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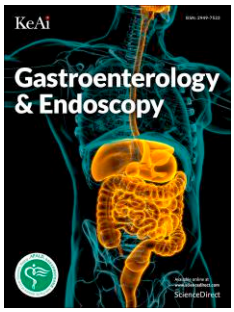


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# **Vitamin D Supplementation for Disease Activity and Maintenance of Remission in Inflammatory Bowel Disease:** *A Systematic Review and Meta-analysis*

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## Abstract

Inflammatory bowel disease (IBD) has been linked to immune dysregulation and vitamin D deficiency, leading to growing interest in vitamin D supplementation as a potential adjunctive therapy. This systematic review and meta-analysis evaluated the effects of vitamin D supplementation on disease activity, inflammatory markers, and vitamin D status in patients with IBD. PubMed (MEDLINE), Embase, and the Cochrane Library were searched according to PRISMA guidelines, and studies were selected via the PICOS framework. Random-effects meta-analyses were conducted in R via restricted maximum likelihood estimation with Hartung–Knapp adjustment, and heterogeneity and influence diagnostics were assessed. Vitamin D supplementation significantly increased serum 25-hydroxyvitamin D levels (11 studies; SMD = 1.24, 95% CI 0.52–1.95; $p < 0.001$), although heterogeneity was substantial ($I^2 \approx 94\%$). In pooled analyses of disease activity (4 studies), vitamin D supplementation was not associated with a statistically significant reduction in disease activity under Hartung–Knapp modeling (SMD = −0.56, 95% CI −1.94-0.82; $p = 0.29$; $I^2 = 87.8\%$). Influence diagnostics identified one trial as a dominant outlier; excluding this study attenuated the pooled effect (SMD = −0.19, 95% CI −0.59 to 0.21; $p = 0.17$) and eliminated heterogeneity. No statistically significant pooled effects were observed for inflammatory markers, including C-reactive protein and TNF-α, although some individual studies reported reductions. Overall, vitamin D supplementation reliably improves serum vitamin D levels in patients with IBD but does not provide consistent or robust evidence of clinically meaningful improvement in disease activity. Any potential clinical benefit appears modest, heterogeneous, and sensitive to influential studies, underscoring the need for larger, well-designed trials with standardized dosing and relapse-based outcomes.



**Keywords:** Vitamin D, Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis, Disease Activity, Remission, Systematic Review, Meta-analysis

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## Introduction

Vitamin D plays a vital role in bone metabolism[1]. However, increasing evidence suggests that it **may influence** immunological regulation and inflammatory pathways relevant to immune-mediated illnesses such as inflammatory bowel disease (IBD)[2]. In vitro and animal studies have indicated that vitamin D plays a crucial role in maintaining the integrity of the gut epithelial barrier. It is linked to the control of defensins, mucins, and a number of junctional proteins [3]. The oral intake of vitamin D follows the pathway of digestion and absorption of lipids [4]. Tumor necrosis factor α (TNFα) and many other proinflammatory cytokines are key factors in the development and maintenance of intestinal inflammation in IBD, which is why anti-TNFα antibodies and other treatments targeting these cytokines are beneficial for IBD patients [5]. Vitamin D may contribute to epithelial barrier integrity, a key defense mechanism against luminal antigens and pathogens, potentially influencing mucosal permeability. Vitamin D also helps control important inflammatory pathways, such as by promoting the production of anti-inflammatory mediators such as interleukin 10 (IL 10) and inhibiting the production of proinflammatory cytokines such as interleukin 12 (IL 12) and interleukin 6 (IL 6) [6]. In the pathophysiology of IBD, where a dysregulated immune response and impaired barrier function are key factors, these pathways are especially important [7].

The bioactive form of vitamin D, 1,25-dihydroxyvitamin $D_3$ [$1,25(OH)_2D_3$], is known to affect bone formation, mineralization, and calcium metabolism [8]. In experimental IBD, vitamin D and vitamin D receptor (VDR) deficiency has been shown to worsen disease severity, whereas $1,25(OH)_2D_3$ therapy has been shown to prevent disease development in animal models [9]. IBD is associated with, rather than caused by, changes in vitamin D status and VDR signaling, as well as an increase in the production of certain proinflammatory cytokines, such as interferon γ (IFN γ) and TNF α [10]. These changes are controlled by abnormal mucosal immune responses and intraluminal antigens in genetically susceptible individuals.

The Crohn's Disease Activity Index (CDAI) is the gold standard for measuring disease activity in Crohn's disease (CD) studies [11]. Laboratory results, physical examination findings, and self-reported CD symptoms for the previous seven days are used to calculate the CDAI [12]. The short

Crohn's Disease Activity Index (sCDAI) follows the same scale as the full CDAI, with scores of 450 indicating severe activity[13]. Similarly, the Mayo score was devised for use in clinical trials to report the disease activity index in patients with ulcerative colitis (UC). The original description of the Mayo score includes an assessment of two patient-reported outcomes (PROs) — stool frequency (SF) and rectal bleeding (RB) — the endoscopic appearance of the mucosa (endoscopic score, ES) — and a physician's global assessment (PGA), each scored on a scale from 0--3, with a maximum total score of 12 [14].

The total 25-hydroxyvitamin D (25(OH)D) level is often assessed in clinical practice to reflect the bioactive vitamin D status of humans[15]. Although there is no globally accepted definition of vitamin D status, a level >75 nmol/L (or >30 ng/mL) is generally considered sufficient. Given the growing body of evidence suggesting a potential link between vitamin D deficiency and IBD, supplementation with vitamin D has been explored as a potential adjunctive strategy to modulate disease activity [16]. However, while some studies suggest that vitamin D supplementation may help reduce disease activity and promote clinical remission in patients with IBD, evidence remains heterogeneous and inconclusive, particularly regarding its ability to prevent relapse after remission.

The primary aim of this study was to evaluate the effect of vitamin D supplementation on the disease course of patients with IBD. We hypothesized that vitamin D supplementation would produce at most a modest and heterogeneous improvement in disease activity rather than a consistent remission-inducing effect. The objectives of this study are as follows:

- To assess the impact of vitamin D supplementation on disease activity in IBD patients.
- To estimate the effect of vitamin D supplementation, compared with placebo/no supplementation/standard care, on the maintenance of remission in patients with CD, UC, or **IBD-unclassified (IBDU)**.

- To analyze the relationship between vitamin D deficiency and disease severity in IBD patients.

- To assess the potential role of vitamin D in reducing the need for conventional immunosuppressive or biological therapies.

## Methods

### Eligibility criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) scheme were utilized to generate the eligibility criteria. [17] Studies were considered eligible for inclusion if they were published between June 2000 and April 2025. The target population included adults (aged ≥18 years) with a confirmed diagnosis of inflammatory bowel disease (Crohn's disease, ulcerative colitis, or IBD-unclassified), either in the active phase or in remission. Studies were considered for inclusion if they presented qualitative or quantitative data on comparative outcomes. The PICOS scheme for the current study is further elaborated in Table 1.

The inclusion criteria were carefully developed after the development of the PICOS criteria for systematic review. The details of the eligibility criteria are provided in table 2.

## Information Sources

The literature search for this study was conducted via several major databases, including MEDLINE (PubMed), Embase, CENTRAL, the Web of Science Core Collection, and Scopus. Relevant trials were retrieved from ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP), and the European Union Clinical Trials Register (EUCTR), whereas gray literature was sourced from ProQuest Dissertations, OpenGray (or its successors), and conference proceedings such as those from the European Crohn's and Colitis Organization (ECCO), the American College of Gastroenterology (ACG), and Digestive Disease Week (DDW). Additionally, the reference lists of the included studies and previous reviews were hand searched, and citation tracking was performed via Scopus and Google Scholar. The search covered the period from June 2000 up to the search date (June 2025), with searches repeated before the final analyses.

## Search strategy

The search strategy was devised following the PICOS scheme to retrieve pertinent data from the digital databases. In the final sample, 14 studies (from a total sample of n = 77) met the eligibility criteria. A search query encompassing the following keywords was formulated:

*("Vitamin D"[MeSH] OR "cholecalciferol"[All Fields] OR "ergocalciferol"[All Fields] OR "vitamin D supplementation"[All Fields]) AND ("Inflammatory Bowel Disease"[MeSH] OR "Crohn Disease"[MeSH] OR "Ulcerative Colitis"[MeSH] OR "IBD"[All Fields]) AND ("disease course"[All Fields] OR "disease activity"[All Fields] OR "progression"[All Fields] OR "clinical outcome"[All Fields]) AND ("systematic review"[Publication Type] OR "meta-analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "clinical trial"[Publication Type]).*

## Selection process

The screening and selection process was facilitated via Rayyan.ai, an evidence-based platform designed to streamline reviews of primary and secondary sources. [18] Following title and abstract screening, potentially eligible studies underwent full-text review. Articles were excluded if they targeted a nonrelevant population, used the wrong study design, did not assess IBD-related clinical

or biochemical outcomes (e.g., disease activity, relapse, inflammatory markers), or presented a high risk of bias. In several cases, studies were excluded for more than one of these reasons.

A total of 77 records were identified from three databases: PubMed (26), Cochrane (34), and Embase (17). After 14 duplicate records were removed, 12 records were marked as ineligible by automation tools, and 8 were removed for other reasons, leaving 43 records for screening. Of these, 19 records were excluded on the basis of title and abstract, and 24 reports were sought for retrieval. Two reports were unavailable. Upon further assessment, 22 reports were evaluated, but 6 were excluded because of an incorrect population (4), an incorrect outcome (2), or an incorrect study design (2). In total, **14 studies were included in the final review**.

**Data Items**

After the secondary screening process was complete, the overall sample size (n=14) of the selected studies was assessed. Age was inconsistently reported across the included studies, with formats ranging from mean age to median age, age ranges, or categorical bands. Owing to heterogeneity in reporting, age could not be synthesized quantitatively and was therefore summarized narratively in study characteristics tables. To create a PRISMA flow chart that followed the rules of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA), we used articles from reputable journals and other sources. [19]

**Risk of bias**

We conducted a comprehensive analysis of bias in each study selected for quality assessment. Since most included studies were randomized controlled trials (RCTs), the Cochrane Risk of Bias 2 (ROB2) tool was used to assess bias across domains [20]. For nonrandomized studies, the Risk of Bias In Nonrandomized Studies of Interventions (ROBINS-I) tool was applied [21]. The results were summarized via traffic light and domain summary plots.

**Standardization of Nonpoolable Data**

To ensure consistency in data synthesis and enable quantitative pooling in the meta-analysis, studies reporting continuous outcomes as medians with interquartile ranges (IQRs) were converted to means and standard deviations (SDs) via the method proposed by Wan et al. (2014) [22], which provides validated estimators on the basis of medians, quartiles, and sample size. When quartiles were available, the sample mean was approximated as:

$$\textbf{Mean} \approx \textbf{(Q1 + Median + Q3)/3}$$

and the SD as:

$$\textbf{SD} \approx \textbf{(Q3 − Q1)/1.35}$$

where Q1 and Q3 represent the first and third quartiles, respectively.

When continuous outcomes were reported with means and confidence intervals (CIs), standard errors (SEs) were derived as follows:

$$\textbf{SE} = \textbf{(Upper CI − Lower CI)/(2 × t}\alpha\textbf{/2,df)}$$

and the SDs were calculated as:

$$\textbf{SD} = \textbf{SE} \times \sqrt{\textbf{n}}$$

in accordance with the Cochrane Handbook recommendations [23].

For studies reporting only minimum and maximum values, SDs were estimated via established range-based approximations, acknowledging underlying distributional assumptions:

$$\textbf{SD} \approx \textbf{(Max − Min)/4}$$

or, where applicable, uniform-distribution approximations.

These transformations assume approximately symmetrical or moderately skewed distributions, which may not hold for all biomarkers or clinical indices. **Sensitivity analyses excluding converted studies were conducted to assess the robustness of pooled estimates and minimize potential bias introduced by distributional assumptions.**

**Statistical analysis:**

All extracted outcomes were treated as continuous or dichotomous variables. For continuous outcomes, standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated.

The meta-analyses were conducted in R (metafor package) via random effects models with restricted maximum likelihood (REML) estimation. Given the small number of studies and anticipated heterogeneity, Hartung–Knapp adjustment was applied to derive more conservative confidence intervals.

Between-study heterogeneity was quantified via $\tau^2$ and the $I^2$ statistic, with $I^2$ values >50% considered indicative of substantial heterogeneity. Prediction intervals were calculated to reflect the range of true effects across populations.

Influence diagnostics and leave-one-out analyses were performed to assess robustness and identify influential studies. Sensitivity analyses excluded influential trials to evaluate the stability of pooled estimates.

Forest plots were generated to visualize pooled effects, with a null-effect reference line and diamonds representing combined effect estimates.

RevMan and R version 4.3 were used.

[24].

**Results**

**1. Characteristics of the Included Studies**

Fourteen studies encompassing a range of designs and geographical locations were selected for this systematic review. These included randomized double-blind placebo-controlled trials (RCTs), prospective interventional cohort studies, observational follow-up studies, and cross-sectional analyses. The studies were conducted in various countries, including Denmark, Brazil, Iran, the Netherlands, Belgium, Canada, China, India, and Ireland. The participant populations consisted

primarily of patients with Crohn's disease (CD) and ulcerative colitis (UC), both in active disease phases and in remission.

Across studies, participants were predominantly adult patients, typically aged between 18 and 70 years, with reported mean ages generally in the fourth decade of life where specified. Both male and female participants were represented in all included studies. However, demographic reporting formats varied substantially across trials, with some reporting age ranges, others mean or median ages, and several not providing detailed sex distributions, limiting pooled demographic analyses. Consequently, demographic characteristics are summarized descriptively in **Table 3.**

Baseline vitamin D levels were often used as inclusion criteria, and many studies focused on patients with vitamin D deficiency or insufficiency. The common outcomes investigated included disease activity indices, inflammatory biomarkers (such as C-reactive protein, fecal calprotectin, and erythrocyte sedimentation rate), serum vitamin D levels, clinical relapse outcomes, maintenance of remission, and health-related quality of life. A summary of study characteristics and outcomes is reported in **Table 3.**

### 2.1 Rate of Clinical Relapse and Maintenance of Remission

The impact of vitamin D supplementation on clinical relapse rates and maintenance of remission was heterogeneous and inconsistent across the included studies. Overall, 10 of the 14 studies reported favorable associations between vitamin D supplementation and outcomes related to disease activity (e.g., relapse rates, remission status, inflammatory biomarkers, or quality of life), three studies reported no statistically significant associations, and one study reported mixed results depending on dose and outcome [34,35].

Across pooled analyses, the summary effect on disease activity was modest and did not remain statistically significant under random-effects Hartung–Knapp adjustment, indicating uncertainty in the magnitude and robustness of the observed benefit.

A reduction in relapse was reported in selected Crohn’s disease (CD) cohorts. Remission appeared more frequently among CD patients with serum vitamin D levels >30 ng/mL [25]. In one trial, no

relapses occurred among vitamin D-treated CD patients, whereas 6 of 20 placebo patients experienced relapses over 12 months [26]. Another study reported lower relapse rates in vitamin D-treated CD patients (13% vs. 29%, p = 0.06) [38]. A separate cohort study revealed higher remission rates among supplemented CD patients (83.8% vs. 61.6%, p = 0.030), with greater benefit observed among individuals with baseline vitamin D deficiency [30].

Among ulcerative colitis (UC) patients, oral nanovitamin D supplementation was associated with greater improvement in the UC Disease Activity Index (UCDAI), with a 3-point reduction observed more frequently in the vitamin D group (53% vs. 13%, p = 0.001), particularly among those who achieved posttreatment vitamin D levels >40 ng/mL [36]. Dose-dependent effects were reported in selected studies. According to a per-protocol analysis, high-dose vitamin D was associated with lower relapse rates than low-dose supplementation was (0% vs. 37.5%, p = 0.049) [31]. Additionally, CD patients receiving high-dose vitamin D required less infliximab dose escalation than did placebo-treated patients (14% vs. 46%, p = 0.05) [26].

However, several studies reported no statistically significant benefit. High-dose vitamin D did not reduce postoperative endoscopic or clinical recurrence in patients with CD (18.1% vs. 18.3%, p = 0.91) [28]. Another study reported no additional remission benefit among patients who already responded to infliximab despite low baseline vitamin D levels [34]. Overall, the evidence suggests a possible modest association between vitamin D supplementation and relapse prevention, but the results remain inconsistent, and heterogeneity in disease state, dosing regimens, co-therapy exposure, and study design limits definitive causal inference.

### 2.2 Biochemical activity

Across the included studies, the biochemical outcomes revealed heterogeneous and inconsistent responses to vitamin D supplementation. While nine studies reported favorable changes in inflammatory biomarkers or immune mediators, three studies reported no statistically significant additional benefit in terms of biochemical disease activity endpoints [27,29].

In patients with Crohn's disease (CD), the level of fecal calprotectin (FC) decreased significantly in the highest-dose vitamin D group (50,000 IU/week; p = 0.04), although the level of C-reactive protein (CRP) did not change overall after 52 weeks. Patients who achieved serum vitamin D levels

>30 ng/mL presented lower FC (p = 0.02) and CRP (p = 0.01) than did those whose levels remained below this threshold [25]. Among ulcerative colitis (UC) patients, high-sensitivity CRP (hs-CRP) decreased significantly in the vitamin D group (p = 0.023), and the erythrocyte sedimentation rate (ESR) also decreased following supplementation [36]. However, pooled meta-analytic estimates for CRP did not demonstrate a statistically significant overall effect, indicating variability across studies.

Cytokine-focused studies reported the modulation of mucosal immune signaling. High-dose vitamin D, alone or in combination with infliximab, was associated with reduced mucosal expression of IL-17A, IFN-γ, and IL-10 in the treatment groups (p values ranging from 0.002--0.04) [32]. Despite these immunological changes, high-dose vitamin D monotherapy did not significantly reduce systemic CRP or calprotectin levels. Additional findings included higher baseline IL-6 levels among patients with low vitamin D status (p = 0.004) and lower IL-12 levels in CD patients initiating infliximab (p = 0.006) [34]. At week 14, the IL-8 levels were lower in the low vitamin D group (p = 0.005). The serum IL-10 level was significantly increased among CD patients receiving vitamin $D_3$ in combination with infliximab (p = 0.037) [30].Overall, vitamin D supplementation was associated with changes in selected inflammatory and immune biomarkers, but the effects on systemic inflammatory markers such as CRP and TNF-α were inconsistent and not statistically significant in pooled analyses, highlighting substantial between-study heterogeneity.

### 2.3 Health-Related Quality of Life (HRQoL)

Vitamin D supplementation often leads to improvements in patients' reported quality of life. Improvements in the Inflammatory Bowel Disease Questionnaire (IBDQ) score were observed in all the groups, with statistically significant differences between the two high-dose groups (p = 0.04 and p = 0.01) [25]. Patients with serum 25-hydroxyvitamin D [25(OH)D] levels greater than or equal to 75 nmol/L had significantly higher quality of life scores (p = 0.037) [33]. In UC patients, the IBDQ score was significantly greater in the high-dose vitamin D group than in the low-dose vitamin D group (p = 0.07) [35].

## 2. Secondary Outcomes

Several studies have explored secondary outcomes related to immunological mechanisms, vitamin D metabolism, and safety.

### 3.1 **Vitamin D levels and safety**

All studies in which vitamin D supplementation was administered reported significant increases in serum 25-hydroxyvitamin D [25(OH)D] levels, confirming the biochemical effectiveness of supplementation in improving vitamin D status [26]. Across pooled analyses, vitamin D supplementation was associated with a large standardized mean increase in circulating 25(OH)D, although between-study heterogeneity was substantial.

Examples of observed increases include the following:

- A total of 20,000 IU/day for seven weeks increased the serum 25(OH)D level in Crohn's disease (CD) patients by approximately 3.4- to 4.6-fold.
- A total of 1200 IU/day in CD patients increased the mean 25(OH)D from 69 nmol/L to 96 nmol/L after three months.
- High-dose vitamin D (10,000 IU/day) in CD patients in remission increased the mean 25(OH)D from 73.5 nmol/L to 160.8 nmol/L [38].
- In ulcerative colitis (UC), a single intramuscular dose of 300,000 IU increased the mean 25(OH)D concentration from 33.3 ng/mL to 40.8 ng/mL.

Across trials, high-dose vitamin D regimens were generally well tolerated. No cases of hypercalcemia or hyperphosphatemia were reported, and the serum calcium and phosphate levels remained within reference ranges, including in studies in which prolonged high-dose supplementation was administered. Safety assessments consistently revealed that the high doses of vitamin D used were well tolerated across studies [31]. No hypercalcemia or hyperphosphatemia was reported, and the calcium ion and phosphate levels remained within the reference ranges, especially in CD patients.

**Results of the Quality Assessment**

A total of 10 included studies were analyzed via the Cochrane ROBv2 tool, and the remaining two studies were assessed via the ROBINS-1 tool. The risk of bias in individual studies was represented as a "traffic light" plot. The risk in the individual domains was further demonstrated via a "summary plot" (Figures 2-5).

**Meta-Analysis**

**Primary outcomes**

1. **Target vitamin D levels**

One of the primary outcomes of this study was to determine whether vitamin D supplementation in patients with inflammatory bowel disease (**IBD**) achieved target therapeutic levels. A total of 11 studies provided quantifiable data for this outcome. However, one study (Jørgensen et al., 2010) was removed from the analysis because all participants in the cohort were administered supplementary doses of vitamin D either before the intervention or during follow-up.

As evident from the analysis, all 10/10 (100%) of the remaining studies showed a significant improvement in vitamin D levels across all patient cohorts. The overall effect size was **SMD = 1.41** (95% CI: 0.86 to 1.96). These findings indicate that vitamin D supplementation significantly increases serum vitamin D levels in IBD patients. The *p* value

However, the **$I^2$** value was 89%, indicating high heterogeneity across the included studies. Despite the significant overall effect, the high heterogeneity suggests that factors such as the form of vitamin D used (cholecalciferol vs. ergocalciferol), the dose, and/or patient characteristics may have influenced the results.

The forest plot for this analysis is provided in **Figure 6**.

**Figure 7.** Forest plot showing the effect of vitamin D supplementation on serum 25(OH)D levels in patients with inflammatory bowel disease. Effect sizes are expressed as standardized mean differences (SMDs) via a random-effects model with restricted maximum likelihood estimation and Hartung–Knapp adjustment. Vitamin D supplementation was associated with a large increase in serum 25(OH)D levels, although **substantial heterogeneity was observed across studies ($I^2 \approx 94\%$)**.

**2. Disease activity index (CDAI score >150)**

The forest plot presents the effect of vitamin D supplementation on Crohn's Disease Activity Index (CDAI) scores >150, indicating mild disease activity. In pooled random-effects meta-analysis using restricted maximum likelihood estimation with Hartung–Knapp adjustment, vitamin D supplementation was not associated with a statistically significant reduction in disease activity (SMD = −0.56, 95% CI −1.94--0.82; p = 0.29). Between-study heterogeneity was substantial ($I^2$ = 87.8%), indicating considerable variability in effect estimates across the included trials. Influence diagnostics identified one study (Raftery et al., 2015) as a dominant outlier. After excluding this study from the sensitivity analysis, heterogeneity was eliminated ($I^2$ = 0%), and the pooled effect remained nonsignificant (SMD = −0.19, 95% CI −0.59--0.21; p = 0.17; Supplementary Figure S1A–B).

These findings suggest that any potential effect of vitamin D on CDAI scores is modest, inconsistent, and sensitive to influential trials, and the current evidence does not support a robust clinically meaningful reduction in disease activity (Figure 7).

**Figure.** Forest plot showing the effect of vitamin D supplementation on CDAI scores >150 in patients with inflammatory bowel disease. Effect estimates are based on a random-effects model (REML) with Hartung–Knapp adjustment. No statistically significant pooled reduction in disease activity was observed, and substantial heterogeneity was present across studies.

**Secondary Outcomes**

**1. Biochemical changes that predict disease course**

### 1.1 Estimated CRP levels in the experimental and control groups

A forest plot was generated to assess the effects of vitamin D supplementation across various dosing regimens (2000 IU/day, 5000 IU/day, 10,000 IU/day, and 125 IU/day) on C-reactive protein (CRP), a systemic inflammatory biomarker of inflammatory bowel disease. Individual study results were inconsistent, with some trials reporting reductions in CRP following vitamin D supplementation, whereas others reported minimal or no effect. The pooled standardized mean difference (SMD) was −0.06 (95% CI: −0.49--0.37), indicating no statistically significant overall effect of vitamin D supplementation on CRP levels (p = 0.78). Moderate between-study heterogeneity was observed ($I^2$ = 57%), suggesting variability in effect estimates that may reflect differences in study populations, vitamin D dosing protocols, baseline inflammatory activity, and CRP measurement methods. Overall, the findings do not provide evidence of a consistent effect of vitamin D supplementation on CRP levels in patients with IBD (Figure S2).

### 1.2 Estimated TNF-α levels in the experimental and control groups

A forest plot was generated to evaluate the effect of vitamin D supplementation on circulating tumor necrosis factor-α (TNF-α) levels in patients with inflammatory bowel disease. Individual study findings were inconsistent, with some trials reporting reductions in TNF-α following supplementation, whereas others reported no meaningful change. The pooled standardized mean difference (SMD) was 0.37 (95% CI: −0.51--1.25), indicating that vitamin D supplementation had no statistically significant overall effect on TNF-α levels (p = 0.41). Between-study heterogeneity was very high ($I^2$ = 92%), suggesting substantial variability in study design, baseline inflammatory activity, dosing regimens, and laboratory measurement methods. Overall, the available evidence does not support a consistent or reliable effect of vitamin D supplementation on TNF-α concentrations in patients with IBD (Figure S3).

## Discussion

This meta-analysis synthesized data from 14 studies to evaluate the **associations between** vitamin D supplementation and disease activity, remission, and inflammatory markers in patients with IBD. Our comprehensive analysis aimed to demonstrate the effect of vitamin D on the complex disease course of IBD. The findings revealed a multifocal role of vitamin D, demonstrating a significant capacity to increase serum vitamin D levels and a significant, albeit heterogeneous, association with improved disease activity and inflammatory biomarkers, particularly in patients with baseline vitamin D deficiency. Given the clinical and methodological heterogeneity across included trials, pooled findings should be interpreted as hypothesis-generating rather than practice-changing, highlighting the need for adequately powered trials with standardized interventions and relapse-based outcomes.

**Interpretation of Findings**

The meta-analysis consistently demonstrated that vitamin D supplementation significantly increased serum 25-hydroxyvitamin D (25-OHD) levels across all patient cohorts, with a significant overall effect size of SMD=1.41 (95% CI: 0.86, 1.96; $p<0.00001$). This biochemical correction of vitamin D status is a fundamental prerequisite for any potential therapeutic effect, confirming the effectiveness of the various supplementation regimens employed across the included studies. In terms of clinical outcomes, our pooled analysis indicated was not associated with statistically significant reduction in disease activity, as measured by CDAI scores (>150), favoring the vitamin D intervention group ($p=0.01$). These findings suggest that vitamin D supplementation **may be associated with modest changes in disease activity**, although the effects are heterogeneous and not statistically robust under conservative modeling. Consistent with this, the majority of individual studies (10 out of 14) reported a positive association between vitamin D supplementation and improved outcomes related to disease activity, including reduced relapse rates, remission, decreased inflammatory marker levels, and improved quality of life. Furthermore, vitamin D deficiency may partly reflect disease severity and inflammatory burden rather than act as an independent causal factor, making it difficult to disentangle whether supplementation directly improves outcomes or primarily corrects a marker of disease activity.

In contrast, the clinical benefits were not universally consistent across all studies and IBD subtypes. Some trials, such as de Bruyn et al. (2021), reported no significant effect of high-dose

vitamin D on preventing postoperative endoscopic or clinical recurrence of CD (18.1% in the vitamin D group vs. 18.3% in the placebo group; p=0.91) [28]. Reich et al. (2016) even presented an intriguing finding, where patients with low baseline vitamin D initiating infliximab surprisingly achieved better clinical remission at weeks 14 and 22, suggesting that low vitamin D might serve as a marker for TNF-driven disease rather than a direct causative factor for poor response in that context[34]. These findings were further confirmed by previously published evidence in a study by Winter et al. (2017) [39]. Improvements in health-related quality of life (HRQoL) have been frequently reported, with Bafutto et al. (2020) observing statistically significant improvements in the Inflammatory Bowel Disease Questionnaire (IBDQ) in higher-dose groups[25]. Raftery et al. (2015) linked serum 25(OH)D levels greater than or equal to 75 nmol/L to significantly higher quality of life scores[33]. Karimi et al. (2020) reported a significant increase in the IBD-Q score in patients with UC in the high-dose vitamin D group [35]. These findings highlight the patient-related benefits of supplementation beyond those objective disease markers. The findings were consistent, but they could not be pooled into a meta-analysis because of the lack of coherent outcomes reported in different studies.

**Comparison with previous literature**

Different randomized trials and meta-analyses have shown that vitamin D increases 25(OH)D levels and can lower inflammatory marker levels; pooled evidence suggests reduced overall clinical relapse, particularly in patients with Crohn’s disease. However, these trials are small-scale and heterogeneous in dose/formulation, and findings are often inconsistent for ulcerative colitis. [40] According to a recent meta-analysis published in 2021, oral vitamin D supplementation was found to be a safe therapeutic approach that increased the serum 25-hydroxyvitamin D concentration and decreased the serum C-reactive protein level but did not lower the erythrocyte sedimentation rate, disease activity index, or relapse rate. This analysis was based on a pooled analysis of 17 trials involving 1127 patients. [41] These findings are consistent with the findings of the current study, which showed similar results for all the studied variables. These results imply that oral vitamin D supplementation may be useful in the treatment of IBD. Interestingly, in another study, among 458 IBD patients, the pooled risk ratio for clinical relapse was 0.64 (95% CI: 0.46–0.89; I2 = 25%). This appears to be true for people with Crohn's disease (CD), however. In fact, the study included only two studies with 67 ulcerative colitis patients.

**Nutritional status, malnutrition, and precision vitamin D supplementation in IBD**

In addition to immunologic effects, inflammatory bowel disease is increasingly recognized as a condition characterized by the interconnected triad of chronic inflammation, metabolic dysregulation, and disease-related malnutrition, which may influence responsiveness to nutritional interventions and contribute to heterogeneous treatment effects [42]. Recent multicenter evidence has demonstrated a high prevalence of malnutrition and micronutrient deficiencies among patients with IBD, reinforcing the importance of routine nutritional screening and targeted correction of deficiencies, including vitamin D deficiencies [43].

Mechanistic and translational research further supports a biologically plausible role for vitamin D in intestinal barrier integrity, antimicrobial peptide expression, and mucosal immune regulation, emphasizing its function as a host-modulating nutrient rather than a conventional anti-inflammatory drug [44]. These findings align with the variable clinical effects observed in the present meta-analysis and suggest that vitamin D supplementation may exert the greatest benefit in patients with baseline deficiency, elevated inflammatory burden, or specific disease phenotypes. Emerging expert consensus recommends transitioning from uniform supplementation strategies toward precision-nutrition approaches, incorporating baseline vitamin D status, disease activity, inflammatory markers, and individualized dosing frameworks to optimize therapeutic benefit [45]. This targeted model may help explain the heterogeneity observed across trials and provide a framework for future interventional studies seeking to identify patient subgroups most likely to derive meaningful clinical benefit.

**Clinical and Public Health Implications**

Cumulative evidence from this meta-analysis suggests that vitamin D supplementation has significant clinical implications for IBD management. Given its ability to reliably correct vitamin D deficiency and its possible modest association with improved outcomes. [46] This could reduce reliance on conventional immunosuppressive drugs or biologics, thereby mitigating their associated side effects and potentially lowering healthcare costs associated with frequent flare-ups, hospitalizations, and complex treatments. From a public health perspective, these findings highlight the critical importance of routine vitamin D screening in patients with IBD, especially

considering the high prevalence of vitamin D deficiency in this population. [47] Incorporating regular vitamin D supplementation tailored to individual needs and baseline status could be a simple yet impactful component of a broader therapeutic strategy to improve disease outcomes and overall well-being in patients with IBD.

**Recommendations for Future Research**

Despite these promising signals, several critical gaps remain that warrant further investigation to elucidate the role of vitamin D in IBD management.

**1. Optimal Dosage and Formulation:** Substantial heterogeneity in dosing regimens (e.g., Bafutto et al. (2020) tested 2,000 to 50,000 IU/week; Narula et al. (2017) used 1,000 vs. 10,000 IU daily; Sharifi et al. (2016) used a single 300,000 IU IM injection), preventing definitive conclusions regarding the most effective dose, route, and formulation. Future head–to-head dose–finding RCTs are essential to establish optimal vitamin D regimens for IBD patients. [48]

**2. Long-term effects:** Most studies included in this meta-analysis had relatively short follow-up periods (typically 6–12 months). Long-term studies are crucial to determine whether the observed benefits, particularly regarding relapse prevention and sustained remission, are durable over extended periods. Achieving sustained remission while limiting persistent immunosuppression is a major problem for patients with IBD, a chronic illness, to lower risks and maintain future therapeutic options (including effective retreatment with the same medication if necessary). Thus, determining the best time and conditions for biological de-escalation is of clinical interest. [49]

**3. Personalized Approaches:** Given the observed heterogeneity and potential for differential benefits, future research should explore personalized vitamin D supplementation strategies. This includes stratifying patients on the basis of baseline vitamin D levels, disease activity, specific IBD phenotypes (CD vs. UC), and genetic factors to identify subgroups most likely to derive significant clinical benefits.

**4. Mechanisms of action:** While some studies have explored changes in cytokines (e.g., Bendix et al. (2020) on IL-17A, IFNγ, and IL-10) and antimicrobial peptides (Sharifi et al. (2016) on cathelicidin), more in-depth mechanistic studies are needed to fully elucidate how vitamin D

modulates immune function and inflammation in IBD at the molecular level. [50] This includes investigating its interactions with specific immune cells, such as T lymphocytes and dendritic cells.

**5. Interaction with IBD Therapies:** Future studies should prospectively evaluate the long-term safety of vitamin D supplementation and its potential interactions with existing IBD therapies, including biologics. [51] Retrospective data suggest that vitamin D status may influence biological response, but randomized controlled trials are scarce.

**Strengths and Limitations**

This meta-analysis has several strengths. The inclusion of RCTs and observational studies, encompassing diverse IBD subtypes and geographical locations, contributed to the breadth and potential generalizability of the findings. The application of validated statistical techniques, such as SMD for continuous outcomes, allows for the quantitative synthesis of effects across studies, despite varying measurement scales. Furthermore, a detailed assessment of the risk of bias via the RoB 2 tool for RCTs and the ROBINS-I tool for nonrandomized studies contributes to a transparent evaluation of evidence quality. Inflammatory marker dynamics, such as changes in cytokine expression (e.g., IL-17A, IFNγ, and IL-10) and antimicrobial peptides (e.g., cathelicidin), further support the biological plausibility of the anti-inflammatory and mucosal-defense roles of vitamin D in IBD.

Despite these strengths, several limitations of this study warrant careful consideration when our findings are interpreted. Inconsistent reporting of participant age and sex across studies, which restricts subgroup analyses and limits patient-level clinical inference. Another prominent limitation is the significant heterogeneity observed in many analyses, with $I^2$ values as high as 89% for serum vitamin D levels and 78% for CDAI scores. The heterogeneity of TNF-α levels was particularly high ($I^2$=92%). This substantial variability underscores significant differences in study design, patient demographics, disease activity at baseline, intervention protocols (e.g., vitamin D formulations, doses, routes, and duration), and methodologies for outcome assessment. Such heterogeneity can reduce the precision and generalizability of pooled estimates. Second, several included studies were characterized by small sample sizes, which limits their statistical power to detect subtle but clinically meaningful differences, particularly for endpoints, such as relapse rates. The risk of bias assessment also revealed that some studies had a moderate to high risk of bias,

primarily due to issues such as unclear allocation concealment, inadequate blinding, and potential selective reporting. This susceptibility to bias in individual studies could affect the overall reliability of the meta-analysis findings. Furthermore, the short follow-up periods in many studies, typically ranging from 6-12 months, may not be sufficient to capture long-term disease outcomes, particularly concerning relapse prevention or sustained remission. There was also a predominance of data from Crohn's disease patients, particularly those in remission, indicating that the evidence for ulcerative colitis and active disease stages remains comparatively sparse and inconsistent. Finally, inconsistent reporting of intention-to-treat versus per-protocol analyses, as noted by Narula et al. (2017), complicates direct comparisons and can influence perceived efficacy.

## Conclusion

In conclusion, this meta-analysis provides **low-certainty evidence** that vitamin D supplementation effectively increases serum vitamin D levels in patients with IBD and **shows limited and heterogeneous associations** with disease activity and favorable modulation of inflammatory markers, particularly in patients with baseline vitamin D deficiency. Although the high degree of heterogeneity across studies and some inconsistent clinical findings highlight the complexity of this intervention, the overall signal is promising. Further targeted research is essential to optimize dosing strategies, understand long-term effects, clarify mechanisms of action, and refine patient selection criteria to fully understand the therapeutic potential of vitamin D in IBD management.

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**Table 1**

PICOS framework for the literature search

| PICO Element | Description |
|---|---|
| **Population** | Children or adults with Crohn's Disease (CD), Ulcerative Colitis (UC), or Inflammatory Bowel Disease Unclassified (IBDU) in clinical remission at baseline. |
| **Intervention** | Vitamin D supplementation (any route, formulation, dose; either monotherapy or adjunct to usual IBD maintenance therapy). |
| **Comparator** | Placebo, no vitamin D, or standard care without vitamin D. |
| **Outcomes** | *Primary:* Clinical relapse during follow-up (6, 12, or 24 months). *Secondary:* Endoscopic relapse; biochemical activity (fecal calprotectin, CRP, IL-6, IL-10, etc.); health-related quality of life (IBDQ); serum 25(OH)D achieved; adverse events (AEs, serious AEs); hospitalization. Although clinical relapse was defined as the primary outcome, most eligible trials reported disease activity indices (e.g., CDAI or Mayo score) rather than relapse, resulting in a protocol deviation that is explicitly acknowledged in interpretation. |

**Table 2**

Inclusion and Exclusion Criteria for the Review

| Criteria | Inclusion | Exclusion |
|---|---|---|
| Study Design | Randomized controlled trials (parallel or cluster), quasirandomized trials, controlled cohort studies | Cross-sectional studies, case series |
| Participants | Clinically confirmed IBD in active or remission state (by CDAI <150, partial Mayo ≤2 with no subscore >1, physician assessment, or endoscopic remission); Mixed-activity cohorts | Perioperative prophylaxis: Case reports; preinterventional vitamin D supplementation |
| Interventions | Cholecalciferol (D3) or ergocalciferol (D2), oral or IM; daily/weekly/bolus; cosupplementation allowed if identical across arms | Combination drugs not isolating the effect of vitamin D |
| Comparators | Placebo, no vitamin D, or different doses | - |
| Follow-up Duration | ≥24 weeks; plan time-point analyses at 6±2 months and 12±3 months | - |
| Setting | Any | None specified |
| Language/Years | June 2000 to June 2025 | - |

800 **Table 3. Summary of study design, vitamin D regimens, and key clinical outcomes across**
801 **included trials.**

| Author (Year) | Design/Setting | Population (N) | Age (reported) | Sex | Intervention vs Control | Duration | Primary Outcomes | Key Findings |
|---|---|---|---|---|---|---|---|---|
| Bafutto 2020 | Double-blind RCT, Brazil | 30 CD on anti-TNF | 18–70 yrs | Both | VD 2k vs 10k vs 50k IU/week | 52 wks | CDAI, FC, CRP | VD with anti-TNF improved remission; >30 ng/mL better outcomes |
| Bendix 2017 | RCT, Denmark | 40 CD | Adults ≥18 yrs | Both | VD3 1200 IU/day vs placebo | 26 wks | PD-1 expression | VD increased immune tolerance markers |
| Dadaei 2015 | RCT, Iran | 108 IBD | Adults ≥18 yrs | Both | VD3 50,000 IU/week vs none | 12 wks | TNF-α, CDAI | VD increased vitamin D levels; TNF α reduction NS |
| de Bruyn 2021 | Multicenter RCT, NL/BE | 143 CD postresection | Adults ≥18 yrs | Both | VD3 25,000 IU/week vs placebo | 26 wks | Rutgeerts score | No reductio in recurrenc |
| Sharifi 2016 | Double-blind RCT, Iran | 90 UC remission | Adults ≥18 yrs | Both | IM VD3 300,000 IU vs placebo | 3 mo | hs-CRP, ESR | VD reduced inflammator markers |

| Author (Year) | Design/Setting | Population (N) | Age (reported) | Sex | Intervention vs Control | Duration | Primary Outcomes | Key Findings |
|---|---|---|---|---|---|---|---|---|
| Xia 2021 | Retrospective cohort, China | 73 CD on IFX | Mean ≈40 yrs | Both | VD3 125 IU/day vs none | 54 wks | HBI remission | VD improved IFX respons |
| Narula 2017 | Pilot RCT, USA | 34 CD remission | 18–70 yrs | Both | VD3 10,000 vs 1,000 IU/day | 12 mo | Relapse, 25-OHD | High dose safe; relapse difference NS |
| Bendix 2020 | Double-blind RCT, Denmark | 40 active CD | 18–80 yrs | Both | IFX ± VD3 | 7 wks | Mucosal cytokines | VD decreased cytokines; limited clinical change |
| Raftery 2015 | Pilot RCT, Ireland | 27 CD remission | Adults ≥18 yrs | Both | VD3 2000 IU/day vs placebo | 3 mo | Intestinal permeability | VD improved barrier function |
| Reich 2016 | Prospective cohort, Canada | 28 CD starting IFX | Adults ≥18 yrs | Both | VD supplementation if deficient | 22 wks | HBI remission | Low VD predicted better IFX response |
| Karimi 2020 | Double-blind RCT, Iran | 50 active UC | Adults ≥18 yrs | Both | VD 2000 vs 1000 IU/day | 12 wks | hs-CRP, TNF-α | Higher dose reduced inflammatio |
| Ahamed 2019 | Double-blind RCT, India | 60 active UC | Adults ≥18 yrs | Both | Nano-VD3 vs placebo | 4 wks | UCDAI | VD improved |

| Author (Year) | Design/Setting | Population (N) | Age (reported) | Sex | Intervention vs Control | Duration | Primary Outcomes | Key Findings |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | clinical outcomes |
| Bendix 2021 | Follow-up cohort, Denmark | CD on IFX | Adults ≥18 yrs | Both | Prior VD vs placebo | 45 wks | IFX escalation | VD reduced need for IFX escalation |
| Jørgensen 2010 | Multicenter RCT, Denmark | 94 CD remission | Adults ≥18 yrs | Both | VD3 1200 IU + Ca vs Ca | 12 mo | Relapse rate | VD reduced relapse (NS) |

Age and sex reporting varied across studies, and demographic data were inconsistently reported, limiting pooled demographic analysis.

**Figure 1**

PRISMA chart for the systematic review

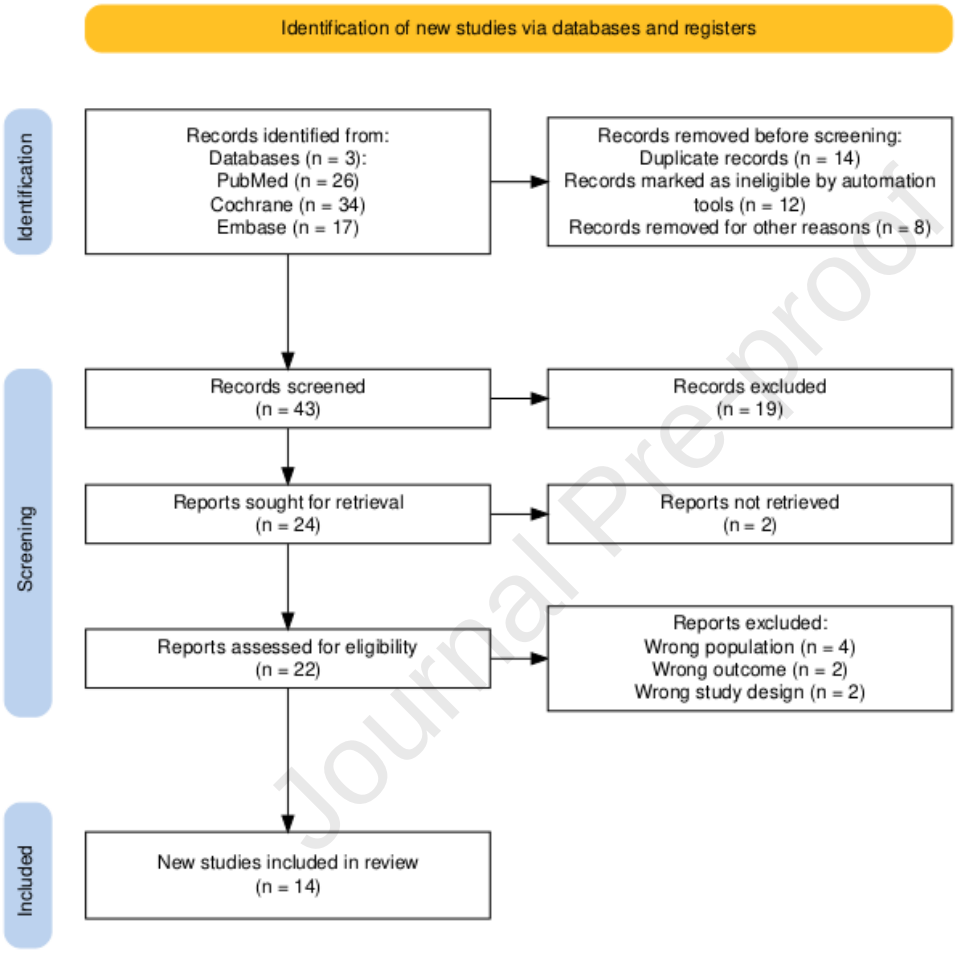
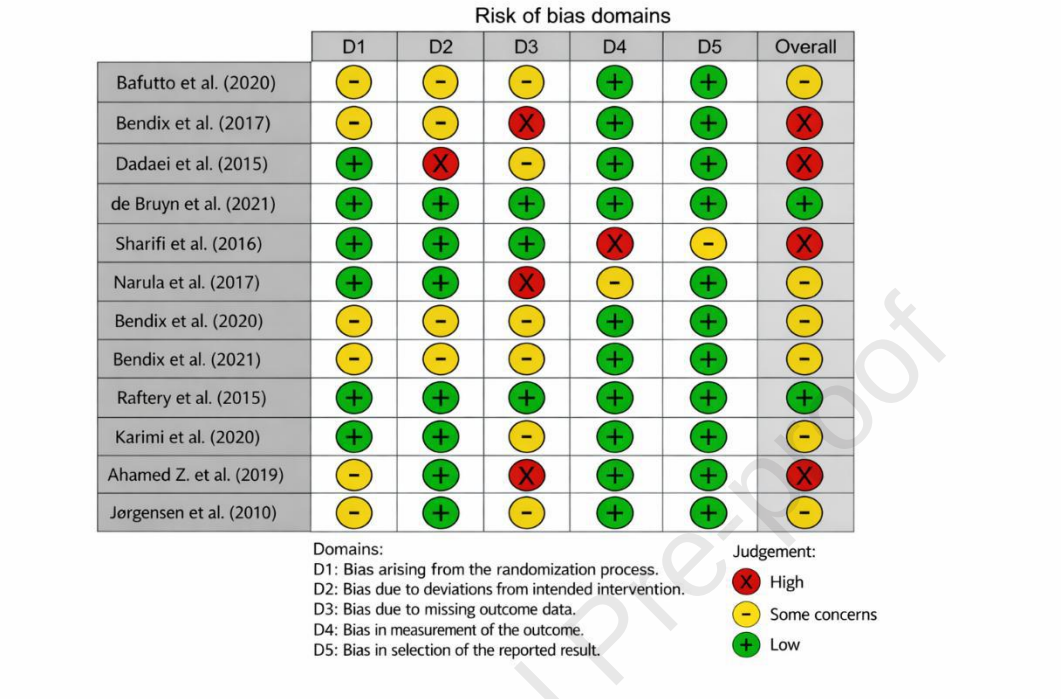


**Figure 2**

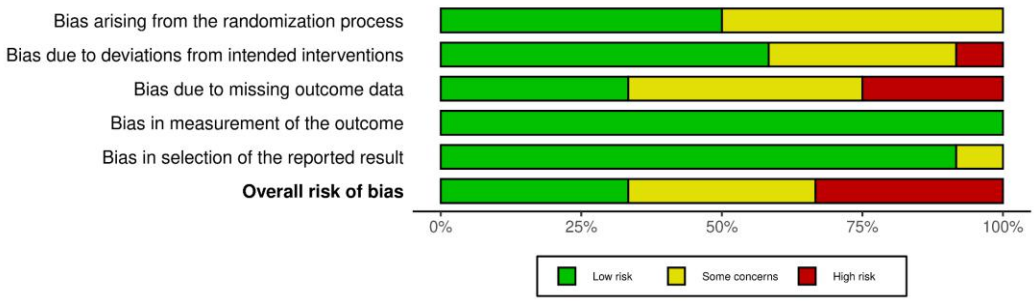
Traffic light plot showing the risk of bias across randomized controlled trials (ROBv2)




Risk of bias summary plot for randomized controlled trials assessed via the Cochrane Risk of Bias 2 (ROB2) tool. Green indicates low risk, yellow indicates some concerns, and red indicates high risk across bias domains.

**Figure 3**

Summary plot for risk across individual domains of bias via the ROBv2 tool




Traffic light plot illustrating study-level risk of bias judgments for randomized controlled trials across ROB2 domains.

**Figure 4**

Traffic lights plot for risk of bias in nonrandomized interventional studies using ROBINS-1

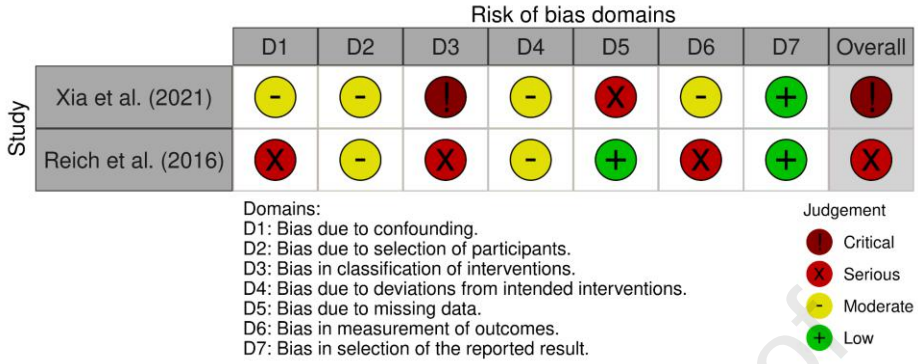



**Figure 5**

Summary plot for risk across individual domains of bias in observational studies (ROBINS-1)

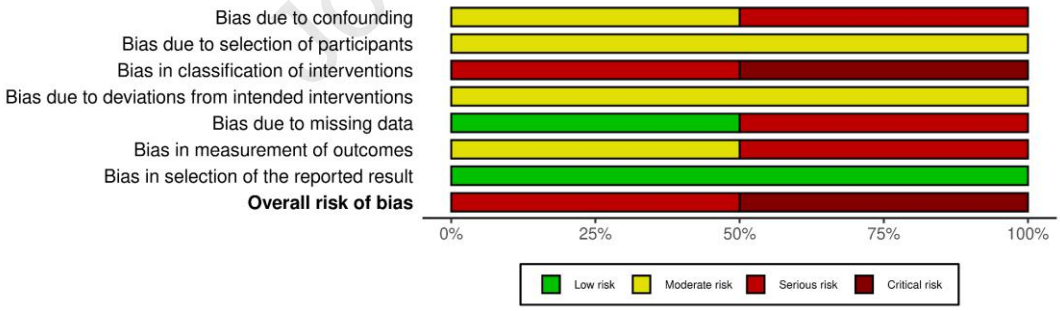


**Figure 6**

Forest plot for target serum vitamin D levels after supplementation (experimental vs. control)

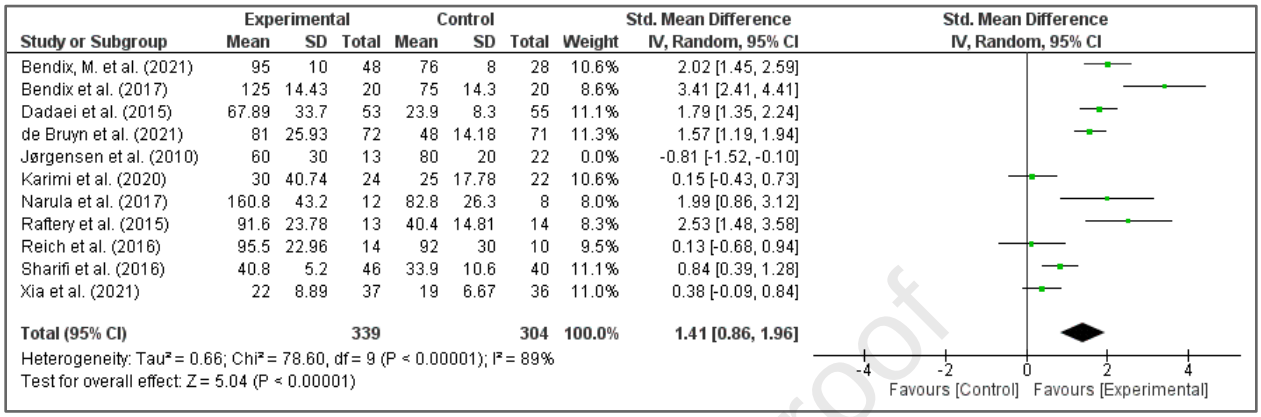
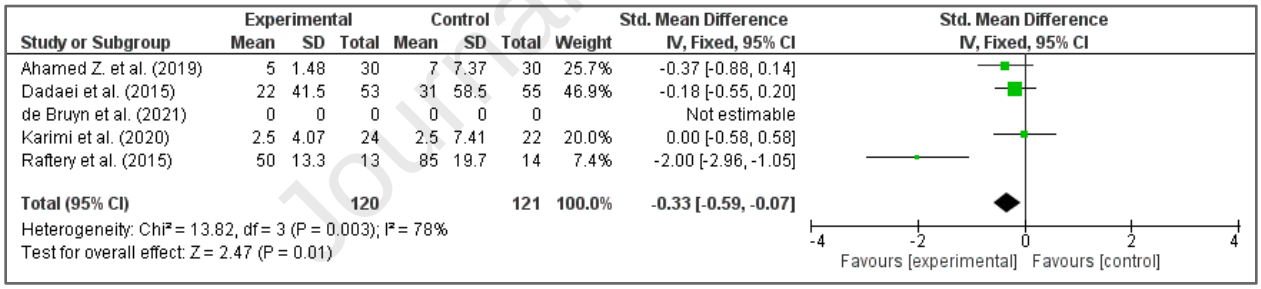



**Figure 7**

Forest plot of the CDAI scores in the experimental and control groups



**Declaration of interests**

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