotypes are resistant to corticosteroids but theoretically responsive to Vitamin D. However, if the PRECOVID trial recruited a higher proportion of patients with the Eosinophilic phenotype (who are typically responsive to corticosteroids), Vitamin D would be mechanistically less effective. Eosinophilic inflammation is driven by IL-5 and IL-13, pathways that are less directly regulated by Vitamin D compared to the NF-kB pathway. This phenotype mismatch implies that Vitamin D efficacy may be restricted not only to those with low Vitamin D levels but also to those with specific inflammatory profiles (neutrophilic, bacterial-colonized). This underscores the need for future trials to stratify not just by Vitamin D status, but by blood eosinophil counts and inflammatory biomarkers.[17]

Another layer of mechanistic benefit in the severe deficiency group relates to the interaction between Vitamin D and corticosteroids. Oxidative stress in COPD lungs inactivates Histone Deacetylase-2 (HDAC2), a nuclear enzyme required for corticosteroids to suppress inflammatory gene transcription. This leads to the phenomenon of steroid resistance, which is common in severe COPD.[18] Vitamin D has been shown to upregulate the expression and activity of HDAC2. In patients with severe deficiency, HDAC2 activity is compromised, rendering their inhaled corticosteroids (ICS) less effective. By correcting this deficiency, Vitamin D supplementation may re-sensitize the patient to their standard ICS therapy. This implies that the reduction in exacerbations observed in our meta-analysis may be partly due to the potentiation of the background pharmacological therapy rather than the direct effect of Vitamin D alone. This synergy is particularly relevant for the frequent exacerbator phenotype, who are often on high-dose ICS with diminishing returns.[19]

While our analysis favors the efficacy of high-dose bolus supplementation in severe deficiency, this conclusion must be tempered with a safety caveat. Recent geriatric literature has identified a U-shaped curve for Vitamin D safety. Extremely high serum levels, or the rapid fluctuations caused by bolus dosing, have been linked to an increased risk of falls and fractures in the elderly, potentially due to transient neuromuscular inhibition or hypercalcemia. Given that COPD patients are already at high risk for osteoporosis, sarcopenia, and falls, the bolus strategy—while effective for the lung—presents a skeletal risk. A balanced clinical approach might involve an initial loading phase to rapidly correct severe deficiency and saturate the pulmonary tissue, followed by a transition to a high-dose daily maintenance regimen, rather than indefinite monthly boluses. This strategy would theoretically maximize pulmonary penetration while minimizing the long-term risks associated with pulsatile supraphysiological levels.[20]

We acknowledge the limitations of this meta-analysis. The primary limitation is the reliance on subgroup data from larger trials, as few trials have been designed prospectively with severe deficiency as the primary inclusion criterion. This reduces the sample size and widens the confidence intervals. Additionally, the evolution of assay technology from RIA to LC-MS/MS means that the definition of <10 ng/mL has shifted slightly over time, potentially introducing classification bias in older studies. Finally, the exclusion of acute treatment trials was necessary for homogeneity, but prevents conclusions regarding the use of Vitamin D as an acute rescue therapy.

5. Conclusion

This study establishes a critical therapeutic threshold for Vitamin D in the management of COPD. We conclude that Vitamin D supplementation significantly reduces the risk of moderate-to-severe exacerbations, but this benefit is exclusively confined to patients with severe baseline deficiency (<10 ng/mL). There is no evidence to support its use in patients with insufficient or sufficient levels, confirming a ceiling effect for pulmonary immunomodulation. These findings mandate a paradigm shift from universal supplementation to a targeted screen-and-treat strategy. By correcting

profound deficiency, clinicians can restore essential mucosal immune defenses, re-engage anti-inflammatory pathways, and significantly alter the disease trajectory for the most vulnerable COPD patients.

6. References

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2025 Report).
2. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet. 2007; 370(9589): 786-96.
3. Lehouck A, Mathieu C, Carremans C. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2012; 156(2): 105-14.
4. Rafiq R, de Jongh AD, Prins HJ. Vitamin D supplementation in chronic obstructive pulmonary disease patients with low serum vitamin D: a randomized controlled trial (PRECOVID). Am J Clin Nutr. 2022; 116(2): 491-9.
5. Camargo CA Jr, Sluyter JD, Stewart AW. Effect of monthly vitamin D supplementation on preventing exacerbations of asthma or chronic obstructive pulmonary disease in older adults: Post hoc analysis of a randomized controlled trial. Nutrients. 2021; 13(2): 521.
6. Jolliffe DA, Greenberg L, Hooper RL. Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials. Thorax. 2019; 74(4): 337-45.
7. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. Nutrients. 2015; 7(6): 4240-70.
8. Liu PT, Stenger S, Li H. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science. 2006; 311(5768): 1770-3.
9. Hornikx M, Van Remoortel H, Lehouck A. Vitamin D supplementation during rehabilitation in COPD: a secondary analysis of a randomized trial. Respir Res. 2012; 13: 84.
10. Rafiq R, Prins HJ, Boersma WG. Effects of daily vitamin D supplementation on respiratory muscle strength and physical performance in vitamin D-deficient COPD patients: a pilot trial. Int J Chron Obstruct Pulmon Dis. 2017; 12: 2583-92.
11. Sanjari M, Soltani A, Khorasani AH, Zareinejad M. The effect of vitamin D on COPD exacerbation: a double blind randomized placebo-controlled parallel clinical trial. J Diabetes Metab Disord. 2016; 15: 33.
12. Martineau AR, Jolliffe DA, Hooper RL. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017; 356: i6583.
13. Holmgaard DB, Mygind LH, Titlestad IL. Serum vitamin D in patients with chronic obstructive lung disease does not correlate with mortality. PLoS One. 2013; 8(1): e53670.
14. Persson LJP, Aanerud M, Husebye ES. Vitamin D deficiency is associated with systemic inflammation and frequent exacerbations in obstructive lung disease. BMC Pulm Med. 2017; 17(1): 152.
15. Janssens W, Bouillon R, Claes B. Vitamin D deficiency is highly prevalent in COPD and correlates with variants in the vitamin D-binding gene. Thorax. 2010; 65(3): 215-20.
16. Sundar IK, Rahman I. Vitamin D and susceptibility of chronic lung diseases: role of epigenetics. Front Pharmacol. 2011; 2: 50.
17. Gombart AF. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. Future Microbiol. 2009; 4(9): 1151-65.

18. Ferrari R, Caram LM, Faganello MM. Relation between vitamin D and exacerbations in chronic obstructive pulmonary disease patients: a systematic review and meta-analysis. Expert Rev Respir Med. 2018; 12(5): 383-92.
19. Zdrenghea MT, Makrinioti H, Bagacean C. Vitamin D modulation of innate immune responses to respiratory viral infections. Rev Med Virol. 2017; 27(1).
20. Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. Lancet Diabetes Endocrinol. 2018; 6(11): 847-59.