

# Impact of oral vitamin D3 supplementation on proximal femur fracture incidence in the elderly population

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## Abstract

**Objective:** To evaluate the effect of oral vitamin D3 supplementation on the incidence of proximal femur fracture (PFF) in the elderly population.

**Materials and Methods:** We searched PubMed and Embase databases for relevant studies from inception to March 2024. Only randomized controlled trials (RCTs) were included. Raw data were extracted into a pre-defined worksheet, and quality analysis of RCTs was performed using the risk-of-bias tool version 2 (RoB2).

**Results:** Thirteen RCTs were included in the meta-analysis. Oral vitamin D3 supplementation alone in the elderly did not show a significant association with PFF incidence (OR = 1.04, 95% CI: 0.94-1.15,  $p$ -value = 0.46 > 0.05). Combined oral supplementation of vitamin D3 and calcium could reduce the incidence of PFF in the elderly population (OR = 0.80, 95% CI: 0.69-0.94,  $p$ -value = 0.005 < 0.05); however, after excluding low-quality RCTs, the protective effect was no longer statistically significant (OR = 0.90, 95% CI: 0.74-1.10,  $p$ -value = 0.32 > 0.05).

**Conclusion:** Limited evidence suggests that combined oral supplementation of vitamin D3 and calcium may reduce the incidence of PFF in the elderly population, as the protective effect was no longer statistically significant after excluding low-quality RCTs.

**Keywords:** Vitamin D3, cholecalciferol, calcium, proximal femur fracture, elderly population, meta-analysis

## Introduction

Osteoporosis is a pathological condition characterized by loss of bone mass and structural deterioration, resulting in increased fracture susceptibility [1]. Epidemiological evidence indicates a significant prevalence of osteoporotic fractures, with an estimated one in two women and one in five men aged 65 years and older expected to experience an osteoporotic fracture during the remainder of their lives [1, 2]. Given the demographic trend toward an increasingly elderly population, prevention of osteoporotic frac-

tures in the elderly is of paramount importance. Among the fractures associated with osteoporosis, proximal femur fracture (PFF), commonly known as hip fracture, has the greatest impact on geriatric patients ( $\geq 65$  years of age) due to its high mortality rate, long-term disability, and loss of independence [3, 4]. The documented one-year mortality after PFF is estimated to range from 14% to 58%, associated with a 4% annual increase in the relative risk of mortality in geriatric patients [5]. In addition, the process of hospitalization, rehabilitation and potential need for long-term care places a significant socioeconomic burden on the healthcare infrastructure. This underscores the critical need for tailored preventive interventions in geriatric PFF patients.

Vitamin D3 (cholecalciferol) plays a critical role in maintaining musculoskeletal health by facilitating calcium absorption, promoting osteoid tissue mineralization in bone, and maintaining muscle function [6, 7]. Vitamin D3 deficiency is commonly defined by experts as a serum 25-hydroxyvitamin D (25(OH)D) level below 20 ng/mL (50 nmol/L), which can lead to secondary hyperparathyroidism, bone demineralization, and muscle weakness [8, 9]. Many previous studies have claimed that daily oral

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**Table 1.** Characteristics of 8 RCTs comparing the incidence of PFF in participants aged 65 years or older between oral vitamin D3 supplementation alone and placebo/no treatment.

Study	Year	Country	Participants, No.	Treatment (vitamin D3 alone)	Mean Age, y	Follow-up, y	PFF, No.
Lips [18]	1996	Netherlands	2578	400 IU/d	80	3.5	106
Meyer [19]	2002	Norway	1144	400 IU/d	84.7	2	97
Trivedi [20]	2003	UK	2686	100,000 IU/4 mo	74.8	5	45
Grant [21]	2005	UK	2675	800 IU/d	77	3.8	88
Lyons [22]	2007	UK	3440	100,000 IU/4 mo	84	3	216
Smith [23]	2007	UK	9440	300,000 IU/y	79.1	3	110
Sanders [24]	2010	Australia	2258	500,000 IU/y	76.1	5	34
Waterhouse [12]	2023	Australia	15306	60,000 IU /mo	65+	5	789

**Table 2.** Characteristics of 6 RCTs comparing the incidence of PFF in participants aged 65 years or older between combined oral vitamin D3 & calcium supplementation and placebo/no treatment.

Study	Year	Country	Participants, No.	Treatment	Mean Age, y	Follow-up, y	PFF, No.
Chapuy [25]	1994	France	2303	800 IU/d vitamin D3, 1200 mg/d calcium	84	3	322
Chapuy [26]	2002	France	583	800 IU/d vitamin D3, 1200 mg/d calcium	85.2	2	105
Grant [21]	2005	UK	2638	800 IU/d vitamin D3, 1000 mg/d calcium	77.5	5	87
Porthouse [27]	2005	USA	3314	800 IU/d vitamin D3, 1000 mg/d calcium	76.8	2	25
Jackson [28]	2006	USA	6340	400 IU/d vitamin D3, 1000 mg/d calcium	70+	7	208
Salovaara [29]	2010	Finland	3195	800 IU/d vitamin D3, 1000 mg/d calcium	67.3	4.3	6

supplementation of vitamin D3 (including vitamin D3 alone and combined supplementation of vitamin D3 and calcium) has the effect of preventing PFF and relieving its symptoms [10, 11]. However, the efficacy of such interventions remains controversial, as evidenced by some recent studies indicating that oral vitamin D3 supplementation is not significantly associated with a reduced risk of PFF in geriatric patients [12-14]. Therefore, we conducted a comprehensive meta-analysis based on relevant randomized controlled trials (RCTs) to evaluate the effect of oral vitamin D3 supplementation (including vitamin D3 alone and combined supplementation with vitamin D3 and calcium) on the incidence of PFF in the elderly population (aged 65 years and older).

## Materials and Methods

### Search strategies

A systematic literature search was conducted in March 2024 using PubMed and Embase databases. To increase the breadth of literature coverage, the reference lists of candidate studies were carefully reviewed by hand to ensure comprehensive access to relevant scientific materials.

### Inclusion and exclusion criteria

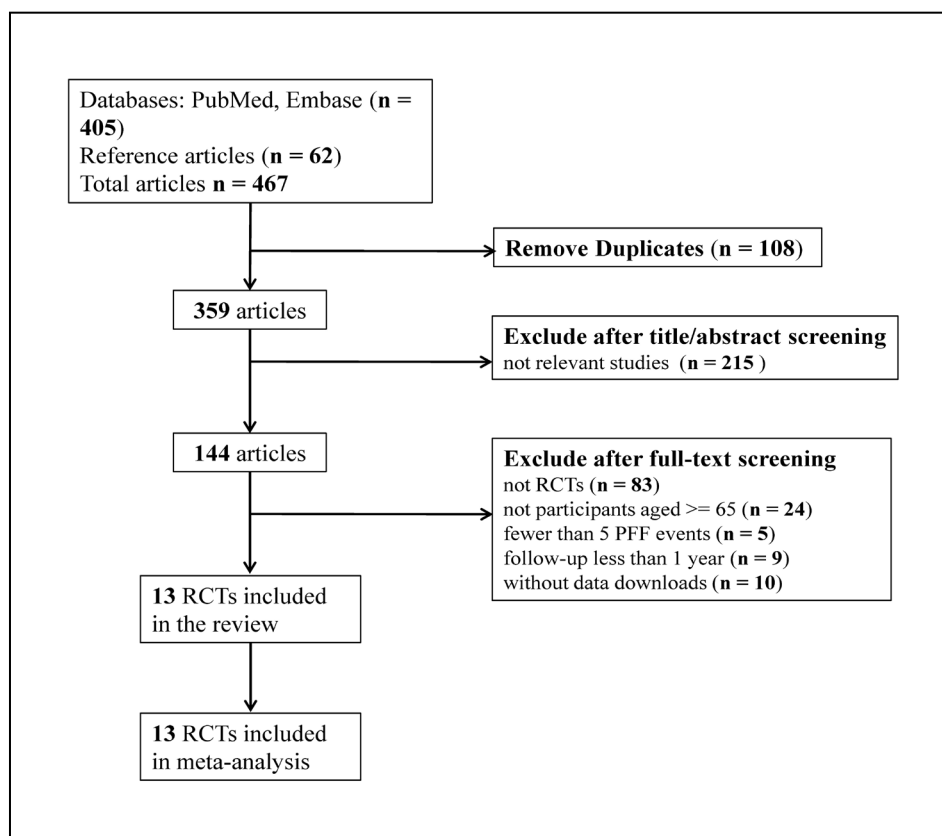
Two reviewers performed independent assessments to determine eligibility of candidate articles. Articles deemed irrelevant after abstract review were excluded. All abstracts meeting the initial criteria were reviewed

as full articles. All abstracts that met the initial criteria were reviewed as full articles. Non-English publications, animal studies, basic science studies, case reports, commentaries, letters, meeting abstracts, protocols, and review articles were excluded from consideration. Studies were selected using the following inclusion criteria: (1) RCTs comparing vitamin D3 alone or combined vitamin D3 and calcium oral supplements with placebo/no treatment; (2) studies that enrolled participants aged 65 years and older (or could extract data only from participants aged 65 years and older); (3) studies with at least 5 PFF events to reduce random error; (4) studies with at least 1 year of follow-up; (5) studies that provided access to raw data. In cases where different studies used overlapping data, the study with the more comprehensive statistics was preferred. Disagreements were resolved through consensus discussions, with the involvement of a third party when necessary.

### Risk of bias assessment

Risk of bias was assessed using the Cochrane risk-of-bias tool version 2 (RoB2), and visual representations were generated using the R package "robvis" [15, 16]. RoB2, which is tailored for RCTs, rigorously assesses each domain for its potential bias and categorizes it as low risk, some concern, or high risk [16]. The RoB2 domains are:

- Bias due to the randomization process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in outcome measurement
- Bias in selection of reported outcome



**Figure 1.** Flow chart of search strategy and study selection.

## Data analysis

The R package "meta" was used for the following statistical analysis [17]. The standardized mean difference (SMD) along with a 95% confidence interval (CI) was used as the statistic for effect analysis of the measures. The degree of heterogeneity was also determined by combining  $I^2$  quantification and Q statistic. If the  $I^2$  value exceeded 50% or the p-value of the Q statistic was less than 0.05, indicating substantial heterogeneity among the included studies, the random effects model was considered more appropriate. Conversely, if these thresholds were not met, the common effect model (also referred to as the fixed effect model) was preferred.

## Sensitivity analysis

In addition, sensitivity analyses were performed to assess the impact of individual studies, particularly those of low quality, on the overall effect size estimate.

## Results

### Search results

A total of 467 articles were identified for the initial review. After comprehensive evaluation of the full texts, 13 RCTs met our criteria for further meta-analysis (Figure 1). Specifically, 8 RCTs used a design that compared the incidence of PFF with oral vitamin D3 supplementation alone versus placebo/no treatment. Six RCTs used a design comparing the PFF incidence of combined oral supplementation with vitamin D3 and calcium versus placebo/

no treatment. Of note, 1 RCT included both of the above experimental designs, resulting in a total of 13 RCTs selected. The characteristics of all included RCTs are listed below (Table 1 & 2).

### Assessment of risk of bias

The result of the RoB2 "risk of bias" assessment for the selected 13 RCTs is shown in Figure 2. Most studies were assessed as having a low or moderate risk of bias, and only 2 studies were assessed as having a high risk of bias in at least one domain.

### Oral vitamin D3 supplementation alone

A total of 8 RCTs evaluated the association between PFF incidence and oral vitamin D3 supplementation alone. Seven RCTs showed no statistically significant association [12, 18-22, 24], while the remaining RCT suggested that oral vitamin D3 supplementation alone may increase the incidence of PFF [23].

No significant heterogeneity was found (Figure 3A,  $I^2 = 0$ , Q-statistic p-value = 0.45 > 0.05); therefore, the fixed-effect model was used. The meta-analysis result showed no significant association between PFF incidence and oral vitamin D3 supplementation alone in the elderly population (Figure 3A, OR = 1.04, 95% CI: 0.94-1.15, p-value = 0.46 > 0.05).

### Combined oral vitamin D3 supplementation and calcium

Six RCTs evaluated the association between PFF incidence and combined oral supplementation with vitamin D3 + calcium. Five RCTs showed no statistically signifi-

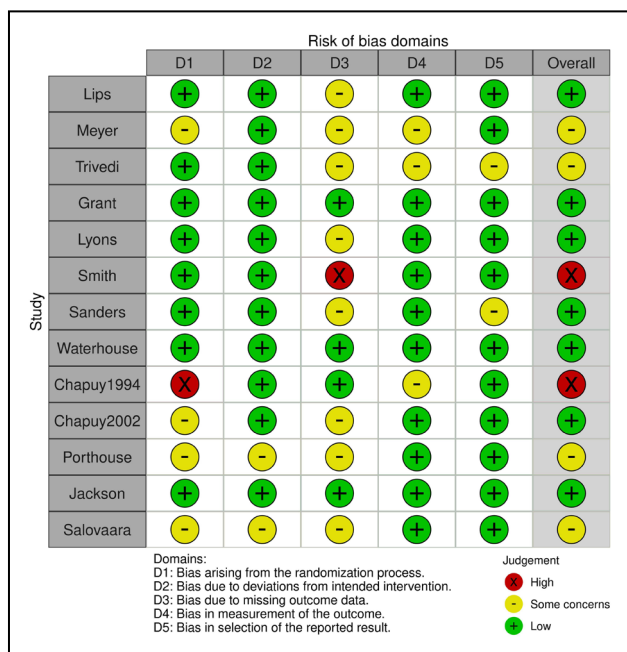


Figure 2. RoB2 risk of bias assessment of the selected 13 RCTs.

cant association [21, 26-29], while the remaining RCT suggested that combined oral supplementation with vitamin D3 + calcium could reduce the risk of PFF [25]. Since  $I^2 = 22\%$  and Q-statistic  $p$ -value = 0.27 > 0.05, we performed fixed model (Figure 3B). The result indicated that combined oral supplementation of vitamin D3 + calcium could significantly reduce the incidence of PFF in the elderly population (Figure 3B, OR = 0.80, 95% CI: 0.69-0.94,  $p$ -value = 0.005 < 0.05).

**Sensitivity analysis**

The result of the sensitivity analysis showed that among the 8 RCTs of oral vitamin D3 supplementation alone, the exclusion of the studies deemed of low quality did not qualitatively change the original findings. When Smith's study was excluded, the lack of a significant association between PFF incidence and oral vitamin D3 supplementation alone in the elderly population persisted (Figure 4A, OR = 1.01, 95% CI: 0.91-1.13,  $p$ -value = 0.86 > 0.05). However, in the sensitivity analysis of 6 RCTs investigating combined oral supplementation with vitamin D3 + calcium, the exclusion of low-quality studies changed the original research results. Specifically, when the 1992 Chapuy study was excluded, we observed that combined oral supplementation with vitamin D3 and calcium no longer had an effect on the incidence of PFF in the elderly population (Figure 4B, OR = 0.90, 95% CI: 0.74-1.10,  $p$ -value = 0.32 > 0.05).

**Discussion**

The present meta-analysis, using rigorous inclusion criteria, included 13 RCTs with a total of 55,830 participants to determine the efficacy of oral vitamin D3 supplementation in reducing the incidence of PFF in the geriatric

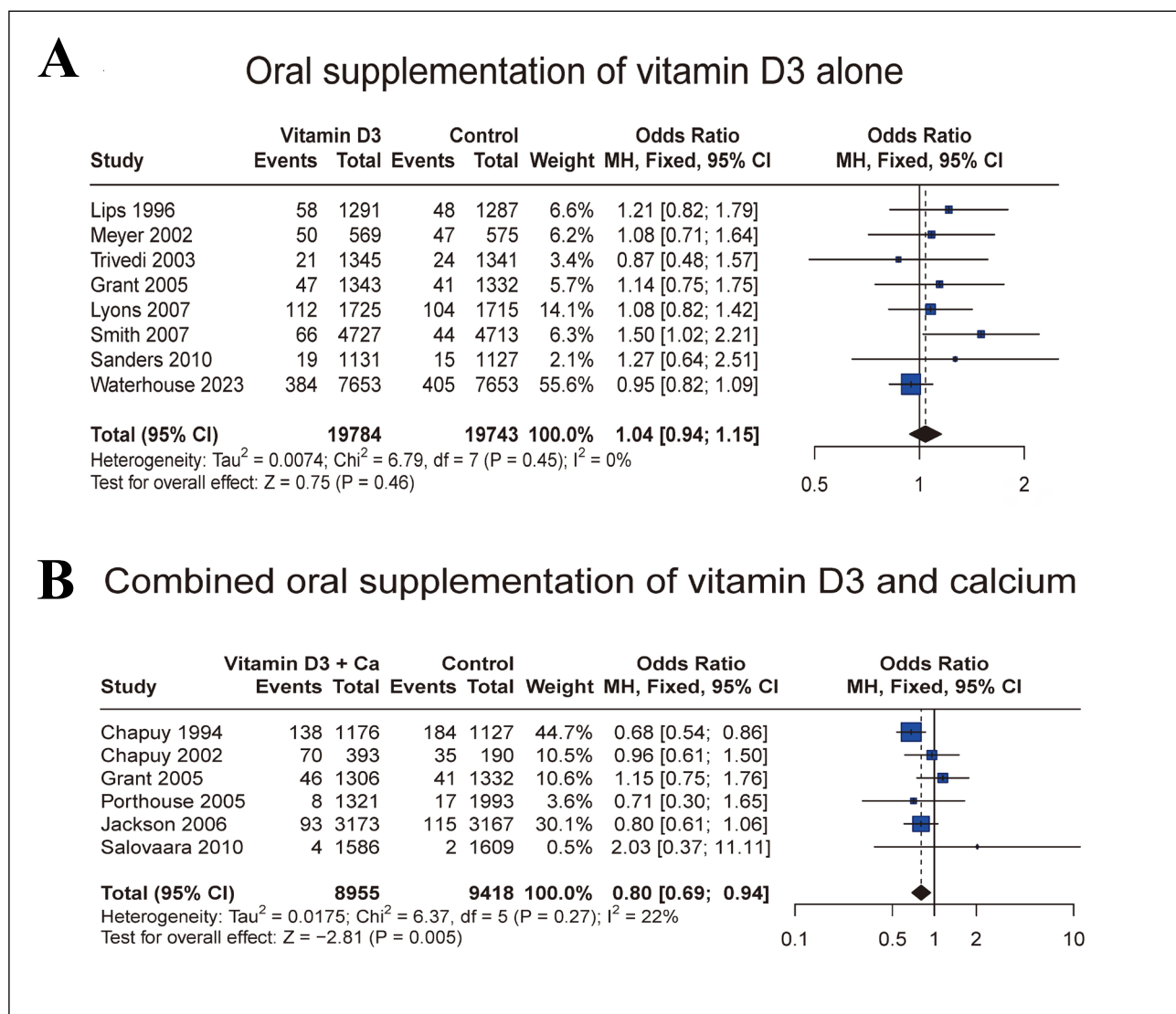
population. Our review shows that oral vitamin D3 alone did not show a significant association with the incidence of PFF in the elderly (OR = 1.04, 95% CI: 0.94-1.15,  $p$ -value = 0.46 > 0.05), a conclusion that remained consistent even after removing the study considered to be of low quality (OR = 1.01, 95% CI: 0.91-1.13,  $p$ -value = 0.86 > 0.05). Meanwhile, when vitamin D3 was combined with calcium and administered orally, a significant reduction in PFF incidence was observed in the elderly (OR = 0.80, 95% CI: 0.69-0.94,  $p$ -value = 0.005 < 0.05). However, after excluding the study of inferior quality, this association lost statistical significance (OR = 0.90, 95% CI: 0.74-1.10,  $p$ -value = 0.32 > 0.05).

Bischoff-Ferrari *et al.* previously found a significant association between daily supplementation with vitamin D3 alone and a lower incidence of PFF in adults aged 65 years or older; however, their previously published pooled analysis suffered from limitations such as inadequate sample size and follow-up duration in some of the included RCTs, which to some extent affected the generalizability and statistical power of the final results [30]. At the same time, Bischoff-Ferrari suggested that the efficacy of daily oral vitamin D3 supplementation in reducing PFF incidence might be significant only at high doses (800 IU or more per day). However, sensitivity analysis in our meta-analysis showed that this association remained statistically insignificant even after excluding RCTs with doses below 800 IU per day [30].

The trials of combined oral supplementation with vitamin D3 + calcium conducted by Avenell and Manoj produced results that were consistent with the results of our meta-analysis, demonstrating that the intervention was effective in reducing the incidence of PFF in the elderly population [31, 32]. It is important to note that our meta-analysis also highlights the influence of low-quality RCTs on the results of the effect analysis. As in previous similar analyses, we included Chapuy's 1994 study [25]. However, the participants in Chapuy's study were restricted to a specific medical institution, which led to its classification as a low-quality RCT in our risk of bias assessment [25]. As explained in the sensitivity analysis section, after excluding this low-quality RCT, the significant association between combined oral vitamin D3 supplementation and calcium and the reduction of PFF incidence in the geriatric population was no longer statistically significant. After excluding low-quality studies, our findings are consistent with those of the US Preventive Services Task Force (USPSTF). The USPSTF concluded that current evidence is insufficient to assess the balance of benefits and harms of combined oral supplementation with doses greater than 400 IU of vitamin D3 and greater than 1000 mg of calcium daily for the primary prevention of osteoporotic fractures in community-dwelling, asymptomatic men and premenopausal women [14].

Admittedly, our study also has some limitations. First, the participants in the selected RCTs were predominantly from developed countries in Europe and North America, with a lack of relevant data from Asia and Africa, which may affect the generalizability of the conclusions. Second, some recent studies have suggested an association be-





**Figure 3.** Forest plot for PFF incidence comparisons between oral vitamin D3 supplementation alone the placebo/no treatment (A) and between combined oral vitamin D3 supplementation + calcium and placebo/no treatment (B).

tween vitamin D3 deficiency and the risk of PFF [33, 34]; however, we did not specifically include this subgroup of individuals. Furthermore, it is important to consider factors that influence vitamin D3 absorption, especially in the elderly population, as this could significantly affect the efficacy of supplementation. In designing future studies, it is important to consider a broader range of confounding factors, such as the importance of monitoring changes in blood levels of vitamin D in PFF patients. Finally, despite the lack of evidence that vitamin D3 can reduce the incidence of PFF, vitamin D3 may still play a role in reducing mortality from PFF and alleviating symptoms in PFF patients, which is a new direction for future research.

## Conclusions

Oral supplementation with vitamin D3 alone in the elderly did not show a significant association with PFF incidence (OR = 1.04, 95% CI: 0.94-1.15,  $p$ -value = 0.46 > 0.05). Limited evidence suggested that combined oral supplementation with vitamin D3 and calcium may reduce the

incidence of PFF in the elderly population (OR = 0.80, 95% CI: 0.69-0.94,  $p$ -value = 0.005 < 0.05), because after excluding low-quality RCTs, the protective effect was no longer statistically significant (OR = 0.90, 95% CI: 0.74-1.10,  $p$ -value = 0.32 > 0.05). Therefore, there is a lack of robust evidence that oral vitamin D3 supplementation could reduce the incidence of PFF in the elderly population.

## Declarations

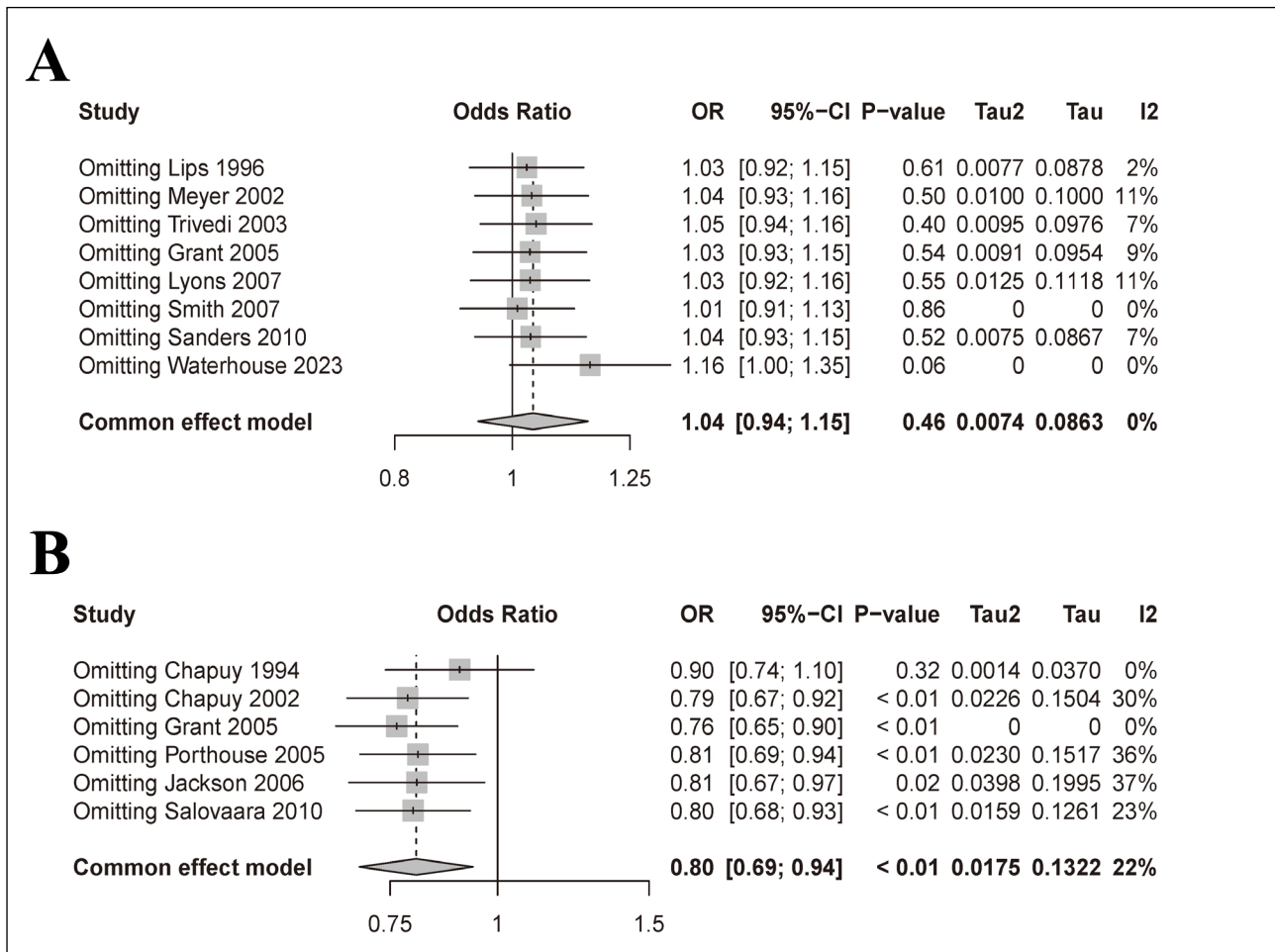
**Availability of data and materials:** Not applicable.

**Financial support and sponsorship:** None.

**Conflict of interest:** All authors declared that there is no conflict of interest.

**Ethical approval and consent to participate:** Not applicable.

**Consent for publication:** Not applicable.



**Figure 4.** Sensitivity analysis of 8 RCTs designed for oral supplementation with vitamin D3 alone (A) and 6 RCTs designed for combined oral supplementation with vitamin D3 + calcium (B).

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