Nutritional therapy of older osteoporotic people with supplemental calcium and vitamin D: side effects, fracture rates, and survival – an internationalised meta-analysis

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Du Jiao and Chao Jiang

Department of Nursing, Huashan Hospital, Fudan University, Shanghai, China

Authors' email addresses and contributions:
DJ: mxi007@163.com
Contribution: conceived the study question, and contributed to the study design, data analysis and interpretation, and writing the manuscript.

CJ: jiangchao-2022@outlook.com
Contribution: undertook data collection and data analysis, and contributed to data interpretation, and writing the manuscript.

Corresponding Author: Chao Jiang, Department of Nursing, Huashan Hospital, Fudan University, 20F, Building 6, 12 Middle Urumqi Road, Shanghai, 200040, P.R. China. Tel: . Email: jiangchao-2022@outlook.com

ABSTRACT

Background and Objectives: Recent controversy over the bone benefits of calcium and vitamin D supplementation, and the potential detrimental effects of excess calcium supplementation, has confused clinicians. To systematically evaluate the effectiveness and safety of vitamin D combined with calcium in preventing and treating osteoporotic symptoms in the elderly. **Methods and Study Design:** Databases were searched to collect randomized controlled trials (RCTs) on vitamin D combined with calcium in the prevention and treatment of osteoporotic fractures in the elderly. After screening the literature, extracting data, and assessing the risk of bias in the included studies, the Meta-analysis was performed. **Results:** 19 RCTs were included, including 69,234 patients. Meta-analysis results showed that the mortality rate of the vitamin D combined with calcium group was not statistically significant compared with the control group; the calcium combined with vitamin D significantly reduced the incidence of fractures compared with the control group，Density and serum 25-hydroxyl concentration，adverse reactions of calcium combined with vitamin D were higher than those in the control group. **Conclusions:** The combination of vitamin D and calcium has no difference in mortality rate, and it can prevent fractures in the elderly, and enhance bone density and serum 25-hydroxyvitamin D concentration, but still need to pay attention to adverse reactions in the gastrointestinal tract.

Key Words: osteoporosis, vitamin D, calcium, meta-analysis

INTRODUCTION

With the aggravation of the aging process of the population, the global prevalence of osteoporosis has increased significantly.[1] Osteoporosis (OP) is a systemic skeletal disease characterized by decreased bone strength and increased risk of fracture, Bone strength depends on bone density and bone quality. The most serious consequence of osteoporosis is that a slight external force can also lead to fractures, which can lead to a range of complications.[2, 3] Osteoporosis not only seriously affects the quality of life of patients, shortens the life expectancy of patients, but also heavy burden to society and economy.[3] In the elderly population, especially women, the incidence of osteoporosis is very high[4] With the aging population in China, the incidence of osteoporosis is also increasing year by year[5] The characteristics of OP patients, such as decreased bone mineral density, decreased number of trabecular bone, thinned bone cortex, abnormal bone microstructure, and accumulation of

microscopic damage, lead to a high complication rate of osteoporotic fractures (19%-25%), High disability rate (31.4%) and high fatality rate (20 % to 25%).[6, 7]

At present, the treatment of osteoporotic fractures in China mostly adopts surgery and internal fixation, still. due to the osteoporosis of patients, the internal fixation effect is often not ideal, and internal fixation will aggravate the bone resorption at the fracture site, resulting in delayed union or nonunion of the fracture, there is a higher risk of secondary fractures. There are also traditional conservative treatments for osteoporotic fractures, such as bed rest, analgesia, and low-back functional exercise. However, they cannot reverse the process of osteoporosis and still cannot reduce the risk of secondary fractures.[8] Therefore, regardless of surgical treatment or conservative treatment, it is necessary to actively treat the primary disease and use anti-osteoporosis drugs at the same time.

Vitamin D (VD) is an important humoral factor that ensures growth and development, regulates bone formation of bone metabolism, and normal function of the muscle system.[9] Hydroxylated vitamin D is also known as active vitamin D. Vitamin D supplementation must ensure a threshold of serum 25(OH) D or it will not provide the desired benefit, some studies have evaluated the anti-fracture efficacy of different doses of vitamin D and found that 400 IU daily is not sufficient to reduce fracture risk, while daily oral administration of 700-800 IU or oral administration of 100,000 IU every 3 months produced anti-fracture effects.[10] Recent controversy over the bone benefits of calcium and vitamin D supplementation, and even the potentially detrimental effects of excess calcium supplementation on cardiovascular health, has confused clinicians and interfered with internationally recognized basic strategies for the prevention and treatment of osteoporosis. On October 25, 2016, the clinical guidelines of the National Osteoporosis Foundation and the American Society of Preventive Cardiology[11] clearly stated that the average healthy adult should take calcium supplements from food or supplements (whether with/without vitamin D or not) has no relationship with its risk of cardiovascular and cerebrovascular diseases, mortality, and all-cause mortality. Vitamin D is a routine drug for osteoporosis. This study collects domestic published randomized controlled trials (RCTs) of calcium and vitamin D in the treatment of osteoporotic fractures, systematic evaluation of effectiveness and safety aims to provide the evidence-based basis for clinical medication.

MATERIALS AND METHODS

Literature search

PubMed, Embase, Cochrane Library, China Biomedical Literature Database, Wanfang Database, CNKI, and VIP database were searched. Chinese search terms consisted of "senile osteoporosis", "calcium", "calcium carbonate D-3", "vitamin D", "vitamin D-3", "fracture", "osteoporosis", "adverse reactions", and "randomized controlled trials"; English search terms The words are "calcium", "vitamin D", "vitamin D-3", "fracture", "osteoporosis", "adverse drug reactions". The retrieval method, the retrieval strategy is determined after multiple pre-searches, supplemented by gray literature retrieval, that is, contacting experts in the field and corresponding authors to obtain important information that cannot be obtained by the above-mentioned retrieval; at the same time, supplemented by manual retrieval of relevant core journals and libraries Related books, retrospectively included references in the study.

Inclusion criteria

(1) Research type: randomized controlled trials (RCT) published internationally. The language type is set to Chinese and English. (2) Research objects: Those who meet the diagnostic criteria for senile osteoporosis in the "Guidelines for the Diagnosis and Treatment of Primary Osteoporosis (2017)"].[12] (3) Intervention measures: the patients in the control group were given calcium preparations, such as Caltrate D, active calcium tablets, and compound amino acid chelated calcium capsules, and the time and method of medication were not limited; Chinese herbal preparations for treatment. (4) Outcome indicators: mortality, bone mineral density, fracture rate after treatment, 25(OH) Vitamin D concentration indicators, and adverse reactions.

Exclusion criteria

(1) Data could not be extracted from the pooled literature. (2) Repeatedly published literature. (3) Non-clinical research. (4) Documents that do not meet the diagnostic criteria of this study. (5) Missing data relevant information was obtained by contacting the authors.

Literature screening and data extraction

Two evaluators read the titles, abstracts, and full texts, and screened the literature strictly according to the inclusion criteria. Disagreement was resolved through discussion or a third party was asked to assist in negotiating whether to include. The extracted data included research interventions, methods used and possible bias, journal name, first author, publication time, sample selection criteria, sample size, baseline characteristics of research subjects,

outcome indicators. Data statistics were independently conducted by 2 evaluators, and relevant information was obtained by contacting the authors for lack of data.

Literature quality evaluation

The methodological quality of the included studies was evaluated according to the quality evaluation criteria recommended by the Cochrane Systematic Review Manual. The main evaluation criteria included: (1) random allocation method; (2) allocation concealment; (3) blinding was used; (4) Integrity; (5) Whether there are other biases. If the evaluation is "low "risk" indicates a low risk of bias, "high risk" indicates a high risk of bias, and "unclear risk" indicates that the literature does not provide sufficient information for bias assessment.

Publication bias

The symmetry of the funnel plot was tested by the Egger method. If $p< 0.05$, it indicated that the funnel plot was asymmetrical, indicating that the outcome indicator had publication bias; otherwise, there was no publication bias. The calculation results and regression charts of the Egger's method test were calculated and generated by STATA12.0.

Statistical analysis

RevMan 5.2 software was used for data analysis, relative risk (RR) was used as the effect size for dichotomous data, and standardized mean difference (SMD) was used as effect size for continuous data, a 95% confidence interval (CI) was drawn. The *p* value of the heterogeneity test results displayed in the forest plot was used to judge whether there was heterogeneity in the included studies, and the size of the heterogeneity was judged according to I^2. If the heterogeneity is not statistically significant ($p \geq 0.1$, $I^2 \leq 50\%$), the fixed effect model is used to combine the effect size; if the heterogeneity is statistically significant ($p < 0.1$, $I^2 > 50\%$), to analyze the source of heterogeneity, using sensitivity analysis, if the reason for the existence of heterogeneity cannot be explained, and these studies have clinical homogeneity, the random effect model is used to combine the effect size.

RESULTS

2,730 papers were obtained through preliminary screening, and 12 additional literatures were obtained through tracking references. (1) Exclude duplicatively collected articles from different databases (1458 articles); (2) Read titles and abstracts to exclude articles (158 articles); (3) Read the full text, screen according to the inclusion criteria and exclude case

reports, clinical symptom analysis, review, and articles that cannot obtain the full text Abstracts of meeting content (27 articles); (4) 9 articles were finally included, including 455 patients and 342 subjects in the control group. The basic information is shown in Table 1, and the literature screening process is shown in Figure 1.

Quality evaluation

Methodological quality evaluation of the included studies, 3 included studies did not mention the concealment of allocation schemes, 2 included studies did not mention blinding of study outcome measures, and 1 included study did not mention selective reporting, it was judged as " Unclear risk of bias"; 2 included studies did not mention whether blinding was used, which was judged as "high risk"; 1 study pointed out that 2 people were lost to follow-up during the trial, which was judged as"high risk"; all studies noted similar baseline conditions in the two groups. The methodological quality evaluation of the included studies is shown in Figure 2 and Figure 3.

Results of meta-analysis

Mortality

There are three reports[13-15] of mortality rate between vitamin D and calcium combined in treatment compared with control. The heterogeneity analysis showed p =0.49, I^2 =0%. There was no significant heterogeneity among the studies, and the fixed-effect model was used for Meta-analysis. The results showed that compared with the control group, the mortality rate of the two groups was not statistically significant [RR=1.03, 95%CI (0.88~ 1.20), p =0.51], the results showed that compared with the control group, there was no difference in the mortality rate of elderly patients with osteoporosis, as shown in Figure 4.

Bone density

Five papers[16-20] reporting on bone mineral density when vitamin D and calcium were used in combination in treatment were included in the meta-analysis. Heterogeneity analysis showed p =0.36, I^2 =8%. There was no significant heterogeneity among the studies, and the fixed-effect model was used for Meta-analysis. The results showed that the vitamin D combined with calcium group had statistically significant bone mineral density compared with the control group [RR =13.23, 95%CI (12.25~13.93), p <0.01], the results show that vitamin D combined with calcium supplementation can increase the bone mineral density of elderly patients with osteoporosis compared with the control group, as shown in Figure 5.

Fracture rate

12 papers[13-15, 17, 21-28] reported the fracture rate between the vitamin D and calcium combination treatment group and control group, heterogeneity analysis showed p=0.52, I^2 =0%. There was no significant heterogeneity among the studies, and the fixed-effect model was used for meta-analysis. The results showed that the vitamin D combined with calcium group had a statistically significant fracture rate compared with the control group [RR=0.94, 95%CI (0.91-0.98). p=0.006], the results showed that compared with the control group, supplementing vitamin D combined with calcium can effectively reduce the incidence of fractures in elderly patients with osteoporosis, as shown in Figure 6.

Serum 25(OH)D concentration

7 papers[19, 20, 22, 24, 29, 30] reported the serum 25(OH)D concentration between vitamin D and calcium combined treatment group and control group, heterogeneity analysis showed p <0.01, I2 =97%. There was considerable heterogeneity among the studies, and a random effects model was used for meta-analysis. The results showed that compared with the control group, the results showed that the effect of increasing serum 25(OH)D concentration in the test group was better than that in the control group, and the difference was statistically significant [RR=0.94, 95%CI (0.91~0.98), p <0.01], indicating that vitamin D combined with calcium supplementation can effectively increase serum 25(OH)D concentration compared with the control group (Figure 7).

Adverse reactions

7 papers[16, 17, 19, 22, 23, 28, 31] reported the adverse reactions between vitamin D and calcium combined treatment group and control group, heterogeneity analysis showed p <0.13, I^2 =39%. There was little heterogeneity among the studies, and a fixed-effects model was used for meta-analysis. The results showed that there was a statistically significant difference in the adverse reaction rate between the vitamin D combined with calcium group and the control group [RR =1.21, 95%CI (1.06~1.37), p =0.004], indicating that vitamin D combined with calcium Compared with the control group, adverse reactions increased (Figure 8).

Publication bias analysis

The number of studies on the outcome indicators affected by this study is small, and the asymmetry test of the funnel plot is of little significance. Therefore, only the funnel plot symmetry of mortality, bone mineral density, fracture rate, serum 25(OH)D concentration,

and adverse reactions were tested by the Eggers method, the *p* values of the five calculation results are all > 0.05, suggesting that the outcome index has no obvious publication bias, see Table 2. The regression chart of the Eggers test method shows that the outcome index has no obvious publication bias (Figure 9).

Sensitivity analysis

Sensitivity analysis was performed on the main outcome indicators, and the difference was still statistically significant and the structure of the forest plot did not changed significantly, indicating that the results of the Meta-analysis were credible. At the same time, low-quality literature was excluded for sensitivity analysis, and the results showed that the heterogeneity and combined effect value did not change significantly, and the results were stable and reliable.

DISCUSSION

Osteoporosis, as a common disease of middle-aged and elderly people, has attracted great attention from society and clinicians and has become a health problem of concern in many countries.[32] It is an insidious, chronic disease that remains asymptomatic until fragility fractures complicated.[33] Osteoporosis is a disease in which excessive osteoclast activity leads to decreased bone density. Calcium and vitamin D, as basic supplements in the prevention and treatment of osteoporosis, play an important role in the maintenance of bone health. On the basis of adequate calcium and vitamin D supplementation, a reasonable selection of anti-osteoporosis drugs can increase bone mineral density and reduce the risk of fracture. This article focuses on the role of calcium and vitamin D in bone metabolism, suggestions, and precautions for calcium and vitamin D supplementation in elderly patients with osteoporosis.

In this study, the method of meta-analysis was used to systematically evaluate the effectiveness and safety of vitamin D and calcium in the treatment of osteoporotic fractures. 19 RCTs studies at home and abroad were integrated for meta-analysis. This systematic review was conducted through extensive database searches. The included studies are all RCTs, and all studies have clear inclusion and exclusion criteria, and all studies' intention-to-treat analysis is suitable for statistical analysis, so there is no possibility of bias. Baseline similarity analysis for most studies had a slight potential for bias. The sensitivity analysis of the results is consistent with the overall conclusions, thus enhancing the reliability of the conclusions of this systematic review.

Studies in recent years have shown that vitamin D is an important endocrine hormone that regulates calcium and phosphorus balance, regulates parathyroid hormone secretion, affects bone turnover, and regulates the expression of various genes in bone cells.[34] It can stimulate the maturation and differentiation of osteoblasts in the body, increase the expression of related drugs, and increase the effect of strengthening osteoblast calcification. Some studies have shown that when the serum 25(OH)D is high, the body's osteoclasts will show low activity.[35] In the in vivo study of normal people, the correlation between serum 25(OH)D and bone mineral density is somewhat controversial, but in patients with type 2 diabetes, many studies have reported that serum 25(OH)D and bone mineral density exist correlation.[36] In this study, the serum 25(OH)D of the osteoporosis group was significantly lower than that of the normal group, and the serum 25(OH)D was positively correlated with bone density.

In a study on the correlation between vitamin D, calcium supplements and bone density, it was found that in different serum 25(OH)D groups, calcium intake was significantly positively correlated with femur and spine bone density, which indicated that The promotion effect of calcium and vitamin D on bone density.[37] A study on the relationship between exercise and dietary calcium and bone mineral density found that exercise produced positive benefits in the higher calcium intake group, but there was no significant difference in the low calcium intake group,38 reflecting the application of a certain amount of calcium in the general population can achieve the effect of enhancing bone density.

Due to factors such as diet, reduced outdoor activities, decreased gastrointestinal absorption, and decreased renal function, the elderly population has become the highest risk group for vitamin D deficiency. Osteoporosis has brought enormous pain to the elderly, and fractures caused by osteoporosis have become an important cause of bed rest and even death for the elderly. This study concluded that there was no significant difference in the mortality rates between the two treatment groups and the control group. The cause of death did not exclude other causes (including geriatric diseases, and primary or secondary causes of osteoporotic fractures, and the study selection did not exclude participants with other causes. Chronic diseases: diabetes, cardiovascular disease)

Calcium combined with vitamin D3 can significantly reduce the incidence of fractures and significantly increase bone density in the elderly over 50 years old compared with the control group. Oral or intramuscular injection of vitamin D and calcium can prevent loose fractures, reduce the incidence of fractures, increase bone density, and is convenient, inexpensive. Suggested clinical application: early postmenopausal women, elderly men, postmenopausal women with or without a history of osteoporotic fractures; middle-aged and elderly people

over 47 years old. The conclusions of this study are mostly statistically significant; when applied to clinical decision-making, the best individualized treatment plan should be explored in combination with expert opinion, doctor's technical proficiency, and the patient's own situation and wishes. Therefore, elderly patients with clear calcium and vitamin D deficiency (even younger) are considered to have a high risk of fracture. To minimize the risk of fractures, high-risk patients should be given a combination of calcium and vitamin D.

Excessive dosage of calcium supplements carries the risk of developing hypercalcemia, which in turn can damage renal function. The risk factors for vitamin D poisoning include high calcium intake, hypercalcemia, idiopathic hypercalcemia, sarcoidosis, excessive production of vitamin D metabolites, and high reactivity to vitamin D. There is no special warning for the use of vitamin D and calcium supplements, especially in postmenopausal women. Calcium supplements may cause gastrointestinal adverse reactions including constipation, nausea, diarrhea, and abdominal pain. Because the meta-included literature in this study is all older than 50 years old. Constipation in the elderly is caused by a variety of factors. The gastrointestinal peristalsis slows down and the digestive function decreases in the elderly, which leads to the long retention time of enteric substances in the body, which makes the water in the intestines excessively absorbed, resulting in dry feces and increasing the difficulty of defecation; in addition, Negative emotions such as loneliness and depression in the elderly can also cause a significant decrease in the sensitivity of the rectal volume stimulation threshold, resulting in difficulty in defecation.[39] The digestive system function of the elderly is weakened or disordered, and they often feel abdominal distension and belching. Therefore, it cannot be determined that the mild symptoms in the literature all come from adverse drug reactions, and the elderly's own activity reduction and slow gastrointestinal motility are also of the reasons.

Limitations of this systematic review: (1) The outcome indicators included in RCTs are not the same, and the number of studies included in some outcome indicators is small, which affects the reliability of the conclusions; (2) The sample size of the included studies varies greatly, which may cause certain heterogeneity sex; (3) This study only included English literature, which may affect the extrapolation of the results; (4) Although all the included studies reported randomization, allocation concealment and blinding methods, some did not report specific implementation methods, which may have implementation bias. (5) The concentration of 25-hydroxyvitamin D in human serum is unavoidably inconsistent in clinical standards and baseline ranges. The results will be affected and changed due to the patient's nutrition, diet, drugs and environment.

In summary, the existing research results show that compared with vitamin D, vitamin D combined with calcium can shorten the fracture healing time and enhance bone density in patients with osteoporotic fractures, and has no effect on mortality, but attention should be paid to the gastrointestinal tract adverse reactions. Large-scale, high-quality clinical randomized controlled studies and subgroup analysis still need to be further carried out to more fully understand the clinical application value of calcium combined with vitamin D in the treatment of senile osteoporosis.

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AUTHORS DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Basic information of the included data

First author	Years	Nation	Number of cases	Age	Sex ratio	Follow-up time/month	Intervention	Outcome measures†
Bess[14]	2000	USA	147/148	73.5	25	36	Ca + VitD3 / NO	2,5
Pfeifer[15]	2000	Germany	70/67	70	25.5	12	Ca + VitD3 / NO	3
Chapuy[16]	2002	France	393/190	75	0	18	Ca + VitD3 / NO	3,4,5
Avenell[17]	2004	UK	35/35	78	0	24	Ca + VitD3 / NO	3,5
Harwood[18]	2004	UK	39/37	67	0	12	Ca + VitD3 / NO	13,
Larsen[19]	2004	Denmark	2491/1210	68.2	39.1	18	Ca + VitD3 / NO	3,4
Flicker[20]	2005	Australia	313/312	75.6	5	24	Ca + VitD3 / NO	3
PortHouse[21]	2005	Germany	714/1391	70	0	18-42	Ca + VitD3 / NO	1,3
Grant[22]	2005	UK	1306/1332	70	15	62	Ca + VitD3 / NO	1,3
Jackson[23]	2006	USA	18716/18106	60	0	60	Ca + VitD3 / NO	2,3,5
Smith[24]	2007	UK	62/61	68.6	28.3	36	Ca + VitD3 / NO	2,4
Pignotti[25]	2009	Brazil	29/29	62.3	0	24	Ca + VitD3 / NO	4
Karkkainen[26]	2010	finland	287/306	67.4	0	48	Ca + VitD3 / NO	2,4,5
Mezquita[27]	2010	Spain	95/97	74.6	0	36	Ca + VitD3 / NO	2,4
Aloia[28]	2013	U.K.	46/31	57.6	31.2	24	Ca + VitD3 / NO	5
Liu[29]	2015	China	50/48	62.1	0	6-14	Ca + VitD3 / NO	3
Travers[30]	2017	US	1156/1147	65.2	76	36	Ca + VitD3 / NO	4
Sullivan[31]	2017	US	7519/10386	63	0	24	Ca + VitD3 / NO	3
Xue[32]	2017	China	139/173	63.6	0	60	Ca + VitD3 / NO	3,5

VitD: vitamin D group; NO: non-intervention group
†1: Mortality rate, 2: Bone density, 3: fracture rate, 4: serum 25(OH)D, 5: adverse reactions.

Table 2. Egger method test calculation results

Std-Eff	Coef	Std.Err	t	P> |t |	95% Conf.	Interval
Egger'test						
Slope	-0.04931	0.0874109	-0.56	0.673	-1.159971	1.061351
bias	0.8089839	0.6178689	1.31	0.415	-7.041785	8.659753
Egger'test						
Slope	-0.432114	0.6296023	-0.69	0.542	-2.435789	1.571561
bias	9.100733	7.588623	1.2	0.317	-15.04965	33.25112
Egger'test						
Slope	-0.027124	0.0217507	-1.25	0.241	-0.0755873	0.0213401
bias	-0.514824	0.3010283	-1.71	0.241	-1.185557	0.155909
Egger'test						
Slope	0.6733353	0.2696617	2.5	0.055	-0.0198523	1.366523
bias	1.544134	2.882277	0.54	0.615	-5.864995	8.953264
Egger'test						
Slope	0.0873203	0.0982201	0.89	0.415	-0.1651625	0.3398031
bias	0.6467187	0.5604543	1.15	0.301	-0.7939751	2.087412

Values were shown as means±SD.

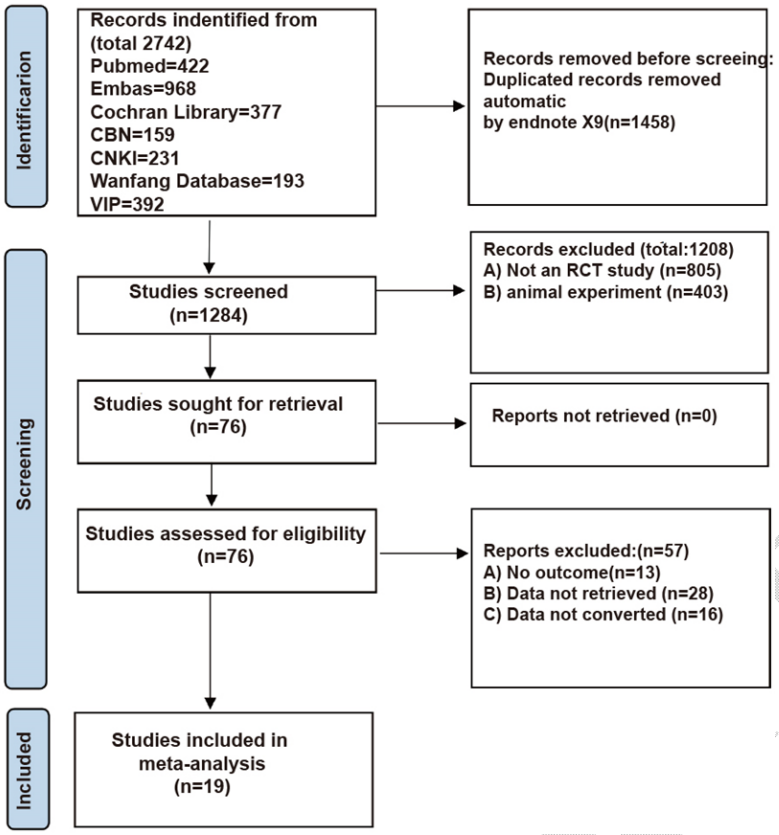

Figure 1. Flow chart of document screening.

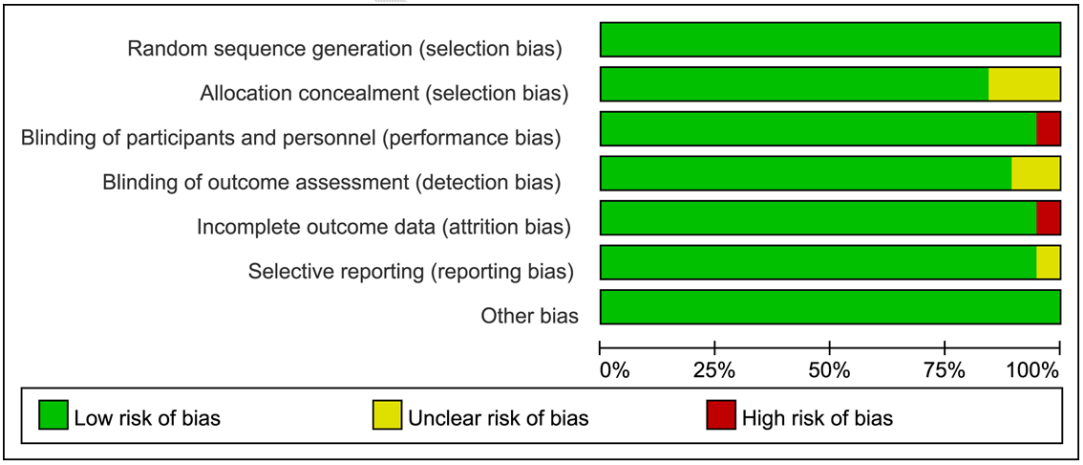

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

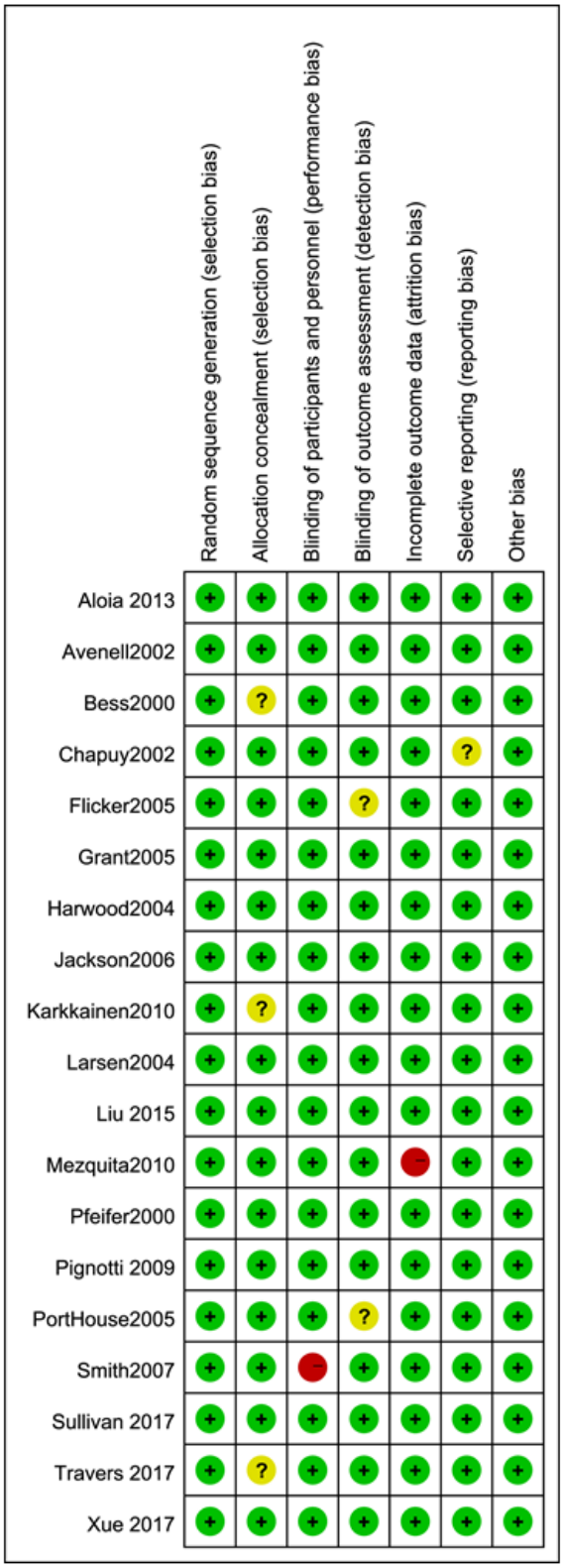

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study

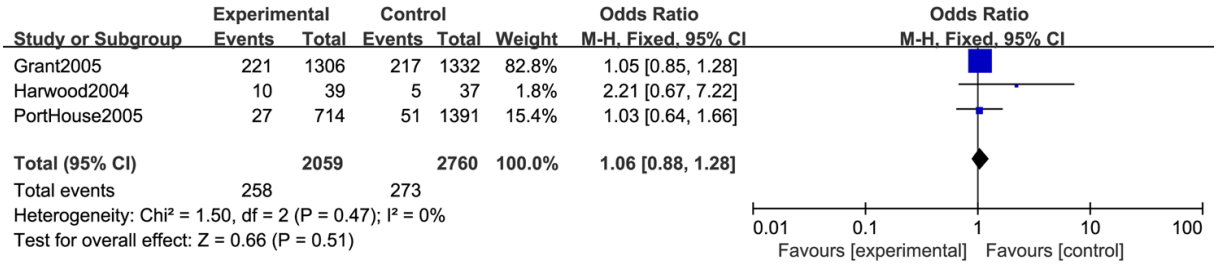

Figure 4. The forest plot of the meta-analysis of the mortality rate of vitamin D combined with calcium compared with the control group

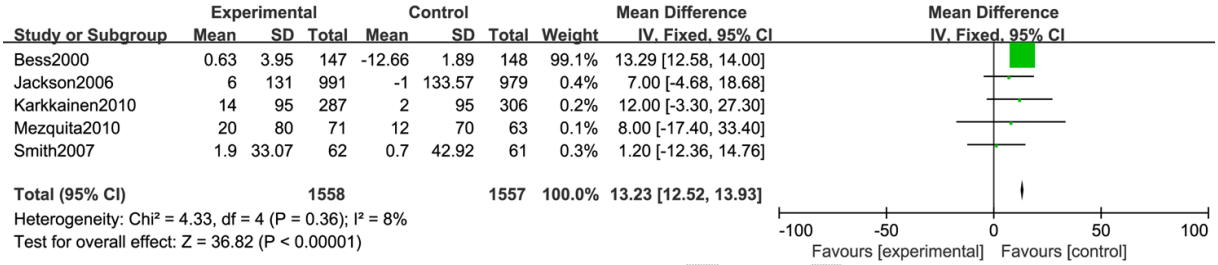

Figure 5. Forest plot of meta-analysis of vitamin D combined with calcium supplements to increase bone density compared with the control group

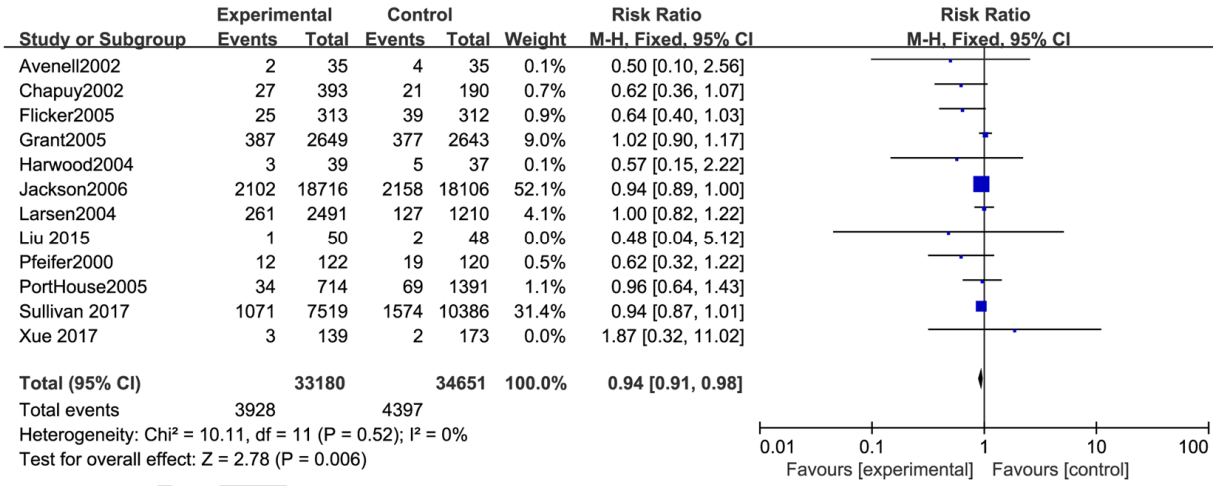

Figure 6. The forest plot of the meta-analysis of the fracture incidence of vitamin D combined with calcium compared with the control group

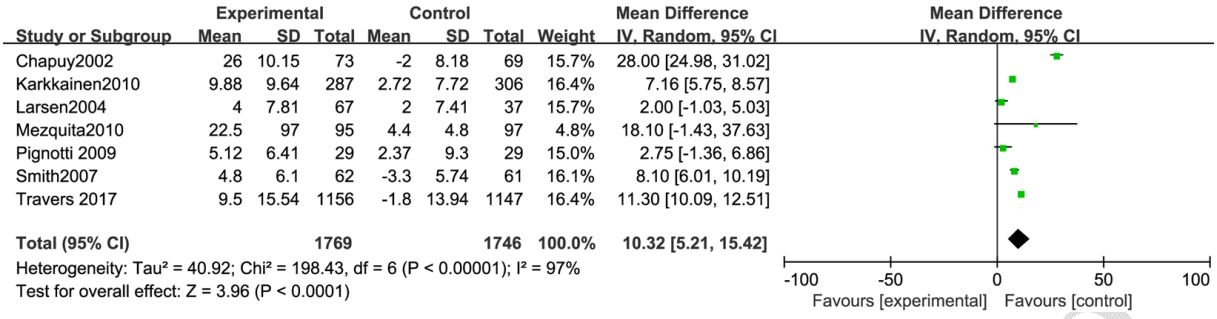

Figure 7. Forest plot of meta-analysis of vitamin D combined with calcium compared with control group to increase serum 25(OH)D concentration

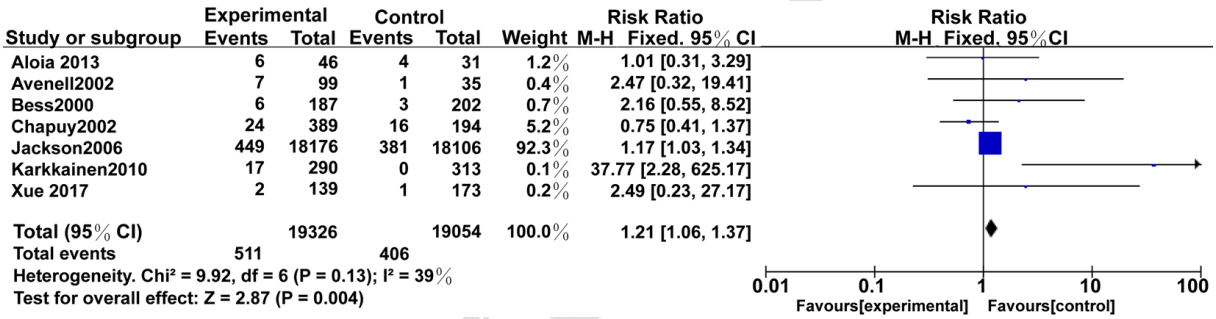

Figure 8. Forest plot of meta-analysis of adverse reactions of vitamin D combined with calcium compared with the control group

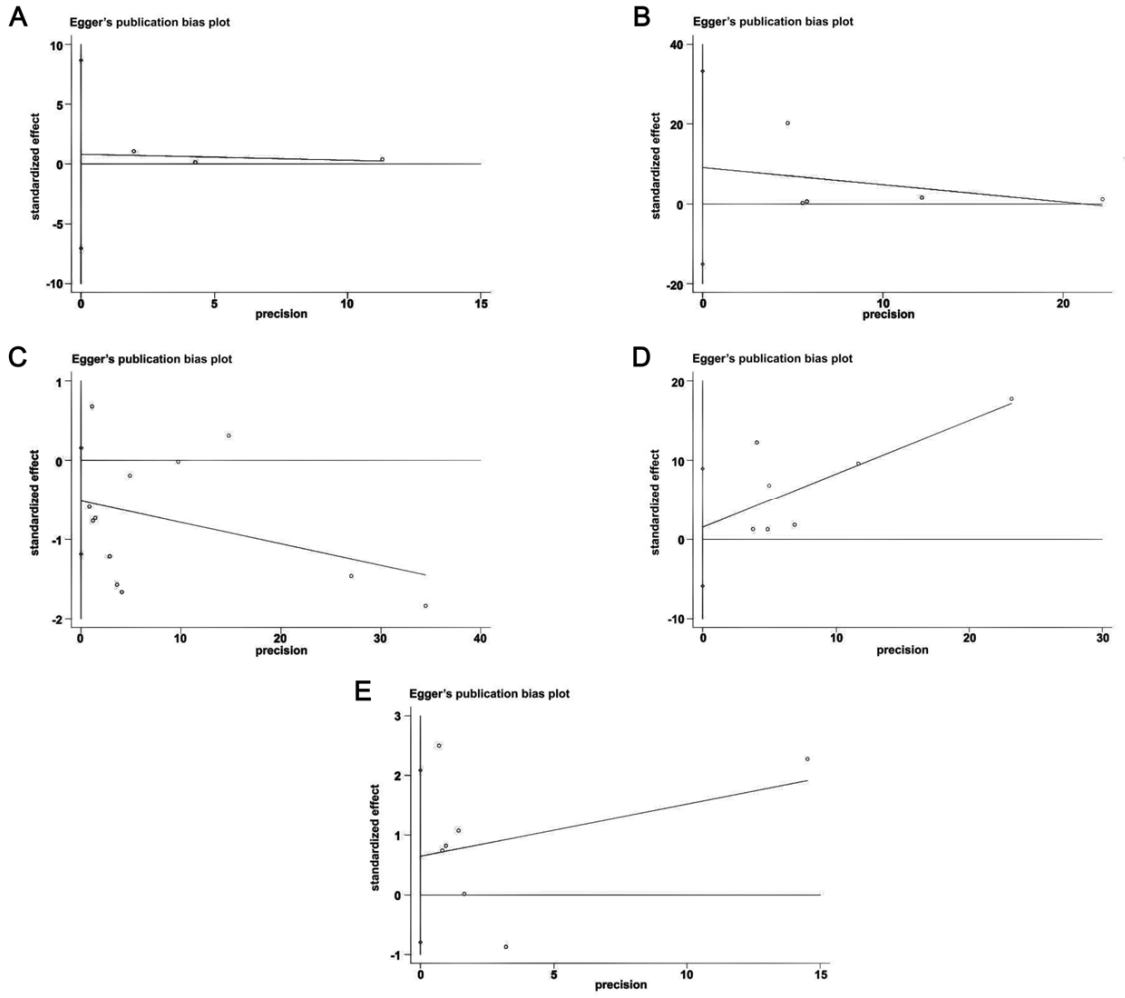

Figure 9. Eggers test method regression chart. A: Mortality, B: Bone density, C: Fracture rate, D: Serum 25(OH)D concentration, E: Adverse reactions