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META-ANALYSIS

Liu et al: Vitamin D for tuberculosis prevention

Vitamin D supplementation for tuberculosis prevention: A meta-analysis

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ABSTRACT

Vitamin D plays an important role in immune regulation, prompting interest in its potential for preventing tuberculosis. However, clinical findings regarding its protective effects against tuberculosis infection and disease remain inconsistent. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the impact of vitamin D supplementation on the prevention of tuberculosis infection and the progression to active tuberculosis. We searched PubMed, Embase, Cochrane Library, and Web of Science databases through January 2025. Eligible studies involved participants without active tuberculosis at baseline and reported outcomes related to tuberculosis. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random-effects model. Subgroup and sensitivity analyses were conducted, and the certainty of evidence was evaluated using the GRADE approach. Six RCTs, involving 15,677 participants, met our inclusion criteria. Compared to placebo, vitamin D supplementation did not significantly reduce the risk of tuberculosis infection (5 RCTs; OR: 0.95; 95% CI: 0.79–1.14; $p = 0.55$) or the development of active tuberculosis (4 RCTs; OR: 0.77; 95% CI: 0.56–1.05; $p = 0.10$). The certainty of evidence was moderate for both outcomes. Subgroup analyses based on baseline vitamin D levels and duration of follow-up yielded consistent results. The incidence of serious adverse events was comparable between the vitamin D and placebo groups (OR: 1.02; 95% CI: 0.76–1.38; $p = 0.87$), and none of the serious events were attributed to vitamin D supplementation. In conclusion, vitamin D supplementation does not significantly reduce the risk of tuberculosis infection or progression to active tuberculosis, although it is safe and well tolerated.

Keywords: Tuberculosis; Prevention; Vitamin D; Supplementation; Meta-analysis.

INTRODUCTION

Tuberculosis remains one of the leading infectious causes of morbidity and mortality worldwide (1, 2). According to the World Health Organization, an estimated 10.6 million people developed tuberculosis in 2021, and 1.6 million people died from the disease, making it the second leading infectious killer after COVID-19 (3). The global burden of tuberculosis is disproportionately concentrated in low- and middle-income countries, with South-East Asia and Africa bearing the highest prevalence (4). Beyond its acute disease burden, tuberculosis has long-term consequences including chronic lung damage, socioeconomic hardship, and increased vulnerability to reinfection and other comorbidities (5, 6). Children, individuals with compromised immune systems (such as those living with HIV), the elderly, and those living in crowded or under-resourced environments are particularly vulnerable to tuberculosis infection and progression to active disease (7, 8). Given the ongoing global burden, the high-risk nature of certain populations, and the limited effectiveness of current control measures in many settings, there is an urgent need to identify additional preventive strategies.

Vitamin D, a fat-soluble secosteroid hormone, is essential for calcium and phosphate metabolism and bone health, but it also plays an increasingly recognized role in modulating the immune response (9, 10). It is synthesized in the skin upon exposure to ultraviolet B radiation or obtained through diet and supplements (11). Once activated to its hormonal form, 1,25-dihydroxyvitamin D, it binds to the vitamin D receptor (VDR), which is expressed in a variety of cells, including immune cells such as monocytes, macrophages, and dendritic cells (12). In the context of tuberculosis, vitamin D enhances the antimicrobial activity of macrophages, promotes the production of cathelicidin and other antimicrobial peptides, and supports autophagy and phagolysosome fusion—mechanisms critical for host defense against *Mycobacterium tuberculosis* (13, 14). It also exerts regulatory effects on the adaptive immune

system by modulating T-cell differentiation and cytokine responses, thus maintaining a balanced immune environment (15).

Observational studies have consistently suggested an association between low serum levels of 25-hydroxyvitamin D and increased susceptibility to tuberculosis infection and progression, and individuals with active or latent tuberculosis tend to have lower circulating vitamin D levels compared to healthy controls (16-19). Furthermore, individuals with vitamin D deficiency may be more likely to progress from latent tuberculosis infection to active disease, particularly in the context of other risk factors such as HIV infection or malnutrition (18, 20, 21). These findings have spurred growing interest in exploring whether vitamin D supplementation could serve as a cost-effective and safe strategy to reduce the risk of tuberculosis (22, 23). Despite promising biological plausibility and observational data, the results of randomized controlled trials (RCTs) investigating the efficacy of vitamin D supplementation in preventing tuberculosis infection or disease have been inconsistent (24-29). Differences in study populations, baseline vitamin D status, supplementation regimens, and tuberculosis outcomes measured have contributed to these divergent findings (24-29). To date, no consensus has been reached on whether routine vitamin D supplementation should be recommended as part of tuberculosis prevention strategies, especially in high-risk populations such as children, individuals with HIV, or those living in endemic areas (30). Given these uncertainties, we performed a meta-analysis in this study aiming to systematically evaluate the influence of vitamin D supplementation on risks of tuberculosis infection and development of active tuberculosis.

MATERIAL AND METHODS

During the design and implementation of this study, we followed the guidelines set forth by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (31, 32)

and the Cochrane Handbook (33). The protocol of the meta-analysis has been registered at PROSPERO with the identifier CRD420251004949.

Study inclusion and exclusion criteria

This meta-analysis included studies that met the inclusion criteria specified in the PICOS principle.

P (Patients): Children or adults without active tuberculosis at baseline.

I (Intervention): Vitamin D supplementation administered in various dosages and durations.

C (Control): Standard treatment, no treatment, or controls with similar appearance and administration route to the intervention.

O (Outcome): Incident tuberculosis infection or development of active tuberculosis, and the methods for the diagnosis of tuberculosis infection or active tuberculosis were consistent with the criteria used in the original studies.

S (Study design): RCTs.

Excluded from the analysis were reviews, editorials, preclinical studies, studies not designed as RCTs, studies involving patients with active tuberculosis, not including vitamin D supplementation as an intervention, or not reporting the outcomes of interest. If studies with overlapped patients were retrieved, the one with the largest sample size was analyzed in the meta-analysis.

Database search

The Medline (PubMed), Embase (Ovid), and CENTER (Cochrane Library), and Web of Science databases were searched using the combination of the following terms: (1) "vitamin D" OR "vitamin D2" OR "vitamin D3" OR "cholecalciferol" OR "ergocalciferol" OR "alphacalcidol" OR "alfacalcidol" OR "calcitriol" OR "paricalcitol" OR "doxerocalciferol");

and (2) "tuberculosis" OR "*Mycobacterium tuberculosis*" OR "tuberculous", limited to clinical studies in human. Only studies that included human subjects and were published in English were considered. The full search strategy for each database is shown in Supplemental File 1. Additionally, references to related reviews and original articles were screened as part of the final database search. The final database search was conducted on January 29, 2025.

Data collection and quality evaluation

Two authors conducted independent database searches, data collection, and quality assessment. In the event of disagreements, discussions were held with the corresponding author. The data collected encompassed various aspects, including overall study information (such as first author, publication year, and study country), study design (double-blind or single blind), participants characteristics (general status, number of participants, mean age, sex, and baseline serum level of 25-hydroxyvitamin D [25(OH)D]), details of intervention with vitamin D supplementation (oral or transdermal, dosages, and treatment frequency), control details, follow-up durations, and definitions and outcomes of tuberculosis infection. The quality of the included RCTs was assessed using the Cochrane Risk of Bias Tool (33). This tool evaluated various aspects such as random-sequence generation, allocation concealment, blinding of participants and outcome assessment, addressing incomplete outcome data, selective reporting, and other sources of bias. In addition, two reviewers evaluated the certainty of evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system, which includes risk of bias, inconsistency, indirectness, imprecision and publication bias (34). The certainty of evidence was classified as very low, low, moderate or high. Disagreements were resolved by discussion with the corresponding author.

Statistical analysis

The influence of vitamin D supplementation on the risk of tuberculosis infection and the development of active tuberculosis as compared to controls was summarized as odds ratio (OR) and corresponding 95% confidence interval (CI) (33). In addition, we compared the incidence of serious adverse events (SAEs) between the two groups, as defined by the criteria used in the original studies. These generally included fatal or non-fatal events leading to discontinuation of the study medication, as well as other monitored safety concerns such as hypercalcemia, hypervitaminosis D, and renal stones. Heterogeneity was assessed using the Cochrane Q test (33). The I^2 statistic was also calculated, with $I^2 < 25\%$, within 25~75%, and > 75% indicating mild, moderate, and substantial heterogeneity (35). A random-effects model was used to pool the results because this model could incorporate the potential influence of heterogeneity (33). The sensitivity analysis by excluding one dataset at a time was performed to evaluate the robustness of the findings (33). In addition, predefined subgroup analyses were also conducted to evaluate the study characteristics on the outcomes, such as the baseline serum level of 25(OH)D, and the follow-up durations. The medians of the continuous variables were used as the cutoff values to define the subgroups. An evaluation of the publication bias was conducted via a visual inspection using funnel plots and by performing Egger's regression asymmetry test (36). A $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using RevMan (Version 5.1; Cochrane, Oxford, UK) and Stata software (version 17.0; Stata Corporation, College Station, TX, USA).

RESULTS

Literature search

Figure 1 depicts the flowchart that outlines the process of database searching and study identification, ultimately leading to the selection of studies for inclusion. Initially, a total of

1,117 articles were obtained through the database search, which was subsequently reduced to 721 after eliminating 396 duplicate records. Subsequently, 700 articles were excluded based on an evaluation of their titles and abstracts, primarily due to their lack of relevance to the objective of the present meta-analysis. Then, 15 out of the remaining 21 articles were excluded after full-text reviews for reasons outlined in Figure 1.Ultimately, six RCTs (24-29) were deemed suitable for quantitative analysis.

Study characteristics and data quality

An overview of the included studies can be found in Table 1. These six randomized, double-blind, placebo-controlled trials were conducted in Mongolia (24, 26), Indonesia (25), Tanzania (27), India (28), and South Africa (29), and published between 2012 and 2023. The studies enrolled both children (ages ranging from under 5 to 15 years) and adults (≥18 years) without active tuberculosis at baseline. A total of 15,677 participants were included, with mean ages ranging from under 5 to 38.7 years, and the proportion of males ranging from 32.0% to 50.7%. Notably, although the title of the Dude et al. (2022) study references "TB recurrence," the trial exclusively enrolled TB-naïve children with no history of infection, aligning with the preventive focus of the present meta-analysis (28). In Yani et al. (2018), although the exact mean age was not reported, all enrolled participants were confirmed to be less than five years old (25). Given the young age and potential influence of BCG vaccination, TST-based diagnoses in this subgroup may be subject to reduced specificity. Four studies included patients with baseline serum level of 25(OH)D < 30 ng/mL (24-27), while another two studies included patients with baseline serum level of 25(OH)D < or ≥ 30 ng/mL (28, 29). Vitamin D_3 supplementation was administered orally in varying doses and regimens, including daily, weekly, or high single doses, for durations ranging from 3 to 36 months. The placebo controls matched the intervention in appearance and administration. Tuberculosis infection was diagnosed using tuberculin skin test (TST) (24, 25) or

QuantiFERON-TB Gold (QFT) or QFT-Plus (26, 28, 29) conversions in five studies, while active tuberculosis was confirmed through clinical symptoms, radiological findings, or microbiological tests in four studies (26-29). The details of study quality evaluation for the RCTs are shown in Table 2. All of the included studies were judged to have low risk of bias across all domains, except for two studies (25, 28), which had unclear risks for random sequence generation and allocation concealment because details of these two domains were not adequately reported in these studies.

Influence of vitamin D supplementation on tuberculosis infection

Five studies reported the influence of vitamin D supplementation on the risk of tuberculosis infection (24-26, 28, 29), with mild heterogeneity (p for Cochrane Q test = 0.34; I^2 = 12%). The pooled results of these studies showed that overall, vitamin D supplementation did not reduce the risk of tuberculosis infection as compared to placebo (OR: 0.95, 95% CI: 0.79 to 1.14, p = 0.55; Figure 2A). Summarized certainty of evidence using the GRADE system is shown in Table 3. We downgraded evidence by one level for the possible publication bias due to limited number of studies included. We judged the evidence to be of moderate certainty. The sensitivity analysis by excluding one dataset at a time showed consistent results (OR: 0.84 to 0.98, p all > 0.05). Subsequent subgroup analyses showed similar results between studies only including patients with baseline 25(OH)D < 30 ng/mL and studies including patients with baseline 25(OH)D < or ≥ 30 ng/mL (OR: 0.91 versus 0.87, p for subgroup difference = 0.89; Figure 2B). In addition, similar results were observed between studies with a follow-up duration of up to 12 months, where tuberculosis infection was defined by TST conversion, and those with a 36-month follow-up, where infection was defined by QFT conversion (OR: 0.60 vs. 0.97; p for subgroup difference = 0.37; Figure 2C).

Influence of vitamin D supplementation on the development active tuberculosis

The results of meta-analysis involving four studies (26-29) suggested that vitamin D supplementation did not reduce the incidence of active tuberculosis as compared to placebo (OR: 0.77, 95% CI: 0.56 to 1.05, p = 0.10; Figure 3A) with no significant heterogeneity (p for Cochrane Q test = 0.47; I^2 = 0%). The certainty of evidence, summarized in Table 3, was rated as moderate due to possible publication bias from the limited number of included studies. The sensitivity analysis by omitting one dataset at a time did not significantly change the results (OR: 0.57 to 0.78, p all > 0.05). Similar results were observed between studies that exclusively included participants with baseline 25(OH)D < 30 ng/mL and those that included participants with baseline levels < or ≥ 30 ng/mL (OR: 0.80 vs. 0.15; p for subgroup difference = 0.12; Figure 3B), as well as between studies with follow-up durations of 12 and 36 months (OR: 0.78 vs. 0.57; p for subgroup difference = 0.57; Figure 3C).

Incidence of adverse events

Across the included studies, SAEs were rare and occurred at similar rates between the vitamin D and placebo groups (27-29). When reported, SAEs were predominantly non-fatal hospitalizations or isolated deaths, and none were attributed to vitamin D supplementation, suggesting that vitamin D is generally safe and well tolerated for tuberculosis prevention. The pooled results of three studies (27-29) showed that the incidence of SAEs were comparable between patients allocated to the vitamin D supplementation and placebo groups (OR: 1.02, 95% CI: 0.76 to 1.38, p = 0.87; Figure 4) with no significant heterogeneity (p for Cochrane Q test = 0.95; I^2 = 0%). The certainty of evidence, summarized in Table 3, was also rated as moderate due to the potential for publication bias stemming from the limited number of included studies.

Publication bias

The funnel plots for the meta-analyses comparing the influences of vitamin D supplementation on tuberculosis infection, development active tuberculosis, and SAEs compared to placebo are shown in Figure 5A to 5C. These plots are symmetrical on visual inspection, suggesting low risks of publication biases. Egger's regression test was unable to perform because only three to five studies were included for these outcomes.

DISCUSSION

This meta-analysis of six high-quality RCTs, involving over 15,000 participants from diverse geographic and demographic backgrounds, found that vitamin D supplementation did not significantly reduce the risk of tuberculosis infection or progression to active tuberculosis when compared to placebo. Pooled results showed no statistically significant effect on either outcome, and consistent findings were observed across various sensitivity and subgroup analyses. Moreover, vitamin D supplementation was safe and well tolerated, with the incidence of serious adverse events comparable between intervention and control groups, and no events attributable to vitamin D.

These findings suggest that, despite strong biological plausibility and supportive evidence from observational studies, vitamin D supplementation alone may not be sufficient to prevent tuberculosis infection or development of active disease. Several physiological and immunological mechanisms may help explain this apparent disconnect. While vitamin D has known immunomodulatory effects, including enhanced macrophage activation, upregulation of antimicrobial peptides such as cathelicidin, and support for autophagy and phagolysosome fusion, these innate defense mechanisms may not be robust enough to fully prevent infection or eliminate *Mycobacterium tuberculosis* once exposure has occurred (37, 38). Additionally, tuberculosis is a complex disease influenced by multiple host, pathogen, and environmental

factors (39). It is possible that in the context of high pathogen load or other immunosuppressive conditions, the protective effects of vitamin D are overwhelmed (40, 41). Furthermore, vitamin D may have more of an adjunctive role—enhancing host immunity but insufficient on its own to confer protection, especially in populations without profound deficiency or in the absence of other supportive interventions (42).

Subgroup analyses based on baseline vitamin D status and follow-up duration provided important insights. The results were similar between studies that enrolled participants with serum 25(OH)D levels consistently below 30 ng/mL and those that included a broader range of baseline levels, suggesting that supplementation may not confer additional protection even in those with deficiency. Likewise, the consistency of findings between studies using different diagnostic definitions of tuberculosis infection—namely, tuberculin skin test (TST) conversion over shorter follow-up durations and interferon-gamma release assay (IGRA, e.g., QFT) conversion over longer durations—suggests that the overall null effect is robust across diagnostic modalities. Notably, TST may overestimate infection rates in BCG-vaccinated populations due to cross-reactivity, while IGRAs offer higher specificity (43, 44). Interestingly, although not statistically significant (p for subgroup difference = 0.37), the subgroup analysis showed a numerically lower odds ratio in studies using TST (OR: 0.60) compared to those using QFT/IGRA (OR: 0.97). This trend may reflect differential sensitivity or specificity of the assays, particularly in BCG-vaccinated populations, and warrants further exploration in future studies with harmonized diagnostic protocols. These subgroup findings support the robustness of the overall results and suggest that the lack of benefit is not confined to specific study designs or populations.

This meta-analysis has several notable strengths. First, we conducted a comprehensive and up-to-date literature search across multiple databases, with strict inclusion criteria limited to double-blind, placebo-controlled RCTs, which are the gold standard for evaluating

intervention efficacy. Second, the included studies spanned diverse populations, from young children to adults with HIV, enhancing the generalizability of our findings. Third, the consistent results observed across sensitivity and subgroup analyses lend confidence to the stability of the findings. Fourth, the risk of bias across most domains was judged to be low in all included studies, further supporting the internal validity of the meta-analysis.

However, several limitations should also be acknowledged. The number of available studies for each outcome was relatively small, which may limit statistical power and precision. While we rated the certainty of evidence as moderate for all outcomes, this reflects a balance between the low risk of bias and consistency of findings, and the potential limitations due to small study numbers, possible undetected publication bias, and imprecise effect estimates. The limited number of studies also precluded meaningful meta-regression or more granular subgroup analyses. In particular, although exploring varying degrees of baseline vitamin D deficiency could yield further insight, this approach was not feasible due to inconsistent reporting and a lack of stratified outcome data across the included trials. Most studies reported only mean or median baseline 25(OH)D levels, and few provided subgroup results based on specific deficiency thresholds, such as < 30 ng/mL (considered insufficient) or < 20 ng/mL (deficient). This highlights a gap in the current literature and underscores the need for future trials to incorporate and report more detailed stratifications of vitamin D status. Variability across studies in terms of participant characteristics (e.g., age, comorbidities), baseline vitamin D status, dosing regimens (including dose, frequency, and duration), and definitions of tuberculosis outcomes introduces heterogeneity that may mask subgroup-specific effects. Other potentially important factors—such as host genetic differences (e.g., vitamin D receptor polymorphisms), local TB transmission dynamics, and variations in nutritional or immune status—could also influence study outcomes. Unfortunately, due to the limited number of studies and the lack of stratified or individual

participant-level data, we were unable to assess these contributors to heterogeneity in our analysis. Although a potential dose–response relationship is of clinical interest, such an analysis was not feasible in this meta-analysis due to the lack of dose-stratified outcome data, substantial variability in dosing regimens (daily, weekly, or bolus), inconsistent reporting of participant body weight, and insufficient number of studies per outcome to permit reliable meta-regression. As summarized in Supplementary File 2, which presents individual dosing regimens and associated effect estimates, no consistent pattern of benefit was observed across different vitamin D schedules, including daily, weekly, or bolus regimens. On the other hand, such clinical heterogeneity may have diluted potential protective effects in more responsive subgroups. Additionally, wide variation in baseline 25(OH)D levels and differing definitions of TB outcomes further complicate interpretation. These differences likely contributed to the overall null effect and highlight the need for more targeted studies in well-characterized populations. Future trials would benefit from more detailed reporting of such variables to better elucidate population-specific responses to vitamin D supplementation. Another important limitation is the restricted geographic representation of the included studies, which were primarily conducted in Asia and Africa. Data from Latin America, Eastern Europe, and other high-burden regions are lacking. Variations in sunlight exposure, dietary patterns, underlying nutritional deficiencies, tuberculosis prevalence, and healthcare infrastructure across different settings may influence both baseline vitamin D status and the potential efficacy of supplementation. Future research should aim to include more geographically diverse populations to enhance the generalizability of findings. Moreover, the possibility of publication bias cannot be excluded, given the small number of available trials and the lack of unpublished or negative findings that may exist outside the published literature (45). While funnel plot inspection suggested low publication bias, the reliability of this assessment is limited by the small number of included studies. Formal tests such as Egger’s regression are

generally underpowered when fewer than 10 studies are available per outcome, which increases the risk of undetected bias. Therefore, the possibility of publication bias—especially for small, negative, or unpublished trials—cannot be ruled out and remains an important limitation of this meta-analysis.

From a clinical perspective, these findings do not support the routine use of vitamin D supplementation solely for the prevention of tuberculosis in the general population or in high-risk groups such as children with tuberculosis contact or people living with HIV. However, personalized approaches that consider individual risk profiles—such as profound vitamin D deficiency, immunosuppression, or high endemic exposure—may still hold value. Assessing baseline 25(OH)D levels and selectively supplementing individuals at greatest risk may offer a more effective and pragmatic strategy in clinical practice. In, addition, vitamin D supplementation remains important for musculoskeletal health and correction of deficiency (46), but its role in tuberculosis prevention appears limited based on current evidence (47). These results also reinforce the complexity of tuberculosis prevention, which likely requires a multifaceted approach including vaccination, chemoprophylaxis in high-risk groups, improved living conditions, and control of comorbid conditions such as HIV (48). Future research should aim to address the remaining uncertainties. Large-scale trials focused on specific subpopulations—such as individuals with profound vitamin D deficiency, genetic variants affecting vitamin D metabolism or receptor function, or those with significant immunosuppression—may help identify groups who might benefit more from supplementation (49). Trials should also explore optimized dosing strategies, including higher or more prolonged regimens, as well as the potential synergistic effects of combining vitamin D with other preventive interventions (49). In our meta-analysis, dosing schedules varied widely across studies, including daily, weekly, and high single-dose bolus regimens. However, no clear trend toward greater efficacy was observed for any particular regimen.

Given this variability and the absence of stratified efficacy results by dosing strategy in the included trials, the comparative effectiveness of different vitamin D supplementation approaches remains an open question for future research. Additionally, mechanistic studies exploring the interaction between vitamin D signaling and host-pathogen dynamics in tuberculosis are warranted to better understand the biological boundaries of its protective effects. Given the limited number of high-quality RCTs currently available, there is a clear need for larger, well-designed, multicenter trials employing standardized dosing regimens, diagnostic criteria, and follow-up durations. Such studies would enhance statistical power, minimize heterogeneity, and provide more definitive conclusions regarding the potential preventive effects of vitamin D against tuberculosis. Additionally, future trials may benefit from focusing on subpopulations with profound vitamin D deficiency or specific genetic variants related to the VDR, which may modulate the immune response to Mycobacterium tuberculosis. Such stratified approaches could improve trial efficiency and yield more clinically actionable insights. Future trials should also be adequately powered to detect a small-to-moderate protective effect (e.g., OR $\leq$ 0.80), with consideration of sample size calculations to ensure sufficient precision. For tuberculosis infection (annual risk ~4.0%), a sample size of approximately 9,200 participants per group would be needed to detect an odds ratio of 0.80 with 80% power and $\alpha = 0.05$. For active tuberculosis (annual risk ~0.5%), more than 70,000 participants per group would be required. These figures emphasize the need for large, multicenter trials to reliably detect modest preventive effects. Finally, to enhance comparability and support future meta-analyses, the development and adoption of a core outcome set—including standardized clinical endpoints for tuberculosis infection and progression, as well as harmonized immunological biomarkers—is strongly encouraged.

CONCLUSION

In conclusion, this comprehensive meta-analysis found that vitamin D supplementation does not significantly reduce the overall incidence of tuberculosis infection or development of active tuberculosis, although it is safe and well tolerated. However, the possibility remains that select high-risk groups—such as individuals with profound vitamin D deficiency, immunosuppression (e.g., HIV), or specific genetic profiles—might derive benefit. These findings highlight the importance of a broader preventive strategy in tuberculosis control while reinforcing the need for further targeted research in vulnerable populations.

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Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Characteristics of the included RCTs

Study	Country	Design	Participant characteristics	No. of participants	Mean age (years)	Male (%)	Baseline serum 25(OH)D	Intervention	Control	Follow-up duration (months)	Diagnosis of TB
Ganmaa et al. 2012	Mongolia	R, DB, PC	Schoolchildren aged 12–15 years in Ulaanbaatar, TST-negative at baseline	117	13.1	49.2	Mean: 7 ng/mL (all < 20 ng/mL; 82% < 10 ng/mL)	800 IU/day vitamin D_3 for 6 months	Placebo capsule, same appearance	6	TB infection as indicated by TST conversion (≥10 mm) and

											confirmed with T-SPOT.TB if converted
Yani et al. 2018	Indonesia	R, DB, PC	Healthy children (under 5 years) with recent TB contact and TST-negative at baseline	66	NR (< 5)	NR	< 30 ng/mL	Two high single doses of vitamin D_3, 6 weeks apart	Placebo	3	TB infection as indicated by TST conversion (induration >10 mm at 12 weeks)
Sudfeld et al. 2020	Tanzania	R, DB,	Adults (≥18 years) with	3639	38.7	32	<30 ng/mL in all	50,000 IU Vit D_3	Identical placebo	12	Active TB as

		PC	HIV initiating ART and serum 25(OH)D <30 ng/mL				participants (48% insufficient, 46% moderately deficient, 6–8% severely deficient)	weekly for 4 weeks, then 2,000 IU daily for 12 months			indicated by Clinical symptoms + sputum AFB smear and/or chest X-ray; GeneXpert used later in the study
Ganmaa et al. 2020	Mongolia	R, DB, PC	Schoolchildren aged 6–13 years, QFT-	8819	9.4	50.7	Mean: 11.9 ng/mL; 95.6% <20	Weekly oral 14,000 IU vitamin	Placebo	36	TB infection as

			negative at baseline, 95.6% had vitamin D <20 ng/mL				ng/mL; 31.8% <10 ng/mL	D_3 for 36 months			indicated by QFT-Gold conversion ; clinical diagnosis for active TB
Dude et al. 2022	India	R, DB, PC	Schoolchildren (aged 6–11 years),with negative QFT-Plus at baseline, no histories of TB	1354	8.9	47.6	Mean: 28.5 ng/mL	Weekly vitamin D_3 350 µg (14,000 IU) for 36 months	Placebo	36	TB infection as indicated by QFT-Plus test; clinical diagnosis

											for active TB
Middelkoop et al. 2023	South Africa	R, DB, PC	Healthy children aged 6–11 years with negative QFT-Plus at baseline, no chronic illness	1682	8.9	47.6	Mean 71.2 nmol/L (28.5 ng/mL); 63.2% <75 nmol/L	Weekly 10,000 IU vitamin D_3 for 3 years	Placebo, identical soft-gel capsule	36	TB infection as indicated by QFT-Plus assay conversion; active TB assessed by clinical evaluation

25(OH)D, 25-hydroxyvitamin D; AFB, acid-fast bacilli; ART, antiretroviral therapy; DB, double-blind; IU, international units; NR, not reported; PC, placebo-controlled; QFT, QuantiFERON-TB Gold; QFT-Plus, QuantiFERON-TB Gold Plus; R, randomized; TB, tuberculosis; TST, tuberculin skin test.

Table 2. Study quality evaluation via the Cochrane Risk of Bias Tool

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting	Other sources of bias
Ganmaa et al. 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Yani et al. 2018	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Sudfeld et al. 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ganmaa et al. 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dude et al. 2022	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Middelkoop et al. 2023	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 3. Summarized certainty of evidence using the GRADE system

Outcome	Quality assessment							Absolute effect OR (95% CI)	Quality
	No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
OR for TB infection	5	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Possible publication bias due to limited number of studies included	0.95 (0.79 to 1.14)	⊕⊕⊕O MODERATE
OR for active TB	4	RCTs	No serious risk of	No serious inconsistency	No serious indirectness	No serious imprecision	Possible publication bias due to	0.77 (0.56 to 1.05)	⊕⊕⊕O MODERATE

			bias				limited number of studies included		
OR for severe AEs	3	RCTs	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Possible publication bias due to limited number of studies included	1.02 (0.76 to 1.38)	⊕⊕⊕O MODERATE

AE, adverse event; CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial; TB, tuberculosis.

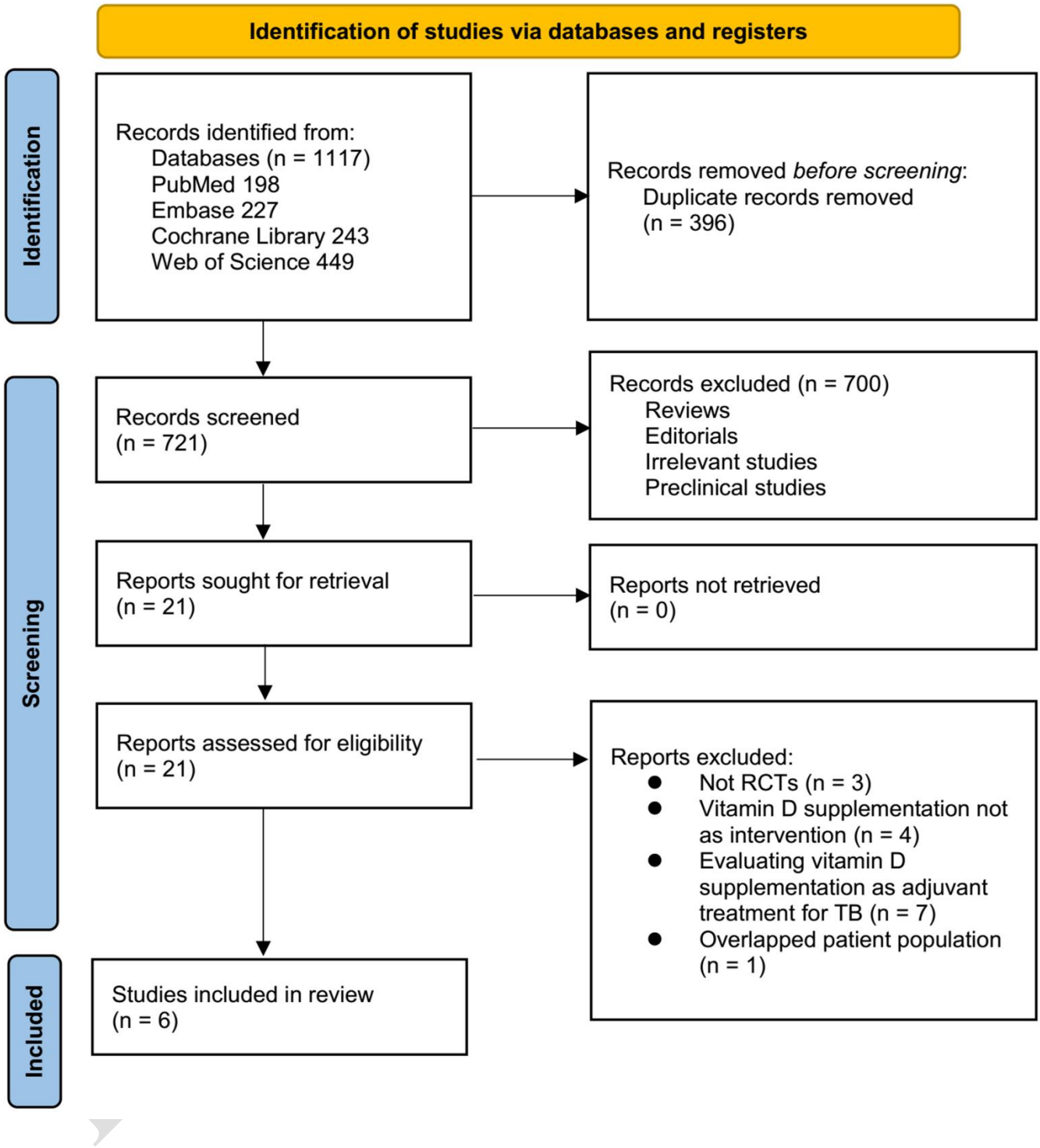
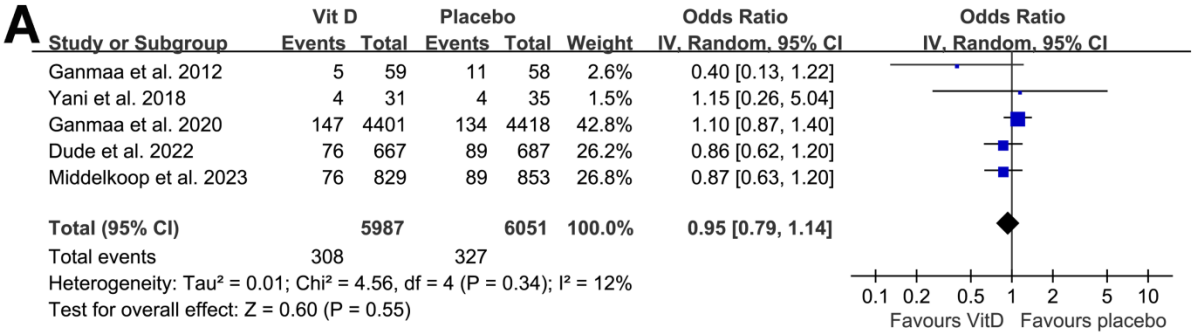
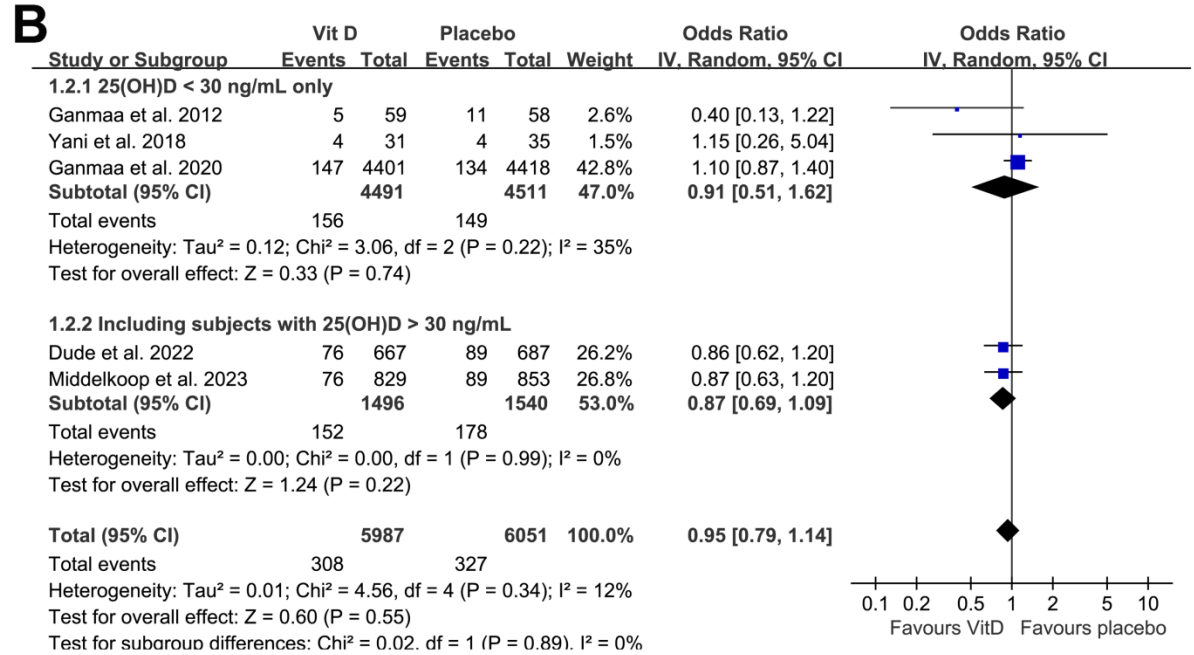


Figure 1. Flowchart for the literature search and study inclusion.

A


Vit D
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Ganmaa et al. 2012 5 59 11 58 2.6% 0.40 [0.13, 1.22]
Yani et al. 2018 4 31 4 35 1.5% 1.15 [0.26, 5.04]
Ganmaa et al. 2020 147 4401 134 4418 42.8% 1.10 [0.87, 1.40]
Dude et al. 2022 76 667 89 687 26.2% 0.86 [0.62, 1.20]
Middelkoop et al. 2023 76 829 89 853 26.8% 0.87 [0.63, 1.20]
Total (95% CI) 5987 6051 100.0% 0.95 [0.79, 1.14]
Total events 308 327
Heterogeneity: Tau² = 0.01; Chi² = 4.56, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.60 (P = 0.55)
0.1 0.2 0.5 1 2 5 10
Favours VitD Favours placebo

B


Vit D
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.2.1 25(OH)D < 30 ng/mL only
Ganmaa et al. 2012 5 59 11 58 2.6% 0.40 [0.13, 1.22]
Yani et al. 2018 4 31 4 35 1.5% 1.15 [0.26, 5.04]
Ganmaa et al. 2020 147 4401 134 4418 42.8% 1.10 [0.87, 1.40]
Subtotal (95% CI) 4491 4511 47.0% 0.91 [0.51, 1.62]
Total events 156 149
Heterogeneity: Tau² = 0.12; Chi² = 3.06, df = 2 (P = 0.22); I² = 35%
Test for overall effect: Z = 0.33 (P = 0.74)
1.2.2 Including subjects with 25(OH)D > 30 ng/mL
Dude et al. 2022 76 667 89 687 26.2% 0.86 [0.62, 1.20]
Middelkoop et al. 2023 76 829 89 853 26.8% 0.87 [0.63, 1.20]
Subtotal (95% CI) 1496 1540 53.0% 0.87 [0.69, 1.09]
Total events 152 178
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.22)
Total (95% CI) 5987 6051 100.0% 0.95 [0.79, 1.14]
Total events 308 327
Heterogeneity: Tau² = 0.01; Chi² = 4.56, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours VitD Favours placebo

C

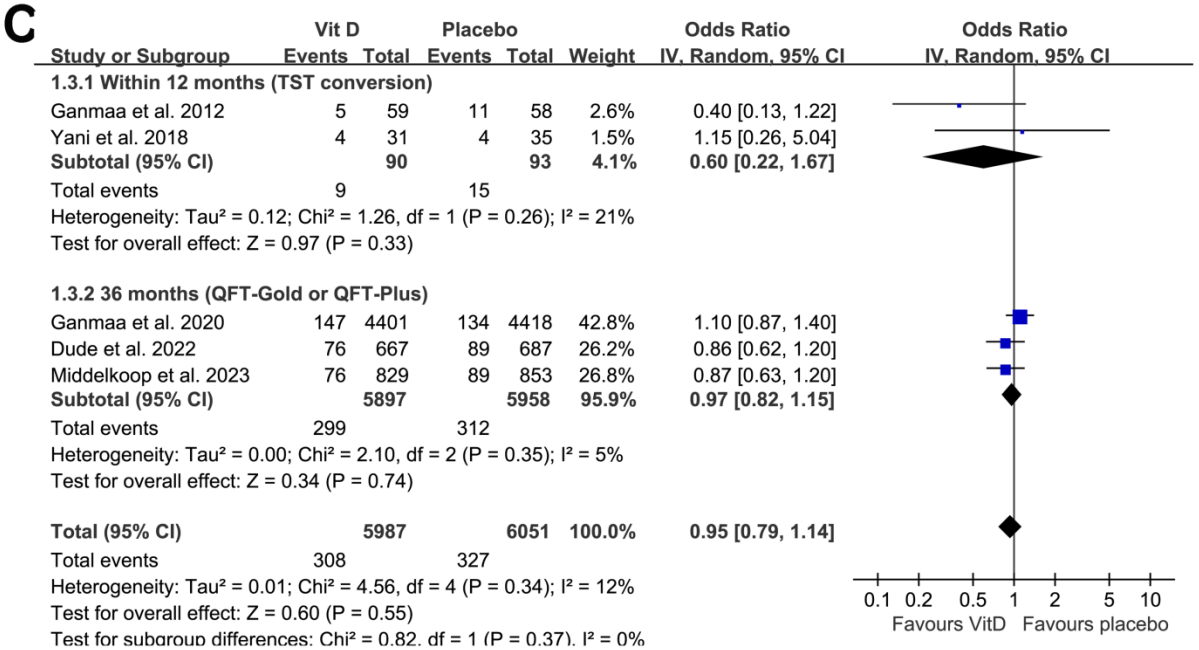
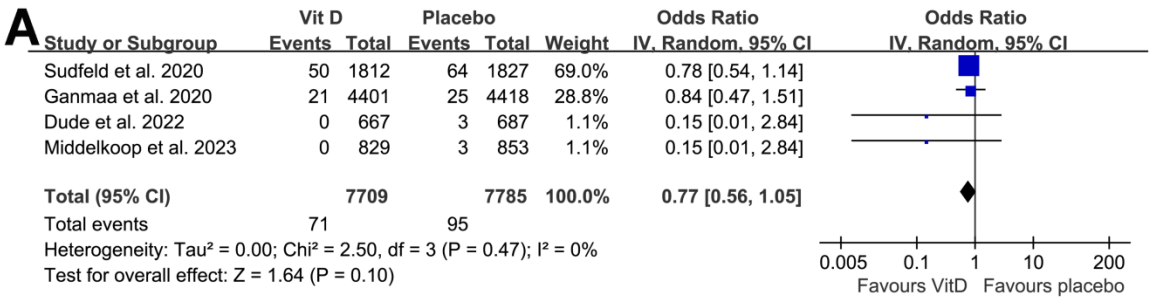
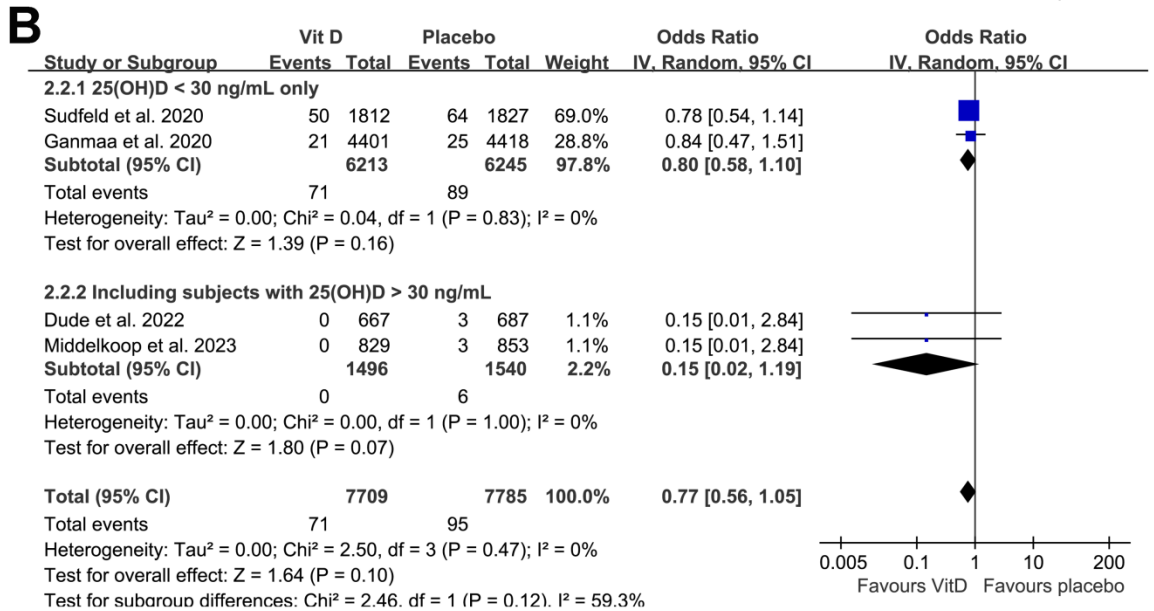

Vit D
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.3.1 Within 12 months (TST conversion)
Ganmaa et al. 2012 5 59 11 58 2.6% 0.40 [0.13, 1.22]
Yani et al. 2018 4 31 4 35 1.5% 1.15 [0.26, 5.04]
Subtotal (95% CI) 90 93 4.1% 0.60 [0.22, 1.67]
Total events 9 15
Heterogeneity: Tau² = 0.12; Chi² = 1.26, df = 1 (P = 0.26); I² = 21%
Test for overall effect: Z = 0.97 (P = 0.33)
1.3.2 36 months (QFT-Gold or QFT-Plus)
Ganmaa et al. 2020 147 4401 134 4418 42.8% 1.10 [0.87, 1.40]
Dude et al. 2022 76 667 89 687 26.2% 0.86 [0.62, 1.20]
Middelkoop et al. 2023 76 829 89 853 26.8% 0.87 [0.63, 1.20]
Subtotal (95% CI) 5897 5958 95.9% 0.97 [0.82, 1.15]
Total events 299 312
Heterogeneity: Tau² = 0.00; Chi² = 2.10, df = 2 (P = 0.35); I² = 5%
Test for overall effect: Z = 0.34 (P = 0.74)
Total (95% CI) 5987 6051 100.0% 0.95 [0.79, 1.14]
Total events 308 327
Heterogeneity: Tau² = 0.01; Chi² = 4.56, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.37), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours VitD Favours placebo

Figure 2. Forest plots for the meta-analysis evaluating the influence of vitamin D supplementation on the incidence of tuberculosis infection; A, overall meta-analysis; B, subgroup analysis according to the baseline serum 25(OH)D level; and C, subgroup analysis according to follow-up durations.


A
Vit D
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Sudfeld et al. 2020 50 1812 64 1827 69.0% 0.78 [0.54, 1.14]
Ganmaa et al. 2020 21 4401 25 4418 28.8% 0.84 [0.47, 1.51]
Dude et al. 2022 0 667 3 687 1.1% 0.15 [0.01, 2.84]
Middelkoop et al. 2023 0 829 3 853 1.1% 0.15 [0.01, 2.84]
Total (95% CI) 7709 7785 100.0% 0.77 [0.56, 1.05]
Total events 71 95
Heterogeneity: Tau² = 0.00; Chi² = 2.50, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
0.005 0.1 1 10 200
Favours VitD Favours placebo


B
Vit D
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
2.2.1 25(OH)D < 30 ng/mL only
Sudfeld et al. 2020 50 1812 64 1827 69.0% 0.78 [0.54, 1.14]
Ganmaa et al. 2020 21 4401 25 4418 28.8% 0.84 [0.47, 1.51]
Subtotal (95% CI) 6213 6245 97.8% 0.80 [0.58, 1.10]
Total events 71 89
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.39 (P = 0.16)
2.2.2 Including subjects with 25(OH)D > 30 ng/mL
Dude et al. 2022 0 667 3 687 1.1% 0.15 [0.01, 2.84]
Middelkoop et al. 2023 0 829 3 853 1.1% 0.15 [0.01, 2.84]
Subtotal (95% CI) 1496 1540 2.2% 0.15 [0.02, 1.19]
Total events 0 6
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.80 (P = 0.07)
Total (95% CI) 7709 7785 100.0% 0.77 [0.56, 1.05]
Total events 71 95
Heterogeneity: Tau² = 0.00; Chi² = 2.50, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Chi² = 2.46, df = 1 (P = 0.12), I² = 59.3%
0.005 0.1 1 10 200
Favours VitD Favours placebo

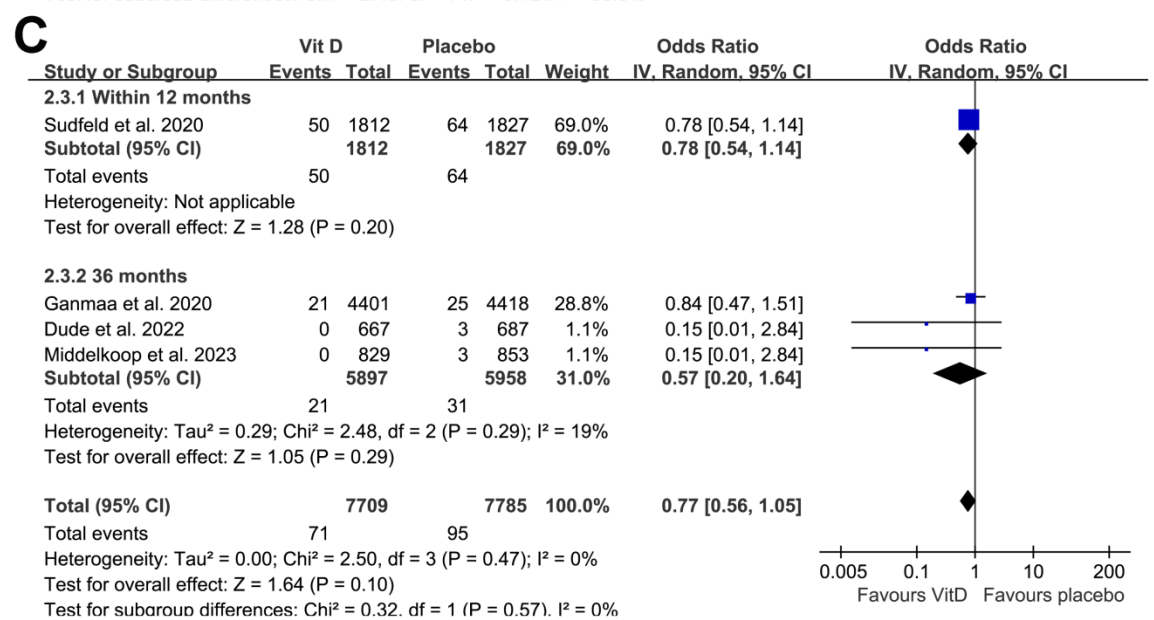

C
Vit D
Placebo
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight IV, Random, 95% CI
IV, Random, 95% CI
2.3.1 Within 12 months
Sudfeld et al. 2020 50 1812 64 1827 69.0% 0.78 [0.54, 1.14]
Subtotal (95% CI) 1812 1827 69.0% 0.78 [0.54, 1.14]
Total events 50 64
Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
2.3.2 36 months
Ganmaa et al. 2020 21 4401 25 4418 28.8% 0.84 [0.47, 1.51]
Dude et al. 2022 0 667 3 687 1.1% 0.15 [0.01, 2.84]
Middelkoop et al. 2023 0 829 3 853 1.1% 0.15 [0.01, 2.84]
Subtotal (95% CI) 5897 5958 31.0% 0.57 [0.20, 1.64]
Total events 21 31
Heterogeneity: Tau² = 0.29; Chi² = 2.48, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 1.05 (P = 0.29)
Total (95% CI) 7709 7785 100.0% 0.77 [0.56, 1.05]
Total events 71 95
Heterogeneity: Tau² = 0.00; Chi² = 2.50, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%
0.005 0.1 1 10 200
Favours VitD Favours placebo

Figure 3. Forest plots for the meta-analysis evaluating the influence of vitamin D supplementation on the incidence of active tuberculosis; A, overall meta-analysis; B, subgroup analysis according to the baseline serum 25(OH)D level; and C, subgroup analysis according to follow-up durations.

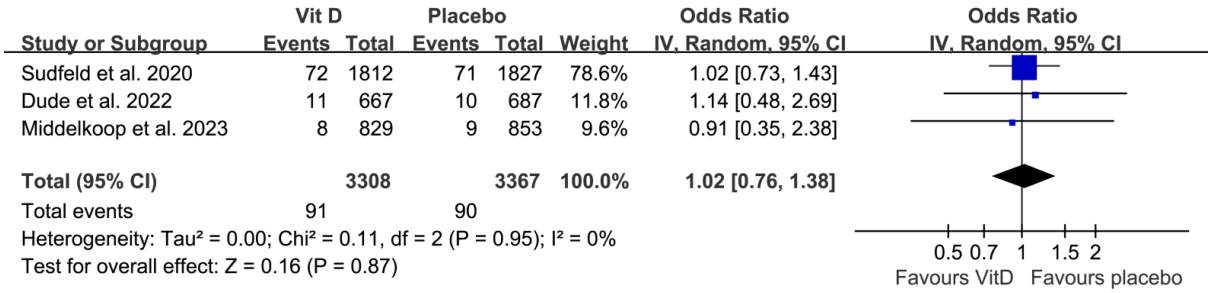
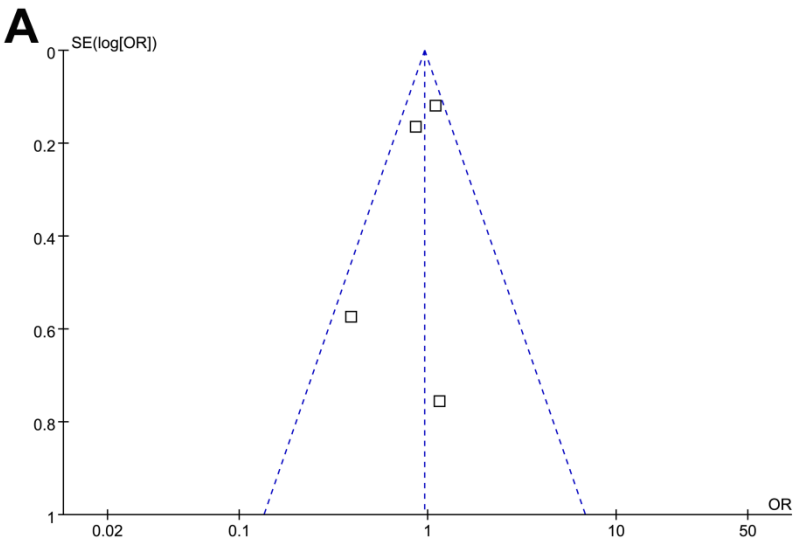
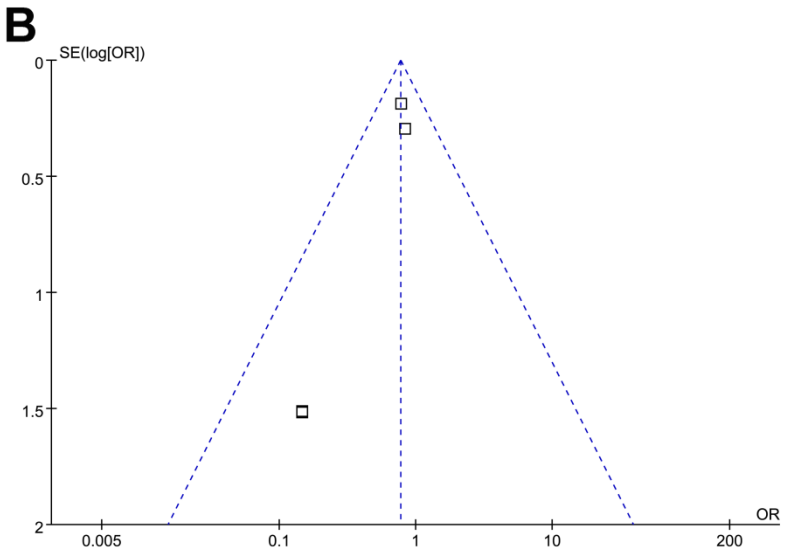


Figure 4. Forest plots for the meta-analysis evaluating the incidence of severe AEs


A
SE(log[OR])
0
0.2
0.4
0.6
0.8
1
0.02
0.1
1
10
50
OR


B
SE(log[OR])
0
0.5
1
1.5
2
0.005
0.1
1
10
200
OR

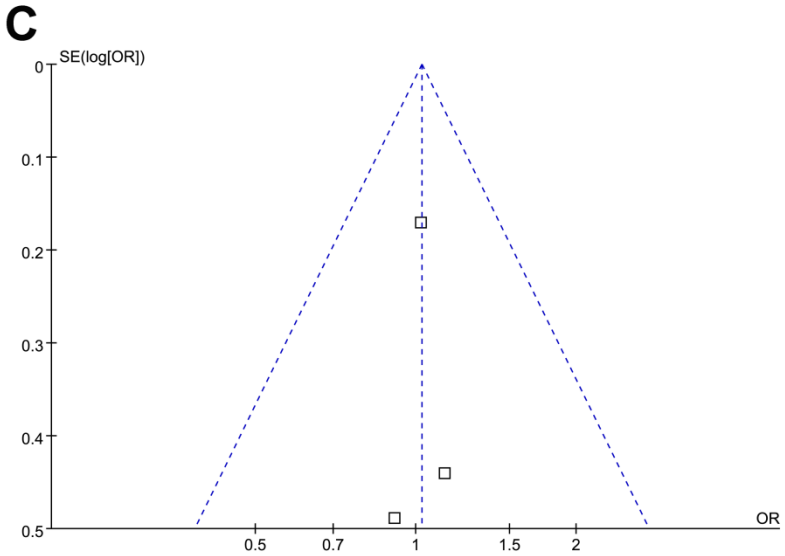

C
SE(log[OR])
0
0.1
0.2
0.3
0.4
0.5
0.5
0.7
1
1.5
2
OR

Figure 5. Funnel plots evaluating the publication bias underlying the meta-analyses; A, funnel plots for the meta-analysis of the incidence of tuberculosis infection; B, funnel plots for the meta-analysis of the incidence of active tuberculosis; and C, funnel plots for the meta-analysis of the incidence severe AEs.

SUPPLEMENTAL DATA

Supplemental file 1. Detailed search syntax for each database

PubMed

(("Vitamin D"[Mesh] OR "Cholecalciferol"[Mesh] OR "Ergocalciferols"[Mesh] OR "Calcitriol"[Mesh] OR "Alfacalcidol"[Supplementary Concept] OR "Paricalcitol"[Supplementary Concept] OR "Vitamin D" OR "Vitamin D2" OR "Vitamin D3" OR "Cholecalciferol" OR "Ergocalciferol" OR "Alphacalcidol" OR "Alfacalcidol" OR "Calcitriol" OR "Paricalcitol" OR "Doxercalciferol")) AND (("Tuberculosis"[Mesh] OR "Mycobacterium tuberculosis"[Mesh] OR "Tuberculosis, Pulmonary"[Mesh] OR "Tuberculous" OR "Tuberculosis" OR "Mycobacterium tuberculosis"))

Embase

('vitamin D'/exp OR 'cholecalciferol'/exp OR 'ergocalciferol'/exp OR 'calcitriol'/exp OR 'alfacalcidol'/exp OR 'paricalcitol'/exp OR 'vitamin D' OR 'vitamin D2' OR 'vitamin D3' OR 'cholecalciferol' OR 'ergocalciferol' OR 'alfacalcidol' OR 'alphacalcidol' OR 'calcitriol' OR 'paricalcitol' OR 'doxercalciferol') AND ('tuberculosis'/exp OR 'mycobacterium tuberculosis'/exp OR 'tuberculous' OR 'tuberculosis' OR 'mycobacterium tuberculosis')

Cochrane Library

("Vitamin D" OR "Vitamin D2" OR "Vitamin D3" OR "Cholecalciferol" OR "Ergocalciferol" OR "Alphacalcidol" OR "Alfacalcidol" OR "Calcitriol" OR "Paricalcitol" OR "Doxercalciferol") AND ("Tuberculosis" OR "Mycobacterium tuberculosis" OR "Tuberculous")

Web of Science

TS=("Vitamin D" OR "Vitamin D2" OR "Vitamin D3" OR "Cholecalciferol" OR "Ergocalciferol" OR "Alphacalcidol" OR "Alfacalcidol" OR "Calcitriol" OR "Paricalcitol" OR "Doxercalciferol") AND TS=("Tuberculosis" OR "Mycobacterium tuberculosis" OR "Tuberculous")

Supplemental file 2. Summary of dosing regimens and study-level effect estimates.

Study	Dosing Regimen	Outcome	OR (95% CI)
Ganmaa et al. 2012	800 IU/day for 6 months	TB infection	0.91 (0.37–2.24)
Yani et al. 2018	Two high single doses, 6 weeks apart	TB infection	0.60 (0.18–1.99)
Ganmaa et al. 2020	14,000 IU/week for 36 months	TB infection	0.95 (0.76–1.19)
Ganmaa et al. 2020	14,000 IU/week for 36 months	Active TB	0.89 (0.40–1.97)
Sudfeld et al. 2020	50,000 IU/week × 4 wks → 2,000 IU/day (12 mo)	Active TB	0.80 (0.46–1.39)
Dude et al. 2022	14,000 IU/week for 36 months	TB infection	0.87 (0.41–1.85)
Dude et al. 2022	14,000 IU/week for 36 months	Active TB	0.65 (0.17–2.43)
Middelkoop et al. 2023	10,000 IU/week for 36 months	TB infection	1.02 (0.70–1.49)
Middelkoop et al. 2023	10,000 IU/week for 36 months	Active TB	0.69 (0.30–1.59)