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Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials

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Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials

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Abstract

Objective Inconsistent findings in regard to association between different concentrations of vitamin D, calcium or their combination and the risk of fracture have been reported during the past decade in community-dwelling older people. This study was designed to compare the fracture risk using different concentrations of vitamin D, calcium or their combination.

Design A systematic review and network meta-analysis.

Data sources Randomized controlled trials in PubMed, Cochrane library, and EMBASE databases were systematically searched from the inception dates to December 31, 2017.

Outcomes Total fracture was defined as the primary outcome. Secondary outcomes were hip fracture and vertebral fracture. Due to the inconsistency of the original studies, an inconsistency model was used to pool the confounder-adjusted relative risk (RR).

Results A total of 29 randomized trials involving 45647 participants fulfilled the inclusion criteria. There was no evidence that the risk of total fracture was reduced by using different concentrations of vitamin D, calcium or their combination compared with placebo or no treatment. No significant associations were found between calcium, vitamin D, or combined calcium and vitamin D supplements and the incidence of hip, or vertebral fractures.

Conclusions The use of supplements that included calcium, vitamin D, or both was not found to be better than placebo or no treatment in terms of risk of fractures among community-dwelling older adults. It means the routine use of these supplements in community-dwelling older people should be treated more carefully.

Prospero registration number CRD42017079624

Keywords: Calcium; Vitamin D; Fractures; network meta-analysis

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Strengths and limitations of this study

- This systematic review and meta-analysis combined the evidence from randomized controlled trials of total fractures, hip fractures and vertebral fractures in older people, examining association between different concentrations of vitamin D, calcium or their combination and the risk of fracture
- Our findings may not support the routine use of these supplements in community-dwelling older people.
- This work does not necessarily preclude any benefit of vitamin D and calcium supplementation in older, frail individuals.
- Potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence.

Introduction

Clinical fractures of the elderly represent a worldwide public health problem that leads to illness and social burden. The patients with osteoporosis in the EU were estimated to be 27.5 million in 2010, and 3.5 million new fragility fractures were sustained[1]. In Asia, the average cost of osteoporotic fractures accounted for 18.95% of the countries' 2014 GDP/capita and increased annually[2-4]. The overall prevalence of osteoporosis or low bone mass in non-institutional population over the age of 50 in the USA was estimated at 10.3% and 43.9%, respectively, which means that 10.2 million elderly people had osteoporosis and 43.4 million people had low bone mass in 2010[5]. With the demographic trend of ageing and the predicted increase in life expectancy, the cost of fracture treatment is expected to rise.

Dietary allowances for calcium range from 700 to 1200 mg/d and vitamin D of 600-800 IU/d have long been recommended for the prevention of osteoporotic fractures in the elderly[6 7]. The supplements of calcium and vitamin D are commonly taken to maintain bone health.

However, the previous RCTs and meta-analyses concerning vitamin D, calcium, or their combination

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for fractures yielded different efficacy outcomes. For instance, two meta-analyses demonstrated calcium or vitamin D supplementation alone has a small benefit on bone mineral density (BMD), but no clinically important to prevent fractures[8 9], while an updated meta-analysis and a pooled analysis found calcium plus vitamin D supplementation can significantly reduce hip fractures by 30% and total fractures by 15%[10 11]. Two RCTs reported that low dose of vitamin D supplementation (less than 800 IU/d) can reduce the incidence of falls[12] and may prevent fractures without adverse effects[13], but other RCTs showed no significant reduction in the incidence of hip or other peripheral fractures[14 15] and its possible effects were seen only in patients with initial calcium insufficiency. What's more, Bischoff-Ferrari et al [16] illustrated that high-dose vitamin D supplementation (800 IU/d or higher) not only reduced the risk of falls and hip fractures, but also prevented non-vertebral fractures. In contrast, a study reported annual high-dose oral vitamin D resulted in an increased risk of falls and fractures [17]. On the other hand, low-dose calcium supplementation (less than 800mg/d) effectively led to a sustained reduction in the rate of bone loss [18] and turnover. Although it was also reported that the high dose of calcium (800 mg/d or higher) was associated with a lower risk of clinical fractures [19]. The high-dose calcium with high-dose vitamin D can't prevent fractures according to the evidence from reported RCT [20], but a meta-analysis supported their combination can prevent bone loss and significantly reduce the risk of hip fractures and all osteoporotic fractures [21]. Thus, it's a challenging to conclude a dose-response relation between the intakes of vitamin D, calcium, or their combination and the main outcomes in these heterogeneous literatures.

Therefore, this study was designed to compare the fracture risk using different concentrations of vitamin D, calcium or their combination, and comprehensively evaluate the optimal concentration to guide clinical practice and public prevention in community-dwelling older people.

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Methods

Search strategy and selection criteria

This review and meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for network meta-analysis. Our meta-analysis was registered prospectively in PROSPERO (CRD42017079624) and the Checklist PRISMA 2009 (**Supplementary Table 1**) will be used and check our final reports [22].

We restricted our meta-analysis to the inclusion criteria should meet following details: (1) RCTs; (2) Interventions must be one of the following three: vitamin D only, calcium only, both vitamin D and calcium; (3) Complete outcome data of fracture; (4) Trials enrolling adults older than 50 years and living in their communities; Exclusion criteria were (1) Non-randomized trials; (2) Observational and experimental studies; (3) Case reports, case series, case control studies and reviews; (4) Calcium or vitamin D combined with other therapies (eg: hormones, exercise); (5) Trials in which vitamin D analogues (eg: calcitriol) or hydroxylated vitamin D were used; (6) Trials in which dietary intake of calcium or vitamin D (eg: from milk) was evaluated; (7) Patients suffering from illness or long-term use of certain drugs affecting the stability of the calcium metabolism, such as metabolic bone disease, bone tumour and so on.

Participants must be randomly assigned to two or more following groups: (1) high calcium (800 mg/d or higher) only; (2) low calcium (less than 800 mg/d) only; (3) high vitamin D (800 IU/d or higher) only; (4) low vitamin D (less than 800 IU/d) only; (5) high calcium (800 mg/d or higher) + high vitamin D (800 IU/d or higher); (6) high calcium + low vitamin D (less than 800 IU/d); (7) low calcium (less than 800 mg/d) + high vitamin D; (8) low calcium + low vitamin D; (9) placebo. The interventions should be compared with placebo.

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Two authors independently searched the electronic literature database of PubMed, Embase, Cochrane database on December 31, 2017. Related articles and reference lists were searched to avoid original miss. The reference studies of previous systematic reviews, meta-analysis, and included studies were manually searched to avoid initial miss. After 2 authors assessed the potentially eligible studies independently, any disagreement was discussed and resolved with the third independent author.

Data collection and assessment of risk of bias

Two reviewers independently extracted data, and the third reviewer checked the consistency between them. A standard data extracted form was used at this stage, including the authors, publishing date, country, participant characteristics; doses of calcium, vitamin D, or their combination; dietary calcium intake; baseline serum 25-hydroxyvitamin D concentration; and trial duration. For continuous outcomes, the mean, SD (standard deviation) and participant number will be extracted. For dichotomous outcomes, we extracted the total numbers and the numbers of events of both groups. The data in other forms was recalculated when possible to enable pooled analysis.

We used the Cochrane risk of bias tool to assess risk bias of included studies. The tool has seven domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The classification of the judgment for each domain was low risk of bias, high risk of bias, or unclear risk of bias and two authors independently evaluated the risk of studies.

Data synthesis and statistical analysis

The data was extracted and input into the STATA software (version 12.0; StataCorp, College Station, TX, USA) for network meta-analysis. And we generated network plots for each outcome to illustrate which interventions had been compared directly in the included studies. Network meta-analysis is an

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extension of standard meta-analysis to compare multiple treatments based on randomized controlled trial evidence, which forms a connected network of comparisons. Treatment effect estimates from network meta-analysis exploit both the direct comparisons within trials and the indirect comparisons across trials. Relative risk (RR) was calculated for dichotomous outcomes while weighted mean difference (WMD) for the continuous both with 95%CI for direct comparisons or 95%CrI for indirect comparisons. Our network was a closed triangular circular network including both direct and indirect evidences. The model (which was proposed by Anna Chaimani, downloaded from www.mtm.uoi.gr) we used was fit for all kinds of networks. To the only one triangular circular, we used ifplot command proposed by Anna Chaimani to evaluate the consistency of direct and indirect estimates. Then the operational model was chosen according to the inconsistency test, which was the basis of forest maps' calculation. We used the surface under the cumulative ranking probabilities (SUCRA) to indicate which treatment was the best one. The funnel plot was used to identify possible publication bias if the number of studies was larger than 10.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, and no patients were involved in developing plans for design or implementation of the study. Furthermore, no patients were asked to advice on interpretation or writing up of results. Since this meta-analysis used aggregated data from previous trials, it is unable to disseminate the results of the research to study participants directly.

Result

Data Retrieval

In summary, a total of 7909 potential records were initially identified through PubMed (5187),

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Embase (2688), Cochrane Data base (34). Based on our review of the title and abstract, 99 full-text papers were reviewed and 29 studies met inclusion criteria (**Figure 1)**.

Study and Patient Characteristics

The characteristics of all 29 included studies were summarized and shown in **supplementary Table 2**. And the detailed data of outcomes was collected in **supplementary Table 3**. The papers had similar distributions of sex, age, country, intervention and all of them were community-dwelling older people. Hansson et al[23] did not report the residential status of participants, although a previous meta-analysis classified this status as community[24]. The trial by Hansson et al[23] was included, but a sensitivity analysis was performed that excluded that trial (**supplementary Figure 1**). Inkovaara et al[25] did not report whether the data represent the number of fractures or participants with fracture. The trial by Massart et al[26] was included, which adult maintenance hemodialysis patients were the participants. We suspected that the maintenance hemodialysis or the underlying disease might result in the imbalance of calcium in the body. Patients on haemodialysis may also be receiving 1,25-dihydroxyvitamin D, which may affect their response to vitamin D supplementation. The data were included, but a sensitivity analysis was performed that excluded both of two trials (**supplementary Figure 2**).

supplementary Figure 3 and supplementary Figure 4 showed the assessment of the risk of bias. All studies were randomized; 21 were double-blind, placebo-controlled trials; 16 trials described an adequate random sequence generation process; and 13 trials described the methods used for allocation concealment. Only one study showed low quality[25], so we also made a sensitivity analysis by excluding that trial (**supplementary Figure 2**). No obvious publication bias was reported according to the **supplementary Figure 5, supplementary Figure 6** and **supplementary Figure 7**.

Primary outcome: total fracture

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For estimating the vitamin D, calcium or their combination efficacy against total fractures, we looked at data from 27102 individuals from 22 studies. Pooled estimates included 18 studies with one treatment, 1 study with two treatments, and 3 studies with three treatments.

The inconsistency between direct and indirect evidence based on both comparisons of consistency and inconsistency model was found according to inconsistency test (**supplementary Figure 8**), so we adopted an inconsistency model to deal with this problem.

The network plot of comparisons on total fractures was shown in **Figure 2A**. The forest plot for the network meta-analysis was shown in **Figure 3A**. We also made ranking graph of distribution of probabilities on total fractures in **supplementary Figure 9**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between interventions and placebo. Based on SUCRA, high calcium plus low vitamin D group (0.726) ranked the first, the second was high calcium plus high vitamin D group (0.642) and the last was low calcium plus high vitamin D group (0.217). In a separate sensitivity analysis, we excluded Inkovaara's [25] and Massart's [26] studies (**supplementary Figure 2**). However, there was still no significant association of vitamin D, calcium or their combination with total fracture.

Secondary outcomes: **hip fracture and vertebral fracture**

A total of 42531 individuals were included from 17 studies for evaluate the drug efficacy against hip fractures. Pooled estimates included 14 studies with one treatment, 1 study with two treatments, and two studies with three treatments.

We adopted an inconsistency model to deal with this problem according to inconsistency test (**supplementary Figure 10**). The network plot of comparisons on hip fractures was shown in **Figure**

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2B. The forest plot for the network meta-analysis was shown in **Figure 3B**. We also made ranking graph of distribution of probabilities on hip fractures in **supplementary Figure 11**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between drug experimental groups and placebo. Based on SUCRA, high calcium plus high vitamin D group (0.791) ranked the first, the second was placebo or no treatment group (0.6753) and the last was high calcium group (0.198).

A total of 17612 individuals were collected from 12 studies involving vertebral fractures. Pooled estimates included 10 studies with one treatment, and two studies with three treatments.

We adopted an inconsistency model to deal with this problem according to inconsistency test (**supplementary Figure 12**). The network plot of comparisons on vertebral fractures was shown in **Figure 2C**. The forest plot for the network meta-analysis was shown in **Figure 3C**. We also made ranking graph of distribution of probabilities on vertebral fractures in **supplementary Figure 13**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between drug experimental groups and placebo. Based on SUCRA, high calcium plus high vitamin D group (0.825) ranked the first, the second was high calcium group (0.649) and the last was high vitamin D group (0.186). In a separate sensitivity analysis, we excluded Hansson's study[23] (**supplementary Figure 1**). However, there was still no significant association of vitamin D, calcium or their combination with total fracture.

Discussion

Vitamin D supplementation and calcium are suggested as interventions to treat and prevent fracture. We found the previous meta-analyses and RCTs are critically inconsistent in efficacy of different doses

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of vitamin D with calcium on fractures.

Results of this meta-analysis showed that calcium, calcium plus vitamin D, and vitamin D supplementation alone were not significantly associated with a lower incidence of hip, vertebral, or total fractures in community-dwelling older adults. Sensitivity analyses that excluded low-quality trials and studies that exclusively enrolled patients with particular medical conditions did not alter these results.

A meta-analysis conducted by Jia-Guo Zhao et al[27] showed that no significant difference was found in the incidence of hip or other fractures, which was similar to our result. However, it did not focus on the effect of different concentrations of vitamin D, calcium or their combination and we supposed that a network meta-analysis might be more reasonable. And in this meta-analysis the participants of the included study reported by Massart[26] were adult maintenance hemodialysis patients, which may resulted in the imbalance of calcium in the body. Patients on haemodialysis may also be receiving 1,25-dihydroxyvitamin D, which may affect their response to vitamin D supplementation. And we suspected that a network meta-analysis might be a more suitable choice concerning all these different interventions mixed.

Bischoff-Ferrari et al [28] reported that high-dose vitamin D supplementation (800 IU/d or higher) played an important role in the reduction of the risk of falls and hip fractures, as well as prevented non-vertebral fractures in adults 65 years or older. However, their findings may have been influenced by the trial of Chapuy et al [29], which only enrolled participants living in an institution. What's more, differences in conclusions of previous meta-analyses and the current meta-analysis were due to the recently published trials which reported neutral or harmful associations of vitamin D supplementation and fracture incidence more and more. Study findings here indicated that vitamin D might result in a

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higher risk for hip fracture, but this conclusion did not reach statistical significance. This finding may be attributable to lack of statistical power in this meta-analysis.

However, possible limitations of this study protocol include potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence. Some RCTs were of poor quality and, for example, used unclear allocation concealment. So we made a sensitivity analysis by excluding low-quality trials. And some study characteristics such as sex, baseline serum 25-hydroxyvitamin D concentrations, duration of follow-up, performance bias and detection bias might be potential obstacles to the outcomes of our article, but we performed some subgroup analyses before statistical analysis and found no statistical differences between these subgroups. What's more, we combined bolus dosing by injection with oral supplements taken daily/monthly/yearly, which might have different effects on vitamin D status in the body. In addition, this work does not necessarily preclude any benefit of vitamin D and calcium supplementation in older, frail individuals.

Conclusions

In this meta-analysis of randomized clinical trials, we found that the use of different concentrations of vitamin D, calcium or their combination in community-dwelling older adults was not associated with a lower risk of fractures. Our findings may not support the routine use of these supplements in community-dwelling older people.

Contributors

ZCH and AMW conceived the study. The search strategy was developed by LT and XBL. ZHF, GZ and QT will complete electronic search, select publications and assess their eligibility. ZHS and XBL will extract information of the included studies after screening. JWX will check the data entry for accuracy and completeness. ZCH and LT will give advice for data analysis and presentation of study

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result. WFN and AMW supervised the overall conduct of the study. All the authors drafted and critically reviewed and approved the final manuscript.

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Conflicts of interest

None declared

Patient consent

Not required.

Provenance and peer review

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Data sharing statement

No additional data are available.

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Figure 1. The selection of literature for included studies.

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Figure 2. The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral fractures (C). A=high calcium (800 mg/d or higher)；B=low calcium (less than 800 mg/d)；C=high vitamin D (800 IU/d or higher)；D=low vitamin D (less than 800 IU/d)

Figure 3. The forest plot for the risk of total fractures (A), hip fractures (B) and vertebral fractures (C). A=high calcium (800 mg/d or higher)；B=low calcium (less than 800 mg/d)；C=high vitamin D (800 IU/d or higher)；D=low vitamin D (less than 800 IU/d)

supplementary Figure 1. A sensitivity analysis excluded the trial of Hansson et al. A=high calcium (800 mg/d or higher)；B=low calcium (less than 800 mg/d)；C=high vitamin D (800 IU/d or higher)；D=low vitamin D (less than 800 IU/d)

supplementary Figure 2. A sensitivity analysis excluded the trial of Inkovaara et al. A=high calcium (800 mg/d or higher)；B=low calcium (less than 800 mg/d)；C=high vitamin D (800 IU/d or higher)；D=low vitamin D (less than 800 IU/d)

supplementary Figure 3. Risk of Bias Assessment of All Included Studies

supplementary Figure 4. Risk of Bias Assessment of All Included Studies

supplementary Figure 5. Publication bias for the total fractures. A=high calcium (800 mg/d or higher)；B=low calcium (less than 800 mg/d)；C=high vitamin D (800 IU/d or higher)；D=low vitamin D (less

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than 800 IU/d)

supplementary Figure 6. Publication bias for the hip fractures. A=high calcium (800 mg/d or higher); B=low calcium (less than 800 mg/d); C=high vitamin D (800 IU/d or higher); D=low vitamin D (less than 800 IU/d)

supplementary Figure 7. Publication bias for the vertebral fractures. A=high calcium (800 mg/d or higher); B=low calcium (less than 800 mg/d); C=high vitamin D (800 IU/d or higher); D=low vitamin D (less than 800 IU/d)

supplementary Figure 8. Inconsistency test for the total fractures. A=high calcium (800 mg/d or higher); B=low calcium (less than 800 mg/d); C=high vitamin D (800 IU/d or higher); D=low vitamin D (less than 800 IU/d)

supplementary Figure 9. Ranking graph of distribution of probabilities for total fractures. A=high calcium (800 mg/d or higher); B=low calcium (less than 800 mg/d); C=high vitamin D (800 IU/d or higher); D=low vitamin D (less than 800 IU/d)

supplementary Figure 10. Inconsistency test for the hip fractures. A=high calcium (800 mg/d or higher); B=low calcium (less than 800 mg/d); C=high vitamin D (800 IU/d or higher); D=low vitamin D (less than 800 IU/d)

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supplementary Figure 11. Ranking graph of distribution of probabilities for hip fractures. A=high calcium (800 mg/d or higher)；B=low calcium (less than 800 mg/d)；C=high vitamin D (800 IU/d or higher)；D=low vitamin D (less than 800 IU/d)

supplementary Figure 12. Inconsistency test for the vertebral fractures. A=high calcium (800 mg/d or higher)；B=low calcium (less than 800 mg/d)；C=high vitamin D (800 IU/d or higher)；D=low vitamin D (less than 800 IU/d)

supplementary Figure 13. Ranking graph of distribution of probabilities for vertebral fractures. A=high calcium (800 mg/d or higher)；B=low calcium (less than 800 mg/d)；C=high vitamin D (800 IU/d or higher)；D=low vitamin D (less than 800 IU/d)

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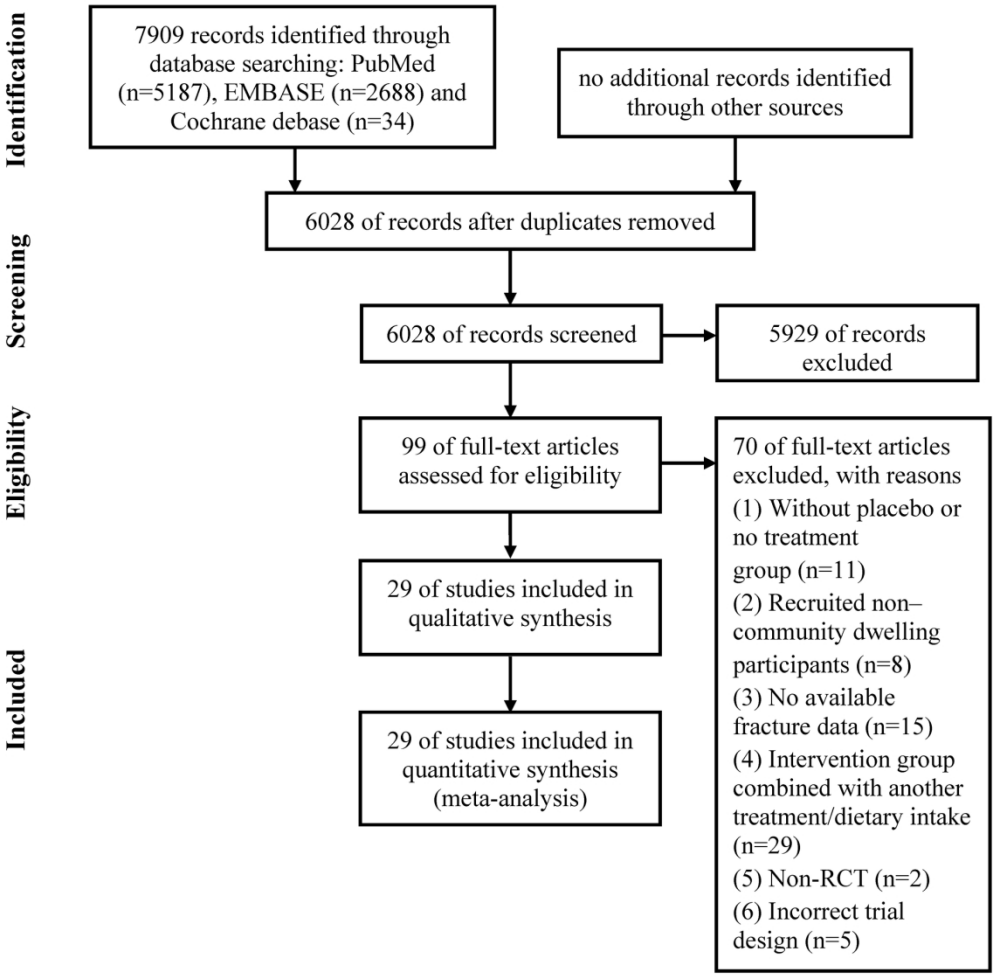

The selection of literature for included studies

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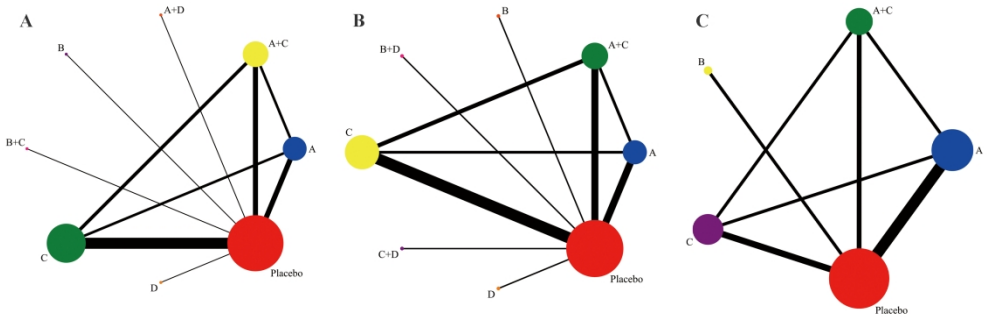

The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral fractures (C). A=high calcium (800 mg/d or higher) ; B=low calcium (less than 800 mg/d) ; C=high vitamin D (800 IU/d or higher) ; D=low vitamin D (less than 800 IU/d)

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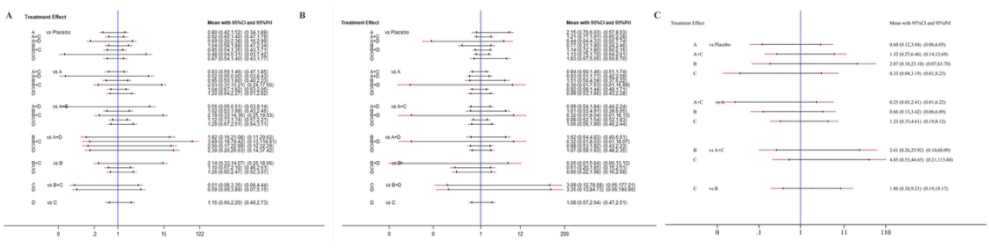

The forest plot for the risk of total fractures (A), hip fractures (B) and vertebral fractures (C). A=high calcium (800 mg/d or higher) ; B=low calcium (less than 800 mg/d) ; C=high vitamin D (800 IU/d or higher) ; D=low vitamin D (less than 800 IU/d)

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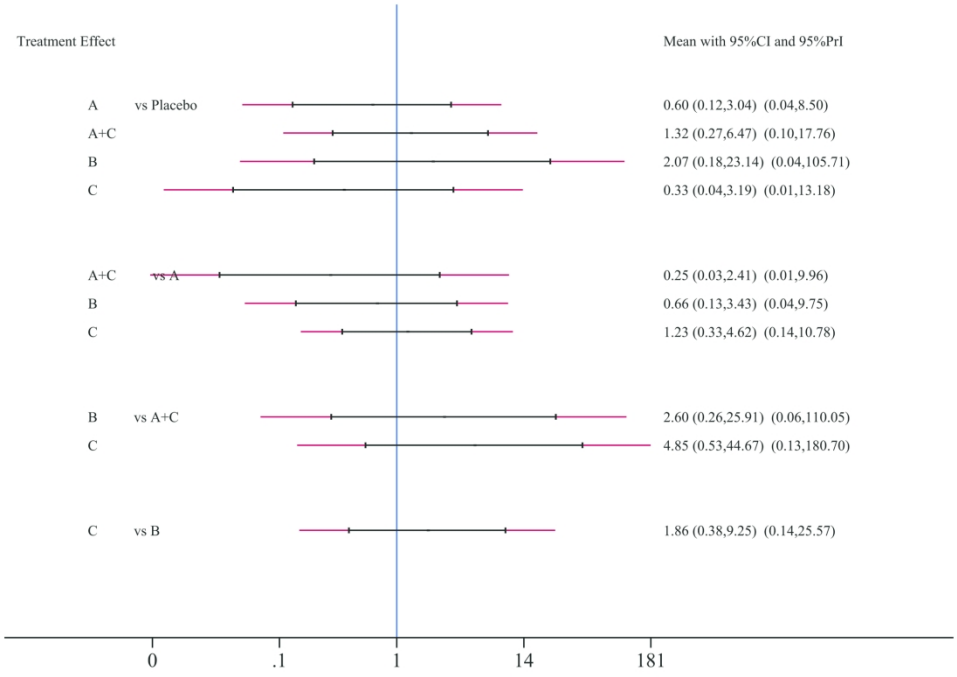

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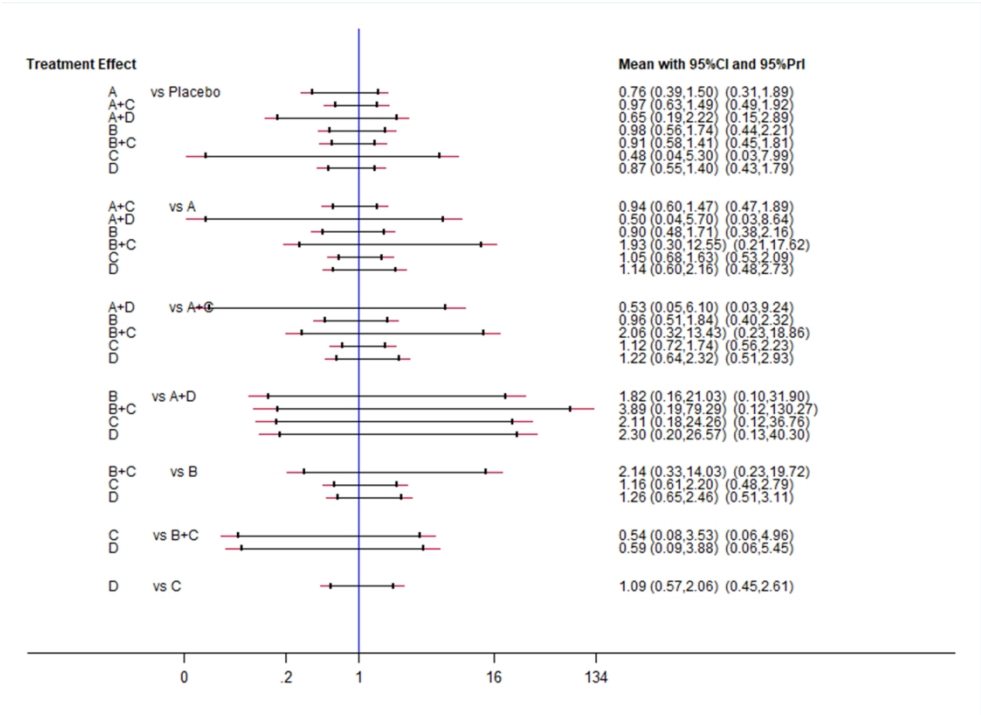

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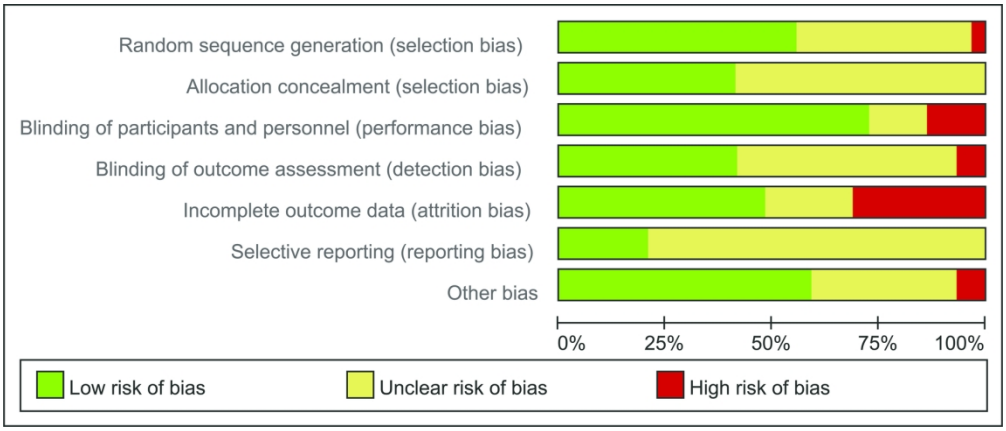

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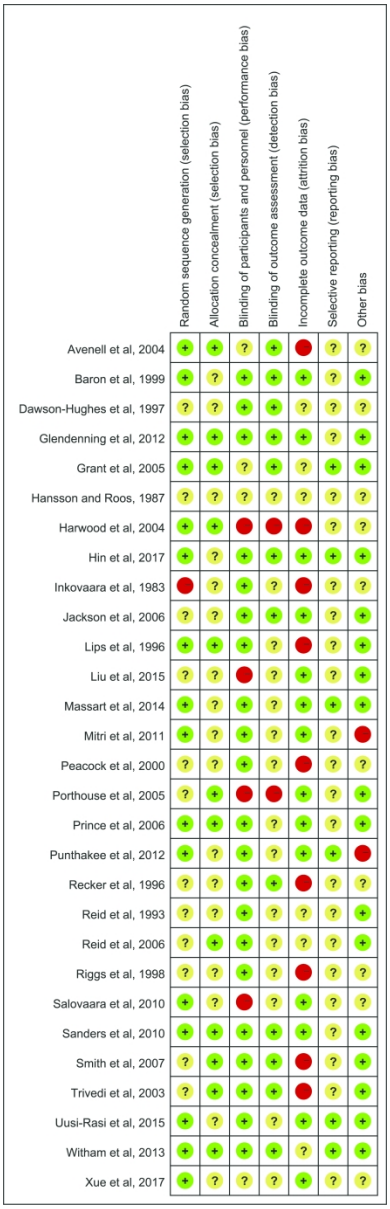

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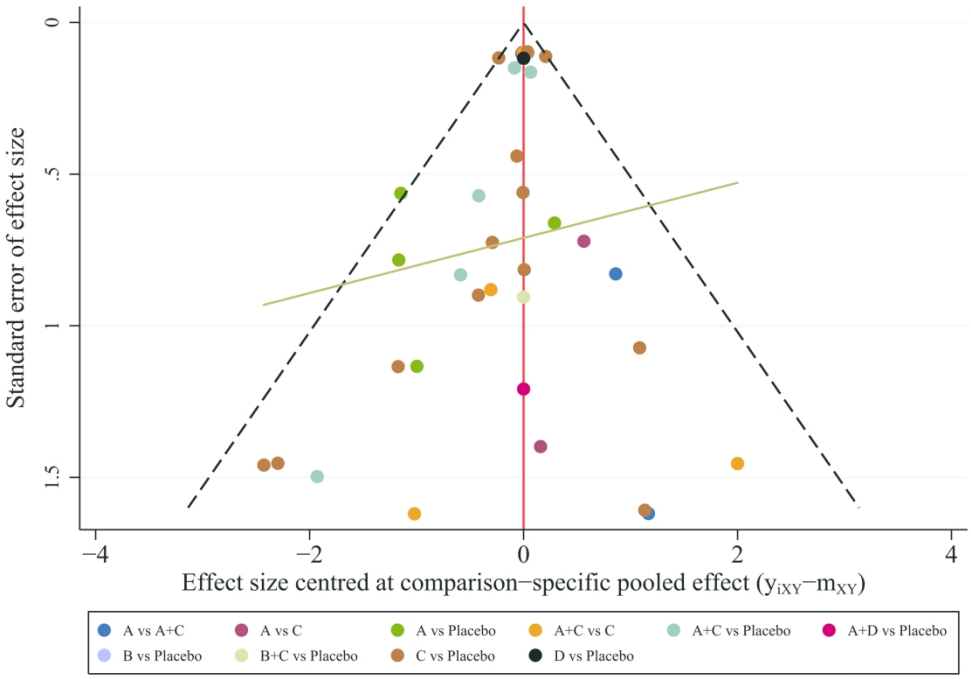

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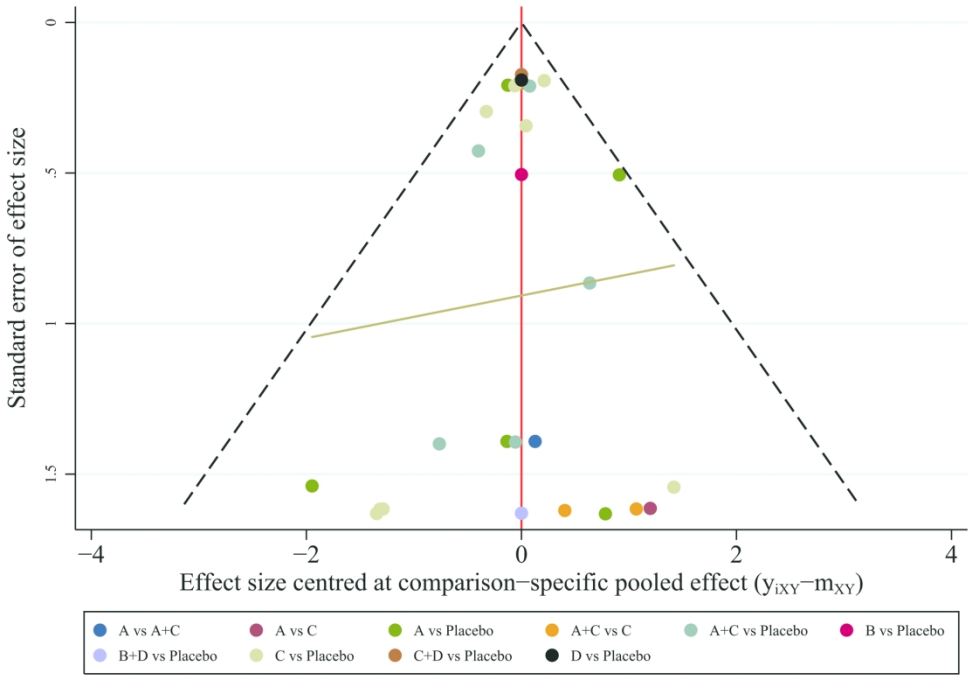

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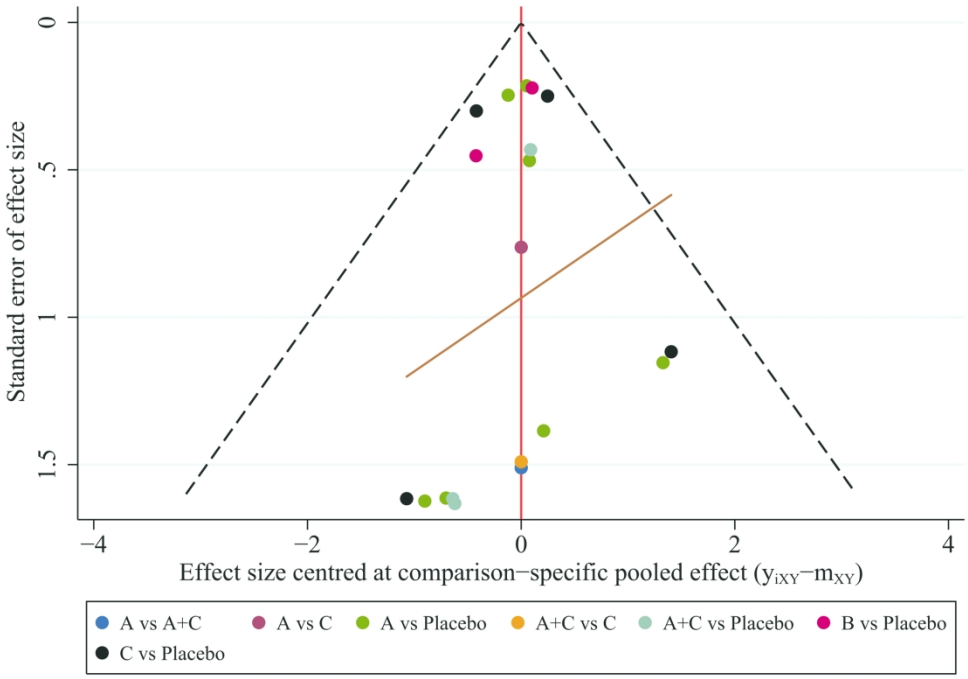

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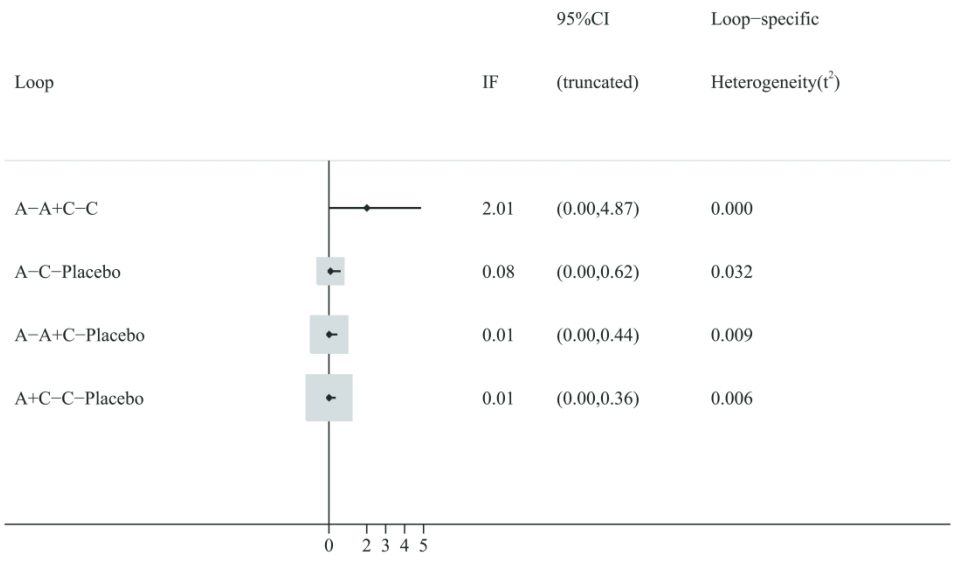

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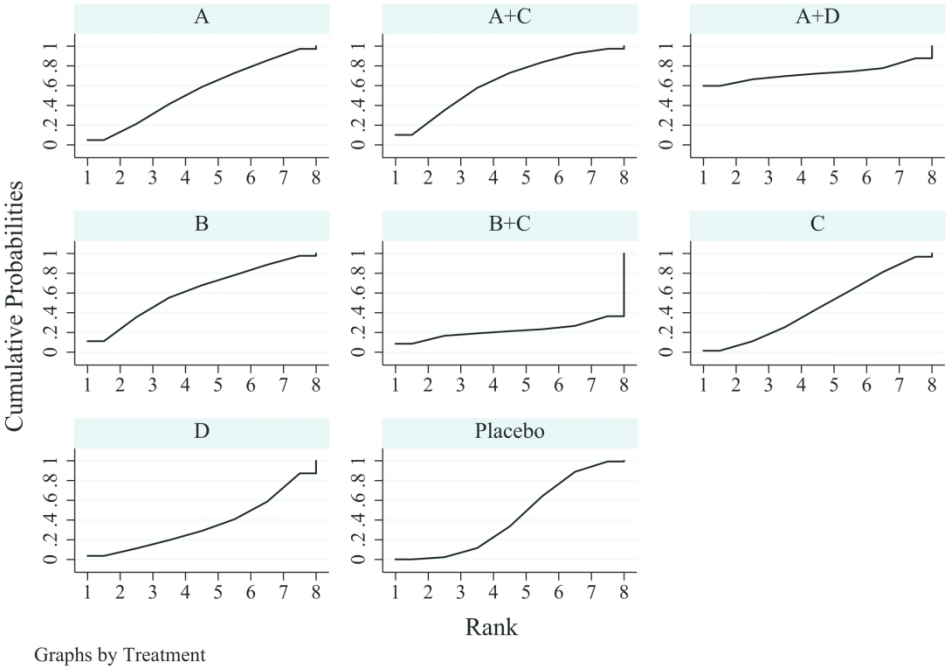

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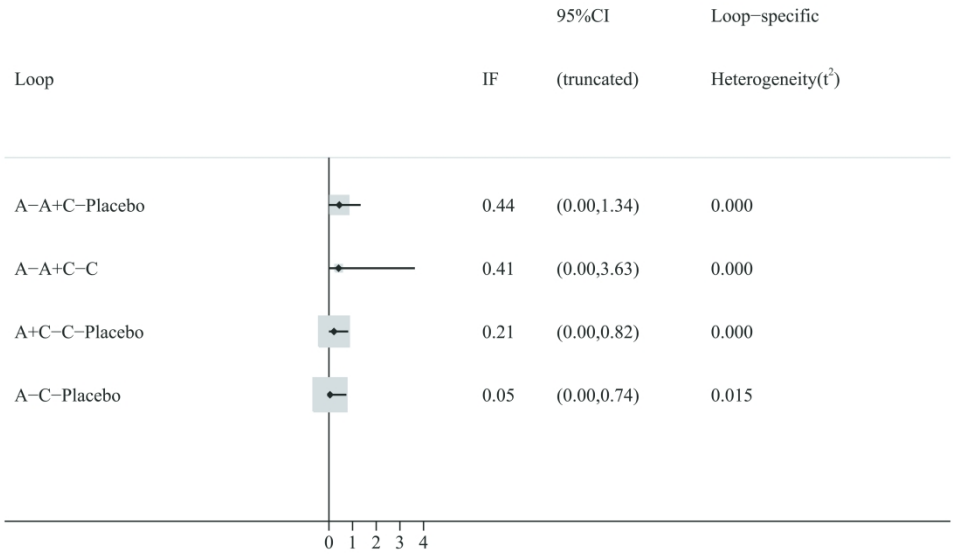

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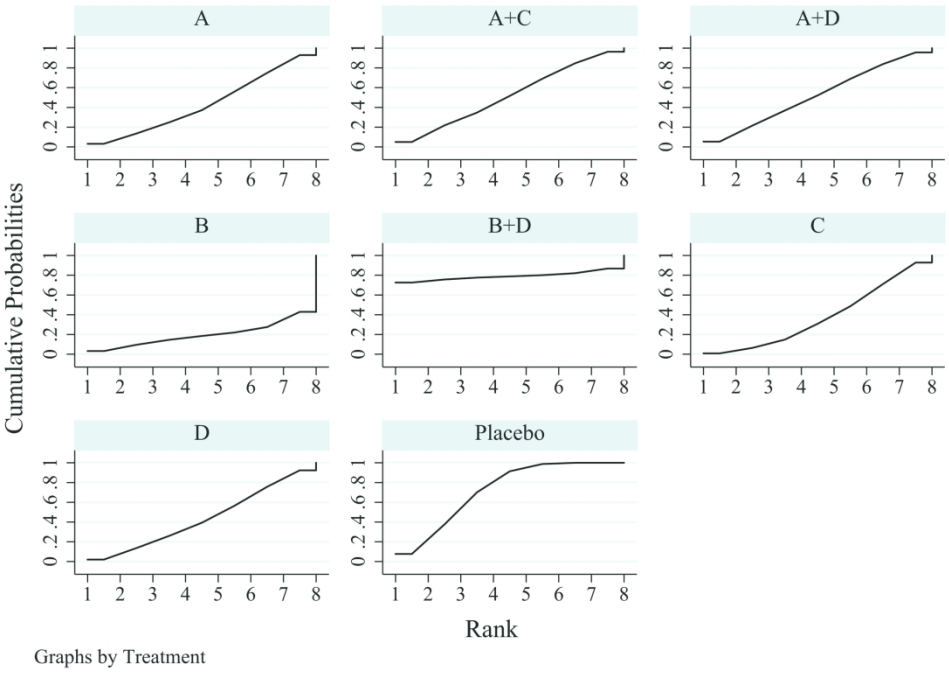

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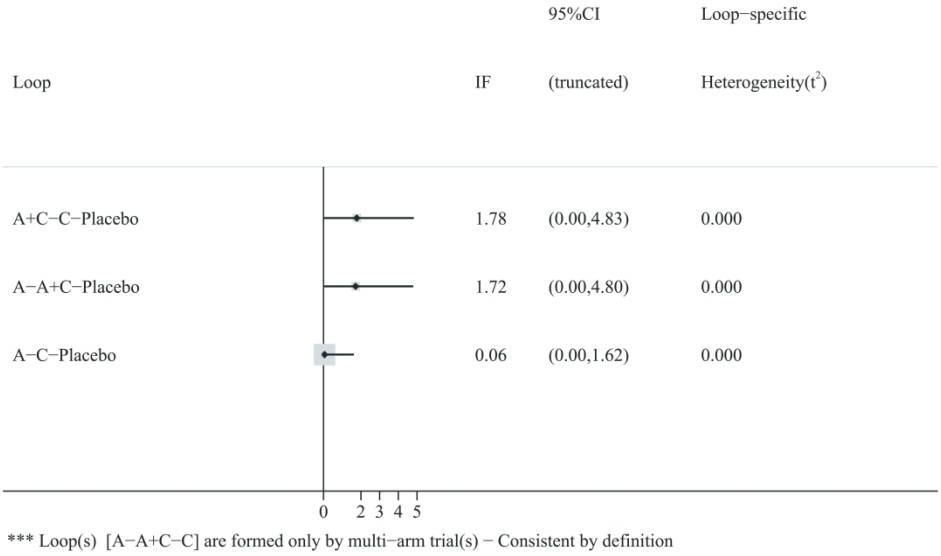

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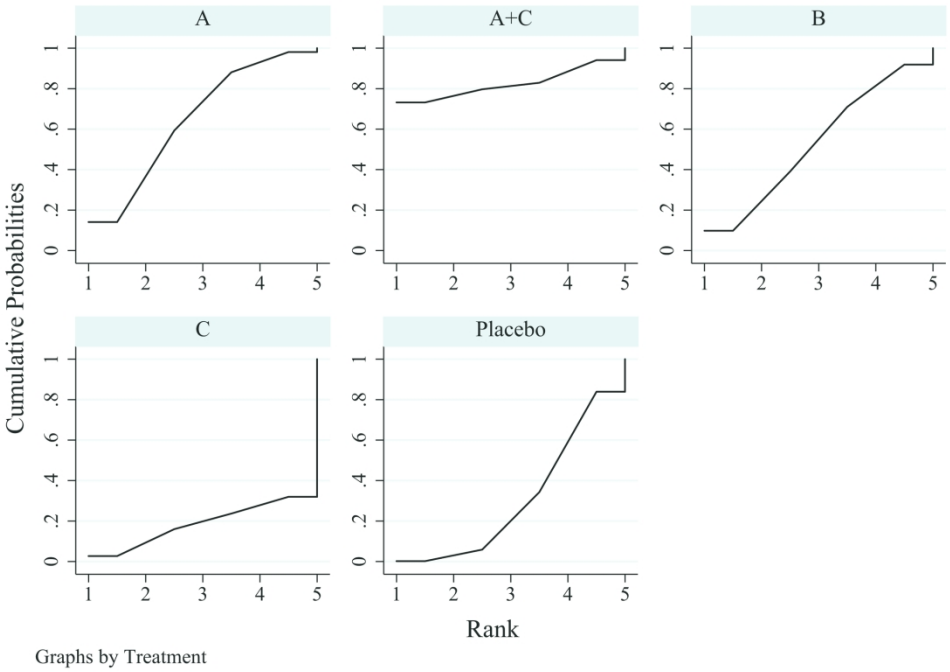

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Supplementary Table S1 - Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	NA

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Section/topic	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	8-10

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Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

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Source	Intervention	Women, No. (%)	Mean Age, y	Previous Fracture	Calcium Intake, mg/d	Baseline 25OHD, ng/mL	Treatment Duration
Avenell et al, 2004 (United Kingdom)[1]	Calcium(1 g/d) (n = 29) No treatment (n = 35)	NA a (83)	78 [b]	Yes	NA	NA	3.8 y
	D_3(800IU/d) (n = 35) No treatment (n = 35)	NA a (83)	78 [b]	Yes	NA	NA	3.8 y
	Calcium (1g/d) + D_3 (800IU/d) (n = 35) No treatment (n = 35)	NA a (83)	78 [b]	Yes	NA	NA	3.8 y
Baron et al, 1999 (United States)[2]	Calcium: 1.2 g/d (n = 464) Placebo (n = 466)	258 (28)	61.0	NA	877	NA	4 y
Dawson-Hughes et al, 1997 (United States)[3]	Calcium (0.5g/d) + D_3 (700IU/d) (n = 187) Placebo (n = 202)	213 (54)	71.1	NA	729	29.6 [e]	3 y
Glendenning et al, 2012 (Australia)[4]	D_3(150000 IU every 3 mo) (n = 353) Placebo (n = 333)	686 (100)	76.7	NA	864	26.3 [e]	9 mo
Grant et al, 2005 (United Kingdom)[5]	Calcium(1 g/d) (n = 1311) Placebo (n = 1332)	2241 (85)	77	Yes	NA	15.2 [e,f]	2-5 y
	D_3(800IU/d) (n = 1343) Placebo (n = 1332)	2264 (85)	77	Yes	NA	15.2 [e,f]	2-5 y
	Calcium (1g/d) + D_3 (800IU/d) (n = 1306) Placebo (n = 1332)	2232 (85)	77.5	Yes	NA	15.2 [e,f]	2-5 y
Hansson and Roos, 1987 (Sweden)[6]	Calcium (1g/d) (n = 25) Placebo (n = 25)	50 (100)	65.9	Yes	NA	NA	3 y
Harwood et al, 2004 (United Kingdom)[7]	D_3 (300000 IU once) (n = 38) No treatment (n = 37)	75 (100)	80.5	Yes	NA	11.6	1 y
	Calcium (1g/d) + D_2 (300000 IU once) (n = 36) Calcium (1g/d) + D_3 (800IU/d) (n = 39) No treatment (n = 37)	112 (100)	81.7	Yes	NA	11.9	1 y

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Hin et al, 2017 (United Kingdom)[8]	D_3(4000 IU/d)(n = 102) D_3(2000 IU/d)(n = 102) Placebo (n = 101)	150 (49)	71.7	Partial [c]	710	20.1	1 y
Inkovaara et al, 1983 (Finland)[9]	Calcium (1.2 g/d) (n = 42) Placebo (n = 42)	69 (82)	80.1	NA	NA	NA	9 mo
	D_3(1000 IU/d) (n = 45) Placebo (n = 42)	71 (82)	79.6	NA	NA	NA	9 mo
	Calcium (1.2g/d) + D_3(1000 IU/d) (n = 46) Placebo (n = 42)	69 (78)	79.0	NA	NA	NA	9 mo
Jackson et al, 2006 (United States)[10]	Calcium (1g/d) + D_3 (400 IU/d) (n = 4015) Placebo (n = 3957)	7972 (100)	62.4	Partial [c]	1151	18.9 [e]	7 y
Lips et al, 1996 (The Netherlands)[11]	400 IU/d (n = 1291) Placebo (n = 1287)	1916 (74)	80.0	No hip fracture	868	10.6 [e]	3-4 y
Liu et al, 2015 (China)[12]	Calcium (1.5g/d) + D_3 (600 IU/d) (n = 50) Placebo (n = 48)	98 (100)	62.1	No	1500	NA	1 y
Massart et al, 2014 (Belgium)[13]	D_3(25000 IU every week) (n = 26) Placebo (n = 29)	21 (38)	64.1	NA	881	17.8	3 mo
Mitri et al, 2011 (United States)[14]	D_3(2000 IU/d)(n = 23) Placebo (n = 24)	25 (53)	58.0	NA	926	25.3	4 mo
Peacock et al, 2000 (United States)[15]	Calcium (0.75g/d) (n = 126) Placebo (n = 135)	187 (72)	73.8	Partial [c]	597	25.0	4 y
Porthouse et al, 2005 (United Kingdom)[16]	Calcium (1g/d) + D_3 (800 IU/d) (n = 1321) No treatment (n = 1993)	3314 (100)	76.8	Partial [c]	1080	NA	1.5-3.5 y
Prince et al, 2006 (Australia)[17]	Calcium (0.48g/d) (n = 730) Placebo (n = 730)	1460 (100)	75.2	Partial [c]	915	31.0 [e]	5 y
Punthakee et al, 2012 (Canada)[18]	D_3 (1000 IU/d) (n = 607) Placebo (n = 614)	499 (41)	66.6	Partial [c]	NA	NA	4 mo
Recker et al, 1996 (United States)[19]	Calcium (1.2 g/d) (n = 95) Placebo (n = 102)	197 (100)	73.5	Partial [c]	434	25.5 [e]	4 y
Reid et al, 1993 (New Zealand)[20]	Calcium (1 g/d) (n = 68) Placebo (n = 67)	135 (100)	58	No vertebral fracture	750	37.5	4 y

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Reid et al, 2006 (New Zealand)[21]	Calcium (1 g/d) (n = 732) Placebo (n = 739)	1471 (100)	74.3	Partial [c]	857	20.7	5 y
Riggs et al, 1998 (United States)[22]	Calcium (1.6 g/d) (n = 119) Placebo (n = 117)	236 (100)	66.2	No	714	30.1	4 y
Salovaara et al, 2010 (Finland)[23]	Calcium(1g/d) + D_3 (800 IU/d) (n = 1718) No treatment (n = 1714)	3432 (100)	67.3	Partial [c]	957	19.8 [e]	3 y
Sanders et al, 2010 (Australia)[24]	D_3 (500000 IU every year) (n = 1131) Placebo (n = 1127)	2258 (100)	76.1	Partial [c]	976	19.8 [e]	3-5 y
Smith et al, 2007 (United Kingdom)[25]	D_3 (300000 IU every year) (n = 4727) Placebo (n = 4713)	5086 (54)	79.1	Partial [c]	625 [d]	22.6 [e]	3 y
Trivedi et al, 2003 (United Kingdom)[26]	D_3 (100000 IU every 4 mo) (n = 1345) Placebo (n = 1341)	649 (24)	74.8	NA	742	NA	5 y
Uusi-Rasi et al, 2015 (Finland)[27]	D_3 (800 IU/d) (n = 102) Placebo (n = 102)	204 (100)	73.9	NA	1082	26.7	2 y
Witham et al, 2013 (United Kingdom)[28]	D_3(100000 IU every 3 mo) (n = 80) Placebo (n = 79)	77 (49)	76.8	NA	1125	18.0	1 y
Xue et al, 2017 (China)[29]	Calcium (0.6g/d) + D_3 (800 IU/d) (n = 139) Placebo (n = 173)	312 (100)	63.6	Partial [c]	NA	30.8	1 y

Abbreviation: 25OHD, 25-hydroxyvitamin D; NA, not available

[a] Women accounted for 83% of total participants in this trial, but detailed data not available for each group.

[b] Mean age is 78 y for total participants in this trial, but detailed data not available for each group.

[c] This trial reported partial participants with fracture history.

[d] Partial participants were assessed for dietary calcium intake.

[e] Partial participants received measurement of baseline 25OHD concentrations.

[f] The RECORD trial reported that the mean baseline 25OHD concentrations for a sample of 60 participants was 15.2 ng/mL, but detailed data were not available for each group.

supplementary Table 1. The characteristics of the included studies.

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References

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Source	Treatment Duration	Intervention	No. of Participants		
			Total Fracture	Hip fracture	Vertebral Fracture
Avenell et al, 2004 (United Kingdom)[1]	3.8 y	Calcium(1 g/d) (n = 29)	4	1	0
		D_3(800IU/d) (n = 35)	3	0	0
		Calcium (1g/d) + D_3 (800IU/d) (n = 35)	2	1	0
		No treatment (n = 35)	4	1	1
Baron et al, 1999 (United States)[2]	4 y	Calcium: 1.2 g/d (n = 464)	4	1	
		Placebo (n = 466)	14	0	
Dawson-Hughes et al, 1997 (United States)[3]	3 y	Calcium (0.5g/d) + D_3 (700IU/d) (n = 187)		0	
		Placebo (n = 202)		1	
Glendenning et al, 2012 (Australia)[4]	9 mo	D_3(150000 IU every 3 mo) (n = 353)	10	0	
		Placebo (n = 333)	10	1	
Grant et al, 2005 (United Kingdom)[5]	2-5 y	Calcium(1 g/d) (n = 1311)	166	49	3
		D_3(800IU/d) (n = 1343)	188	47	4
		Calcium (1g/d) + D_3 (800IU/d) (n = 1306)	165	46	0
		Placebo (n = 1332)	179	41	1
Hansson and Roos, 1987 (Sweden)[6]	3 y	Calcium (1g/d) (n = 25)			1
		Placebo (n = 25)			1
Harwood et al, 2004 (United Kingdom)[7]	1 y	D_3 (300000 IU once) (n = 38)	0	0	
		Calcium (1g/d) + D_2 (300000 IU once) (n = 36) Calcium (1g/d) + D_3 (800IU/d) (n = 39)	6	1	
		No treatment (n = 37)	5	1	
Hin et al, 2017 (United Kingdom)[8]	1 y	D_3(4000 IU/d)(n = 102) D_3(2000 IU/d)(n = 102)	6		
		Placebo (n = 101)	1		

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Inkovaara et al, 1983 (Finland)[9]	9 mo	Calcium (1.2 g/d) (n = 42)	1		
		D_3(1000 IU/d) (n = 45)	1		
		Calcium (1.2g/d) + D_3(1000 IU/d) (n = 46)	0		
		Placebo (n = 42)	3		
Jackson et al, 2006 (United States)[10]	7 y	Calcium (1g/d) + D_3 (400 IU/d) (n = 4015)		70	
		Placebo (n = 3957)		61	
Lips et al, 1996 (The Netherlands)[11]	3-4 y	400 IU/d (n = 1291)	135	58	
		Placebo (n = 1287)	122	48	
Liu et al, 2015 (China)[12]	1 y	Calcium (1.5g/d) + D_3 (600 IU/d) (n = 50)	1		
		Placebo (n = 48)	2		
Massart et al, 2014 (Belgium)[13]	3 mo	D_3(25000 IU every week) (n = 26)	0		
		Placebo (n = 29)	5		
Mitri et al, 2011 (United States)[14]	4 mo	D_3(2000 IU/d)(n = 23)	1		
		Placebo (n = 24)	0		
Peacock et al, 2000 (United States)[15]	4 y	Calcium (0.75g/d) (n = 126)			7
		Placebo (n = 135)			13
Porthouse et al, 2005 (United Kingdom)[16]	1.5-3.5 y	Calcium (1g/d) + D_3 (800 IU/d) (n = 1321)	58	8	
		No treatment (n = 1993)	91	17	
Prince et al, 2006 (Australia)[17]	5 y	Calcium (0.48g/d) (n = 730)	110	11	38
		Placebo (n = 730)	126	6	39
Punthakee et al, 2012 (Canada)[18]	4 mo	D_3 (1000 IU/d) (n = 607)	3		
		Placebo (n = 614)	3		
Recker et al, 1996 (United States)[19]	4 y	Calcium (1.2 g/d) (n = 95)			27
		Placebo (n = 102)			34
Reid et al, 1993 (New Zealand)[20]	4 y	Calcium (1 g/d) (n = 68)	2	0	0
		Placebo (n = 67)	7	2	1
Reid et al, 2006 (New Zealand)[21]	5 y	Calcium (1 g/d) (n = 732)	134	17	27
		Placebo (n = 739)	147	5	38
Riggs et al, 1998	4 y	Calcium (1.6 g/d) (n = 119)			8

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(United States)[22]		Placebo (n = 117)			9
Salovaara et al, 2010 (Finland)[23]	3 y	Calcium(1g/d) + D_3 (800 IU/d) (n = 1718)	78	4	9
		No treatment (n = 1714)	94	2	13
Sanders et al, 2010 (Australia)[24]	3-5 y	D_3 (500000 IU every year) (n = 1131)	155	19	35
		Placebo (n = 1127)	125	15	
Smith et al, 2007 (United Kingdom)[25]	3 y	D_3 (300000 IU every year) (n = 4727)		66	
		Placebo (n = 4713)		44	
Trivedi et al, 2003 (United Kingdom)[26]	5 y	D_3 (100000 IU every 4 mo) (n = 1345)	119	21	18
		Placebo (n = 1341)	149	24	28
Uusi-Rasi et al, 2015 (Finland)[27]	2 y	D_3 (800 IU/d) (n = 102)	6	2	
		Placebo (n = 102)	6	0	
Witham et al, 2013 (United Kingdom)[28]	1 y	D_3(100000 IU every 3 mo) (n = 80)	2		
		Placebo (n = 79)	3		
Xue et al, 2017 (China)[29]	1 y	Calcium (0.6g/d) + D_3 (800 IU/d) (n = 139)	3		
		Placebo (n = 173)	2		

Supplementary Table 2. The detailed data of outcomes

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Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials

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Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials

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Abstract

Objective Inconsistent findings in regard to association between different concentrations of vitamin D, calcium or their combination and the risk of fracture have been reported during the past decade in community-dwelling older people. This study was designed to compare the fracture risk using different concentrations of vitamin D, calcium or their combination.

Design A systematic review and network meta-analysis.

Data sources Randomized controlled trials in PubMed, Cochrane library, and EMBASE databases were systematically searched from the inception dates to December 31, 2017.

Outcomes Total fracture was defined as the primary outcome. Secondary outcomes were hip fracture and vertebral fracture. Due to the consistency of the original studies, a consistency model was adopted.

Results A total of 25 randomized controlled trials involving 43510 participants fulfilled the inclusion criteria. There was no evidence that the risk of total fracture was reduced by using different concentrations of vitamin D, calcium or their combination compared with placebo or no treatment. No significant associations were found between calcium, vitamin D, or combined calcium and vitamin D supplements and the incidence of hip, or vertebral fractures.

Conclusions The use of supplements that included calcium, vitamin D, or both was not found to be better than placebo or no treatment in terms of risk of fractures among community-dwelling older adults. It means the routine use of these supplements in community-dwelling older people should be treated more carefully.

Prospero registration number CRD42017079624

Keywords: Calcium; Vitamin D; Fractures; network meta-analysis

Strengths and limitations of this study

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- This systematic review and meta-analysis combined the evidence from randomized controlled trials.
- Our findings may not support the routine use of these supplements in community-dwelling older people.
- This work does not necessarily preclude any benefit of vitamin D and calcium supplementation in older, frail individuals.
- Potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence.

Introduction

Clinical fractures of the elderly represent a worldwide public health problem that leads to illness and social burden. The patients with osteoporosis in the European Union were estimated to be 27.5 million in 2010, and 3.5 million new fragility fractures were sustained[1]. In Asia, the average cost of osteoporotic fractures accounted for 18.95% of the countries' 2014 gross domestic product (GDP)/capita and increased annually[2-4]. The overall prevalence of osteoporosis or low bone mass in non-institutional population over the age of 50 in the USA was estimated at 10.3% and 43.9%, respectively, which means that 10.2 million elderly people had osteoporosis and 43.4 million people had low bone mass in 2010[5]. With the demographic trend of ageing and the predicted increase in life expectancy, the cost of fracture treatment is expected to rise.

Dietary allowances for calcium range from 700 to 1200 mg/d and vitamin D of 600-800 IU/d have long been recommended for the prevention of osteoporotic fractures in the elderly[6 7]. The supplements of calcium and vitamin D are commonly taken to maintain bone health.

However, the previous randomized controlled trials (RCT) and meta-analyses concerning vitamin D, calcium, or their combination for fractures yielded different efficacy outcomes. For instance, two meta-analyses demonstrated calcium or vitamin D supplementation alone has a small benefit on bone

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mineral density (BMD), but no clinically important to prevent fractures[8 9], while an updated meta-analysis and a pooled analysis found calcium plus vitamin D supplementation can significantly reduce hip fractures by 30% and total fractures by 15%[10 11]. Two RCTs reported that low dose of vitamin D supplementation (less than 800 IU/d) can reduce the incidence of falls[12] and may prevent fractures without adverse effects[13], but other RCTs showed no significant reduction in the incidence of hip or other peripheral fractures[14 15] and its possible effects were seen only in patients with initial calcium insufficiency. Based on the evidence from meta-analysis, Bischoff-Ferrari et al [16] illustrated that high-dose vitamin D supplementation (800 IU/d or higher) not only reduced the risk of falls and hip fractures, but also prevented non-vertebral fractures. In contrast, a study reported annual high-dose oral vitamin D resulted in an increased risk of falls and fractures [17]. On the other hand, low-dose calcium supplementation (less than 800mg/d) effectively led to a sustained reduction in the rate of bone loss [18] and turnover. Although it was also reported that the high dose of calcium (800 mg/d or higher) was associated with a lower risk of clinical fractures [19]. The high-dose calcium with high-dose vitamin D can't prevent fractures according to the evidence from reported RCT [20], but a meta-analysis supported their combination can prevent bone loss and significantly reduce the risk of hip fractures and all osteoporotic fractures [21]. Thus, it's challenging to conclude a dose-response relation between the intakes of vitamin D, calcium, or their combination and the main outcomes in these heterogeneous literatures.

Therefore, this study was designed to compare the fracture risk using different concentrations of vitamin D, calcium or their combination, and comprehensively evaluate the optimal concentration to guide clinical practice and public prevention in community-dwelling older people.

Methods

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Search strategy and selection criteria

This review and meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for network meta-analysis. Our meta-analysis was registered prospectively in PROSPERO (CRD42017079624) and the Checklist PRISMA 2009 (**Supplementary Table 1**) will be used and check our final reports [22].

We restricted our meta-analysis to the inclusion criteria should meet following details: (1) RCTs; (2) Interventions must be one of the following three: vitamin D only, calcium only, both vitamin D and calcium; (3) Complete outcome data of fracture; (4) Trials enrolling adults older than 50 years and living in their communities; (5) Only studies that lasted more than a year. Exclusion criteria were (1) Calcium or vitamin D combined with other therapies (eg: hormones, exercise); (2) Trials in which vitamin D analogues (eg: calcitriol) or hydroxylated vitamin D were used; (3) Trials in which dietary intake of calcium or vitamin D (eg: from milk) was evaluated; (4) Patients suffering from illness or long-term use of certain drugs affecting the stability of the calcium metabolism, such as metabolic bone disease, bone tumour, treatment of steroids and so on.

Participants must be randomly assigned to two or more following groups: (1) high calcium (800 mg/d or higher) only; (2) low calcium (less than 800 mg/d) only; (3) high vitamin D (800 IU/d or higher) only; (4) low vitamin D (less than 800 IU/d) only; (5) high calcium (800 mg/d or higher) + high vitamin D (800 IU/d or higher); (6) high calcium + low vitamin D (less than 800 IU/d); (7) low calcium (less than 800 mg/d) + high vitamin D; (8) low calcium + low vitamin D; (9) placebo. The interventions should be compared with placebo.

Two authors (ZHF and GZ) independently searched the electronic literature database of PubMed, Embase, Cochrane database on December 31, 2017 (detailed search strategies are reported

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in **supplementary eTable 1**). Related articles and reference lists were searched to avoid original miss. The reference studies of previous systematic reviews, meta-analysis, and included studies were manually searched to avoid initial miss. After 2 authors assessed the potentially eligible studies independently, any disagreement was discussed and resolved with the third independent author (QT).

Data collection and assessment of risk of bias

Two reviewers (ZHS and XBL) independently extracted data, and the third reviewer (LT) checked the consistency between them. A standard data extracted form was used at this stage, including the authors, publishing date, country, participant characteristics; doses of calcium, vitamin D, or their combination; dietary calcium intake; baseline serum 25-hydroxyvitamin D concentration; and trial duration. For continuous outcomes, the mean, SD (standard deviation) and participant number will be extracted. For dichotomous outcomes, we extracted the total numbers and the numbers of events of both groups. The data in other forms was recalculated when possible to enable pooled analysis.

We used the Cochrane risk of bias tool to assess risk bias of included studies. The tool has seven domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The classification of the judgment for each domain was low risk of bias, high risk of bias, or unclear risk of bias and two authors (ZHF and GZ) independently evaluated the risk of studies.

Data synthesis and statistical analysis

The data was extracted and input into the STATA software (version 12.0; StataCorp, College Station, TX, USA) for network meta-analysis. And we generated network plots for each outcome to illustrate which interventions had been compared directly in the included studies. Network meta-analysis is an extension of standard meta-analysis to compare multiple treatments based on

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randomized controlled trial evidence, which forms a connected network of comparisons. Treatment effect estimates from network meta-analysis exploit both the direct comparisons within trials and the indirect comparisons across trials. The heterogeneity was further assessed with the I^2 statistic and a value of more than 50% was considered as statistically significant heterogeneity. Random effects model was applied when significant heterogeneity existed ($P < 0.05$ or I^2 test exhibited > 50%), otherwise, fixed-effects model was utilized[23]. Relative risk (RR) with 95% confidence intervals (CIs) was calculated for dichotomous outcomes while weighted mean difference (WMD) with 95% CIs for the continuous. Inconsistency refers to differences between direct and various indirect effect estimates for the same comparison. To assess inconsistency, we estimated the inconsistency factors in closed loop based on the method described by Chaimani et al[24]. The heterogeneity in each closed loop was estimated by utilizing inconsistency factor (IF). If the 95% confidence intervals (95% CI) of IF values are not truncated at zero, it suggests that the inconsistency among studies has statistical significance. We used the surface under the cumulative ranking probabilities (SUCRA) to indicate which treatment was the best one. The funnel plot was used to identify possible publication bias if the number of studies was larger than 10.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, and no patients were involved in developing plans for design or implementation of the study. Furthermore, no patients were asked to advice on interpretation or writing up of results. Since this meta-analysis used aggregated data from previous trials, it is unable to disseminate the results of the research to study participants directly.

Result

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Data Retrieval

In summary, a total of 7909 potential records were initially identified through PubMed (5187), Embase (2688), Cochrane Data base (34). Based on our review of the title and abstract, 99 full-text papers were reviewed and 25 studies[13 17 19 20 25-45] met inclusion criteria (**Figure 1)**.

Study and Patient Characteristics

The characteristics of all 25 included studies were summarized and shown in **supplementary Table 2**. And the detailed data of outcomes was collected in **supplementary Table 3**. The papers had similar distributions of sex, age, country, intervention and all of them were community-dwelling older people. Hansson et al[29] did not report the residential status of participants, although a previous meta-analysis classified this status as community. The trial by Hansson et al was included, but a sensitivity analysis was performed that excluded that trial (**supplementary Figure 1**).

Supplementary Figure 2 showed the assessment of the risk of bias. All studies were randomized; 17 were double-blind, placebo-controlled trials; 13 trials described an adequate random sequence generation process; and 11 trials described the methods used for allocation concealment. No obvious publication bias was reported according to the **supplementary Figure 3, supplementary Figure 4** and **supplementary Figure 5**.

Inconsistence and heterogeneity check

The statistical inconsistency between direct and indirect comparisons was generally low according to inconsistency test because the CI values included zero (**supplementary Figure 6, supplementary Figure 7, supplementary Figure 8**). Therefore, we adopted a consistency model in all three groups. Meanwhile, the global heterogeneity parameter I^2 values were 8.4%, 0% and 0% respectively, which indicated no obvious heterogeneity was observed in all these results (**supplementary Figure 9,**

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supplementary Figure 10, supplementary Figure 11).

Primary outcome: total fracture

For estimating the vitamin D, calcium or their combination efficacy against total fractures, we looked at data from 24965 individuals from 18 studies[13 17 19 20 25 26 28 30 31 33-35 37 39 40 43-45]. Pooled estimates included 15 studies with one treatment, 1 study with two treatments, and 2 studies with three treatments.

The network plot of comparisons on total fractures was shown in **Figure 2A**. The forest plot for the network meta-analysis was shown in **Figure 3**. The RR values and 95% CIs are summarized in **Figure 3**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between interventions and placebo (P<0.05). So we didn't continue to make ranking graph of distribution of probabilities on total fractures.

Secondary outcomes: **hip fracture and vertebral fracture**

A total of 41845 individuals were included from 16 studies[13 17 19 20 25-28 30 32 33 37 39 40 42 43] for evaluate the drug efficacy against hip fractures. Pooled estimates included 13 studies with one treatment, 1 study with two treatments, and two studies with three treatments.

The network plot of comparisons on hip fractures was shown in **Figure 2B**. The forest plot for the network meta-analysis was shown in **Figure 4**. The RR values and 95% CIs are summarized in **Figure 4**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between drug experimental groups and placebo (P<0.05). So we didn't continue to make ranking graph of distribution of probabilities on total fractures.

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A total of 17612 individuals were collected from 12 studies[13 17 19 20 25 28 29 36 38-41] involving vertebral fractures. Pooled estimates included 10 studies with one treatment, and two studies with three treatments.

The network plot of comparisons on vertebral fractures was shown in **Figure 2C**. The forest plot for the network meta-analysis was shown in **Figure 5**. The RR values and 95% CIs are summarized in **Figure 5**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between drug experimental groups and placebo ($P<0.05$). So we didn't continue to make ranking graph of distribution of probabilities on total fractures. In a separate sensitivity analysis, we excluded Hansson's study[29] (**supplementary Figure 1**). However, there was still no significant association of vitamin D, calcium or their combination with total fracture.

Discussion

Vitamin D supplementation and calcium are suggested as interventions to treat and prevent fracture. We found the previous meta-analyses and RCTs are critically inconsistent in efficacy of different doses of vitamin D with calcium on fractures.

Results of this meta-analysis showed that calcium, calcium plus vitamin D, and vitamin D supplementation alone were not significantly associated with a lower incidence of hip, vertebral, or total fractures in community-dwelling older adults. Sensitivity analyses that excluded low-quality trials and studies that exclusively enrolled patients with particular medical conditions did not alter these results.

A meta-analysis conducted by Jia-Guo Zhao et al[46] showed that no significant difference was found in the incidence of hip or other fractures, which was similar to our result. However, the object of

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Zhao's study was to investigate whether calcium, vitamin D, or combined calcium and vitamin D supplement are associated with a lower facture incidence while our study was designed to evaluate the optimal concentration of them. Meanwhile, in Zhao's meta-analysis, the participants of the included study reported by Massart[47] were adult maintenance hemodialysis patients, which may result in the imbalance of calcium in the body. Patients on hemodialysis may also be receiving 1,25-dihydroxyvitamin D, which may affect their response to vitamin D supplementation. So we did not include that trial in our network meta-analysis. What's more, we didn't include studies that lasted less than a year because we thought this time-frame was too short to see anti-fracture efficacy. And we suspected that a network meta-analysis might be a more suitable choice concerning all these different interventions mixed.

Bischoff-Ferrari et al [48] reported that high-dose vitamin D supplementation (800 IU/d or higher) played an important role in the reduction of the risk of falls and hip fractures, as well as prevented non-vertebral fractures in adults 65 years or older. However, their findings may have been influenced by the trial of Chapuy et al [49], which only enrolled participants living in an institution. What's more, differences in conclusions of previous meta-analyses and the current meta-analysis were due to the recently published trials which reported neutral or harmful associations of vitamin D supplementation and fracture incidence more and more. Study findings here indicated that vitamin D might result in a higher risk for hip fracture, but this conclusion did not reach statistical significance. This finding may be attributable to lack of statistical power in this meta-analysis.

Most recently there was a meta-analysis published in the Lancet by Bolland et al[50], whose findings suggested that vitamin D supplementation does not prevent fractures or falls, or have clinically meaningful effects on bone mineral density. Although it was similar to our study to some extent, they

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are really different. First, we only included community-dwelling older people. We found that some meta-analyses equated community-dwelling older people with those in nursing institution. The lack of exercise, dietary intake and exposure to sunlight made people in nursing institution turned more susceptible to the use of supplements including vitamin D, calcium or their combination. Although the studies involving participants living in nursing institution were only a small part, but it could change the whole outcomes and produce false positive results. We found only Avenell's study paid attention to this question when they conducted a subgroup analysis, but they did not discussed separately. Meanwhile, we only enrolled adults older than 50 years and trial duration more than 1 year to reduce the statistical heterogeneity in network meta-analysis. Furthermore, the current analyses included calcium supplementation, where the Bolland's study focused on vitamin D.

However, possible limitations of this study protocol include potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence. Some RCTs were of poor quality and, for example, used unclear allocation concealment. So we made a sensitivity analysis by excluding low-quality trials. Although some study characteristics such as baseline serum 25-hydroxyvitamin D concentrations might be to contribute heterogeneity, we could not perform subgroup analysis or meta-regression analysis to evaluate it due to the extreme complexity and the limitation of Stata software for network meta-analysis. What's more, we combined bolus dosing by injection with oral supplements taken daily/monthly/yearly, which might have different effects on vitamin D status in the body. In addition, the report ignored the effect of treatment with vitamin D on plasma 25-hydroxy-vitamin D concentrations and sub-types of fracture, such as pathologic fractures; this work does not necessarily preclude any benefit of vitamin D and calcium supplementation in older, frail individuals.

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Conclusions

In this meta-analysis of randomized clinical trials, we found that the use of different concentrations of vitamin D, calcium or their combination in community-dwelling older adults was not associated with a lower risk of fractures. Our findings may not support the routine use of these supplements in community-dwelling older people.

Contributors

ZCH and AMW conceived the study. The search strategy was developed by LT and XBL. ZHF, GZ and QT will complete electronic search, select publications and assess their eligibility. ZHS and XBL will extract information of the included studies after screening. JWX will check the data entry for accuracy and completeness. ZCH and LT will give advice for data analysis and presentation of study result. LYS and CMS contributed to the text revision. WFN and AMW supervised the overall conduct of the study. All the authors drafted and critically reviewed and approved the final manuscript.

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Conflicts of interest

None declared

Patient consent

Not required.

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Provenance and peer review

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Data sharing statement

No additional data are available.

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Figure 1. The selection of literature for included studies.

Figure 2. The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral fractures (C). A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

Figure 3. The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

Figure 4. The forest plot for the risk of hip fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

Figure 5. The forest plot for the risk of vertebral fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 1. A sensitivity analysis excluded the trial of Hansson et al. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

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supplementary Figure 2. Risk of Bias Assessment of All Included Studies

supplementary Figure 3. Publication bias for the total fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 4. Publication bias for the hip fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 5. Publication bias for the vertebral fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 6. Inconsistency test for the total fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 7. Inconsistency test for the hip fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

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supplementary Figure 8. Inconsistency test for the vertebral fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 9. Heterogeneity test for the total fractures.

supplementary Figure 10. Heterogeneity test for the hip fractures.

supplementary Figure 11. Heterogeneity test for the vertebral fractures.

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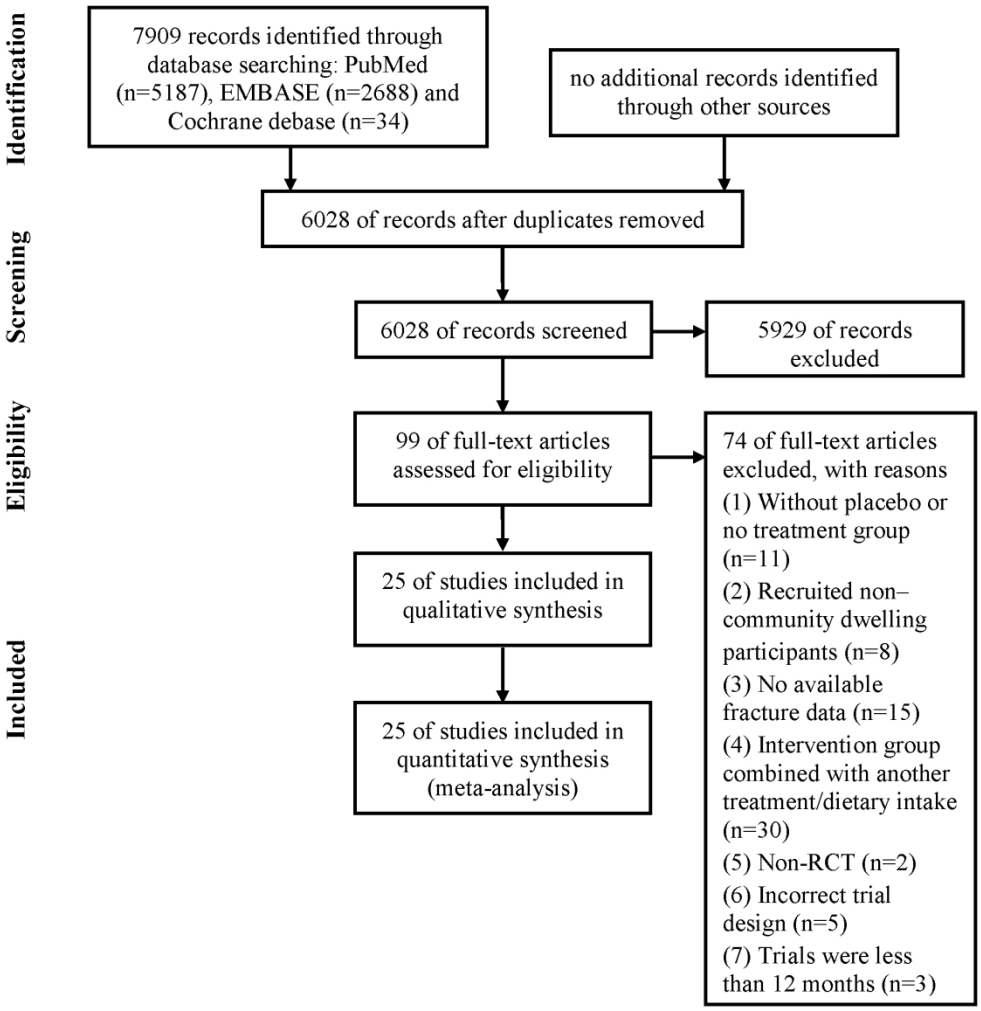

The selection of literature for included studies.

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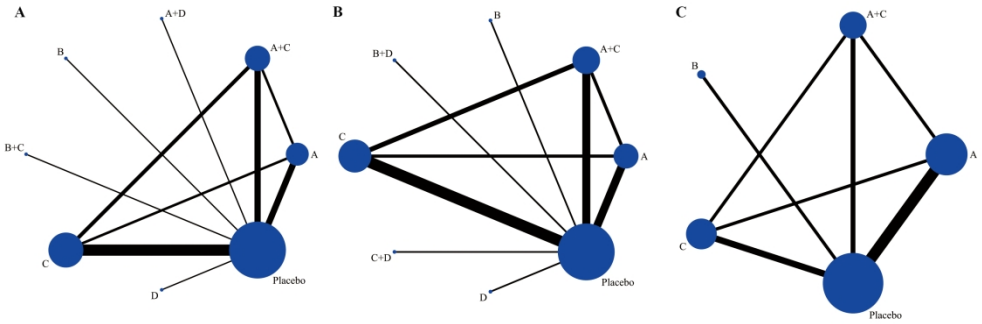

The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral fractures (C). A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)

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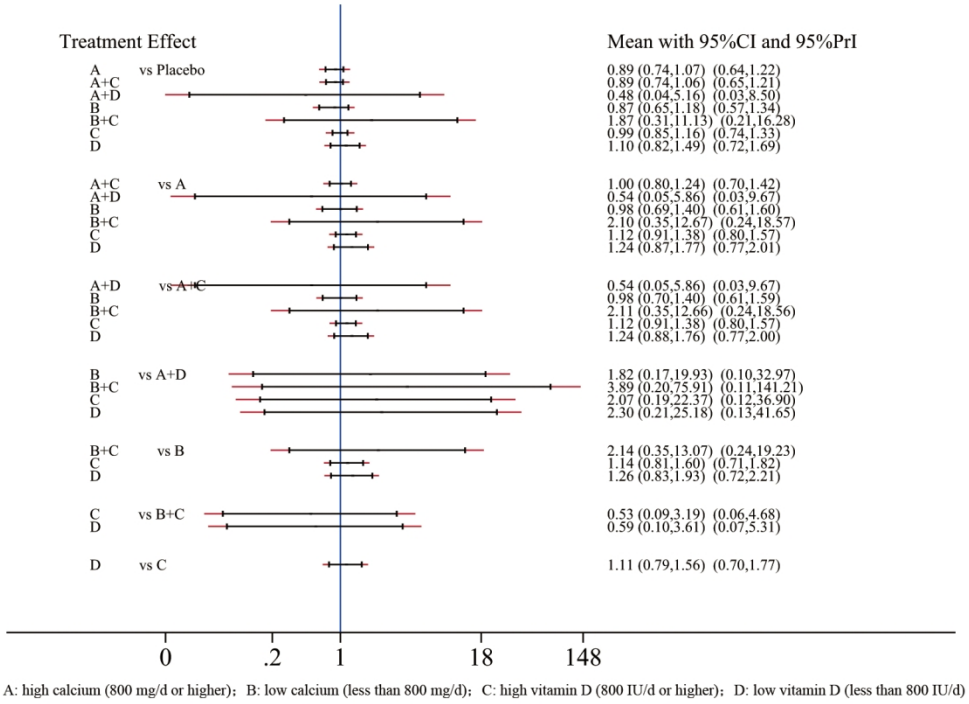
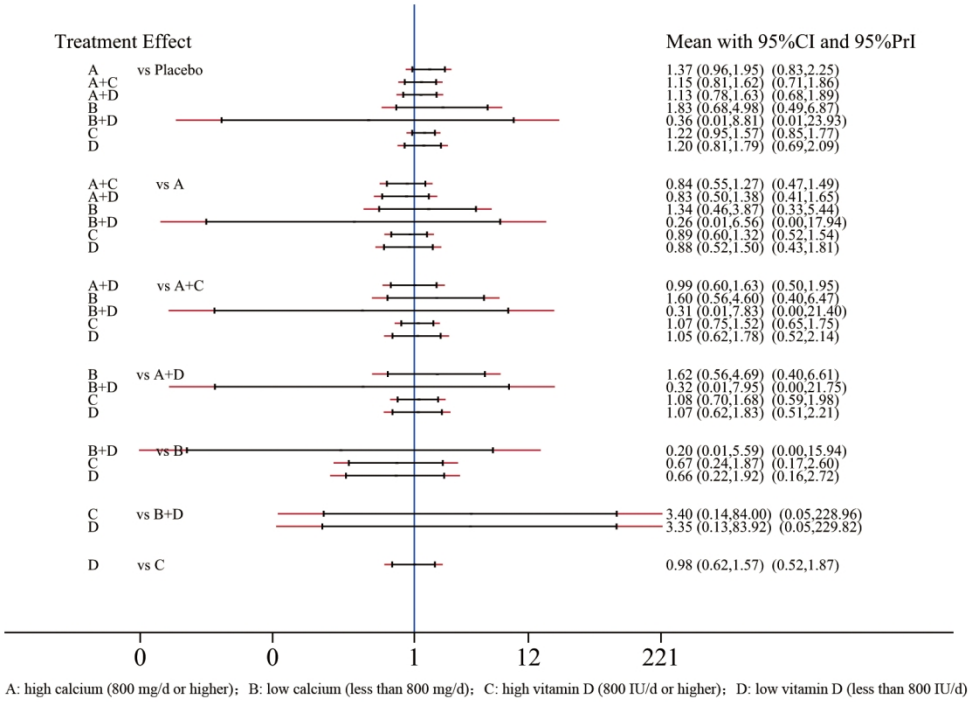
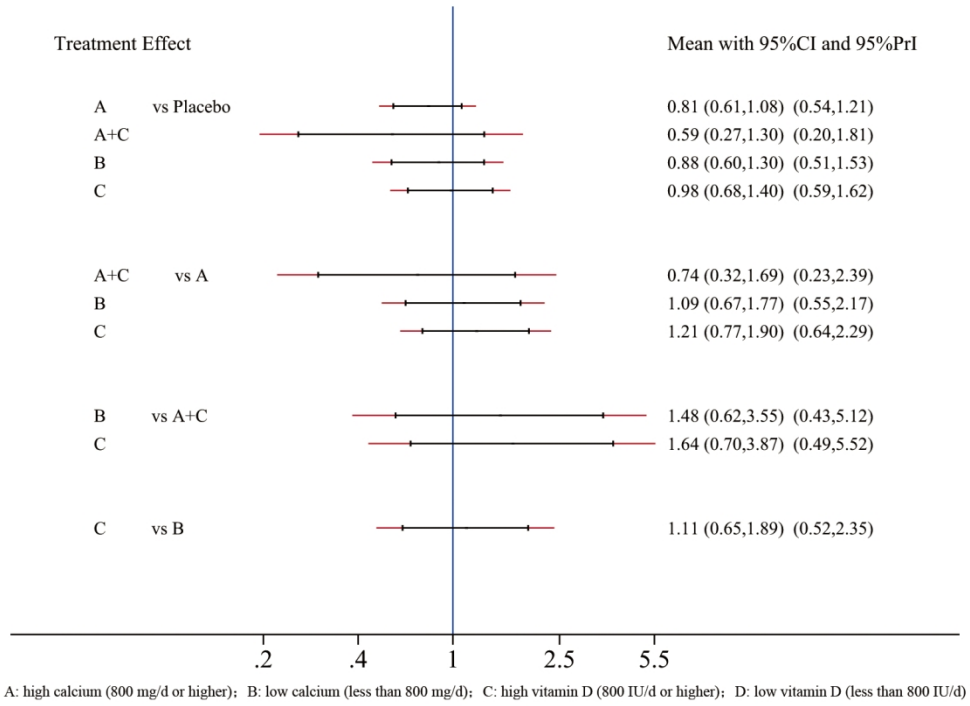


The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)



The forest plot for the risk of hip fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)



The forest plot for the risk of vertebral fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)

Supplementary eTable 1. Search Strategy for Each Database

Database	Search strategy
Pubmed	#1 "calcium"[MeSH Terms] OR "calcium"[All Fields]
	#2 "vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]
	#3 "fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields]
	#4 #1 or #2
	#5 #3 and #4

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Supplementary Table 1 - Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5

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Section/topic	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10

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Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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Source	Intervention	Women, No. (%)	Mean Age, y	Previous Fracture	Calcium Intake, mg/d	Baseline 25OHD, ng/mL	Treatment Duration
Avenell et al, 2004 (United Kingdom)	Calcium(1 g/d) (n = 29)	NA [a] (83)	78 [b]	Yes	NA	NA	3.8 y
	No treatment (n = 35)						
	D_3(800IU/d) (n = 35)	NA [a] (83)	78 [b]	Yes	NA	NA	3.8 y
	No treatment (n = 35)						
	Calcium (1g/d) + D_3 (800IU/d) (n = 35)	NA [a] (83)	78 [b]	Yes	NA	NA	3.8 y
	No treatment (n = 35)						
Baron et al, 1999 (United States)	Calcium: 1.2 g/d (n = 464)	258 (28)	61.0	NA	877	NA	4 y
	Placebo (n = 466)						
Dawson-Hughes et al, 1997 (United States)	Calcium (0.5g/d) + D_3 (700IU/d) (n = 187)	213 (54)	71.1	NA	729	29.6 [e]	3 y
	Placebo (n = 202)						
Grant et al, 2005 (United Kingdom)	Calcium(1 g/d) (n = 1311)	2241 (85)	77	Yes	NA	15.2 [e,f]	2-5 y
	Placebo (n = 1332)						
	D_3(800IU/d) (n = 1343)	2264 (85)	77	Yes	NA	15.2 [e,f]	2-5 y
	Placebo (n = 1332)						
	Calcium (1g/d) + D_3 (800IU/d) (n = 1306)	2232 (85)	77.5	Yes	NA	15.2 [e,f]	2-5 y
	Placebo (n = 1332)						
Hansson and Roos, 1987 (Sweden)	Calcium (1g/d) (n = 25)	50 (100)	65.9	Yes	NA	NA	3 y
	Placebo (n = 25)						
Harwood et al, 2004 (United Kingdom)	D_3 (300000 IU once) (n = 38)	75 (100)	80.5	Yes	NA	11.6	1 y
	No treatment (n = 37)						
	Calcium (1g/d) + D_2 (300000 IU once) (n = 36)	112 (100)	81.7	Yes	NA	11.9	1 y
	Calcium (1g/d) + D_3 (800IU/d) (n = 39)						
	No treatment (n = 37)						
Hin et al, 2017 (United Kingdom)	D_3(4000 IU/d)(n = 102)	150 (49)	71.7	Partial [c]	710	20.1	1 y
	D_3(2000 IU/d)(n = 102)						
	Placebo (n = 101)						
Jackson et al, 2006 (United States)	Calcium (1g/d) + D_3 (400 IU/d) (n = 4015)	7972 (100)	62.4	Partial [c]	1151	18.9 [e]	7 y

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	Placebo (n = 3957)						
Lips et al, 1996 (The Netherlands)	400 IU/d (n = 1291) Placebo (n = 1287)	1916 (74)	80.0	No hip fracture	868	10.6 [e]	3-4 y
Liu et al, 2015 (China)	Calcium (1.5g/d) + D_3 (600 IU/d) (n = 50) Placebo (n = 48)	98 (100)	62.1	No	1500	NA	1 y
Mitri et al, 2011 (United States)	D_3(2000 IU/d)(n = 23) Placebo (n = 24)	25 (53)	58.0	NA	926	25.3	4 mo
Peacock et al, 2000 (United States)	Calcium (0.75g/d) (n = 126) Placebo (n = 135)	187 (72)	73.8	Partial [c]	597	25.0	4 y
Porthouse et al, 2005 (United Kingdom)	Calcium (1g/d) + D_3 (800 IU/d) (n = 1321) No treatment (n = 1993)	3314 (100)	76.8	Partial [c]	1080	NA	1.5-3.5 y
Prince et al, 2006 (Australia)	Calcium (0.48g/d) (n = 730) Placebo (n = 730)	1460 (100)	75.2	Partial [c]	915	31.0 [e]	5 y
Recker et al, 1996 (United States)	Calcium (1.2 g/d) (n = 95) Placebo (n = 102)	197 (100)	73.5	Partial [c]	434	25.5 [e]	4 y
Reid et al, 1993 (New Zealand)	Calcium (1 g/d) (n = 68) Placebo (n = 67)	135 (100)	58	No vertebral fracture	750	37.5	4 y
Reid et al, 2006 (New Zealand)	Calcium (1 g/d) (n = 732) Placebo (n = 739)	1471 (100)	74.3	Partial [c]	857	20.7	5 y
Riggs et al, 1998 (United States)	Calcium (1.6 g/d) (n = 119) Placebo (n = 117)	236 (100)	66.2	No	714	30.1	4 y
Salovaara et al, 2010 (Finland)	Calcium(1g/d) + D_3 (800 IU/d) (n = 1718) No treatment (n = 1714)	3432 (100)	67.3	Partial [c]	957	19.8 [e]	3 y
Sanders et al, 2010 (Australia)	D_3 (500000 IU every year) (n = 1131) Placebo (n = 1127)	2258 (100)	76.1	Partial [c]	976	19.8 [e]	3-5 y
Smith et al, 2007 (United Kingdom)	D_3 (300000 IU every year) (n = 4727) Placebo (n = 4713)	5086 (54)	79.1	Partial [c]	625 [d]	22.6 [e]	3 y
Trivedi et al, 2003 (United Kingdom)	D_3 (100000 IU every 4 mo) (n = 1345) Placebo (n = 1341)	649 (24)	74.8	NA	742	NA	5 y
Yusi-Rasi et al, 2015	D_3 (800 IU/d) (n = 102)	204 (100)	73.9	NA	1082	26.7	2 y

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(Finland)	Placebo (n = 102)						
Witham et al, 2013 (United Kingdom)	D_3(100000 IU every 3 mo) (n = 80) Placebo (n = 79)	77 (49)	76.8	NA	1125	18.0	1 y
Xue et al, 2017 (China)	Calcium (0.6g/d) + D_3 (800 IU/d) (n = 139) Placebo (n = 173)	312 (100)	63.6	Partial [c]	NA	30.8	1 y

Abbreviation: 25OHD, 25-hydroxyvitamin D; NA, not available

[a] Women accounted for 83% of total participants in this trial, but detailed data not available for each group.

[b] Mean age is 78 y for total participants in this trial, but detailed data not available for each group.

[c] This trial reported partial participants with fracture history.

[d] Partial participants were assessed for dietary calcium intake.

[e] Partial participants received measurement of baseline 25OHD concentrations.

[f] The RECORD trial reported that the mean baseline 25OHD concentrations for a sample of 60 participants was 15.2 ng/mL, but detailed data were not available for each group.

supplementary Table 2. The characteristics of the included studies.

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Source	Treatment Duration	Intervention	No. of Participants		
			Total Fracture	Hip fracture	Vertebral Fracture
Avenell et al, 2004 (United Kingdom)	3.8 y	Calcium(1 g/d) (n = 29)	4	1	0
		D_3(800IU/d) (n = 35)	3	0	0
		Calcium (1g/d) + D_3 (800IU/d) (n = 35)	2	1	0
		No treatment (n = 35)	4	1	1
Baron et al, 1999 (United States)	4 y	Calcium: 1.2 g/d (n = 464)	4	1	
		Placebo (n = 466)	14	0	
Dawson-Hughes et al, 1997 (United States)	3 y	Calcium (0.5g/d) + D_3 (700IU/d) (n = 187)		0	
		Placebo (n = 202)		1	
Grant et al, 2005 (United Kingdom)	2-5 y	Calcium(1 g/d) (n = 1311)	166	49	3
		D_3(800IU/d) (n = 1343)	188	47	4
		Calcium (1g/d) + D_3 (800IU/d) (n = 1306)	165	46	0
		Placebo (n = 1332)	179	41	1
Hansson and Roos, 1987 (Sweden)	3 y	Calcium (1g/d) (n = 25)			1
		Placebo (n = 25)			1
Harwood et al, 2004 (United Kingdom)	1 y	D_3 (300000 IU once) (n = 38)	0	0	
		Calcium (1g/d) + D_2 (300000 IU once) (n = 36) Calcium (1g/d) + D_3 (800IU/d) (n = 39)	6	1	
		No treatment (n = 37)	5	1	
Hin et al, 2017 (United Kingdom)	1 y	D_3(4000 IU/d)(n = 102) D_3(2000 IU/d)(n = 102)	6		
		Placebo (n = 101)	1		
Jackson et al, 2006 (United States)	7 y	Calcium (1g/d) + D_3 (400 IU/d) (n = 4015)		70	
		Placebo (n = 3957)		61	

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Lips et al, 1996 (The Netherlands)	3-4 y	400 IU/d (n = 1291)	135	58	
		Placebo (n = 1287)	122	48	
Liu et al, 2015 (China)	1 y	Calcium (1.5g/d) + D_3 (600 IU/d) (n = 50)	1		
		Placebo (n = 48)	2		
Mitri et al, 2011 (United States)	4 mo	D_3(2000 IU/d)(n = 23)	1		
		Placebo (n = 24)	0		
Peacock et al, 2000 (United States)	4 y	Calcium (0.75g/d) (n = 126)			7
		Placebo (n = 135)			13
Porthouse et al, 2005 (United Kingdom)	1.5-3.5 y	Calcium (1g/d) + D_3 (800 IU/d) (n = 1321)	58	8	
		No treatment (n = 1993)	91	17	
Prince et al, 2006 (Australia)	5 y	Calcium (0.48g/d) (n = 730)	110	11	38
		Placebo (n = 730)	126	6	39
Recker et al, 1996 (United States)	4 y	Calcium (1.2 g/d) (n = 95)			27
		Placebo (n = 102)			34
Reid et al, 1993 (New Zealand)	4 y	Calcium (1 g/d) (n = 68)	2	0	0
		Placebo (n = 67)	7	2	1
Reid et al, 2006 (New Zealand)	5 y	Calcium (1 g/d) (n = 732)	134	17	27
		Placebo (n = 739)	147	5	38
Riggs et al, 1998 (United States)	4 y	Calcium (1.6 g/d) (n = 119)			8
		Placebo (n = 117)			9
Salovaara et al, 2010 (Finland)	3 y	Calcium(1g/d) + D_3 (800 IU/d) (n = 1718)	78	4	9
		No treatment (n = 1714)	94	2	13
Sanders et al, 2010 (Australia)	3-5 y	D_3 (500000 IU every year) (n = 1131)	155	19	35
		Placebo (n = 1127)	125	15	28
Smith et al, 2007 (United Kingdom)	3 y	D_3 (300000 IU every year) (n = 4727)		66	
		Placebo (n = 4713)		44	
Trivedi et al, 2003 (United Kingdom)	5 y	D_3 (100000 IU every 4 mo) (n = 1345)	119	21	18
		Placebo (n = 1341)	149	24	28

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Uusi-Rasi et al, 2015 (Finland)	2 y	D_3 (800 IU/d) (n = 102)	6	2
		Placebo (n = 102)	6	0
Witham et al, 2013 (United Kingdom)	1 y	D_3(100000 IU every 3 mo) (n = 80)	2	
		Placebo (n = 79)	3	
Xue et al, 2017 (China)	1 y	Calcium (0.6g/d) + D_3 (800 IU/d) (n = 139)	3	
		Placebo (n = 173)	2	

Supplementary Table 3. The detailed data of outcomes

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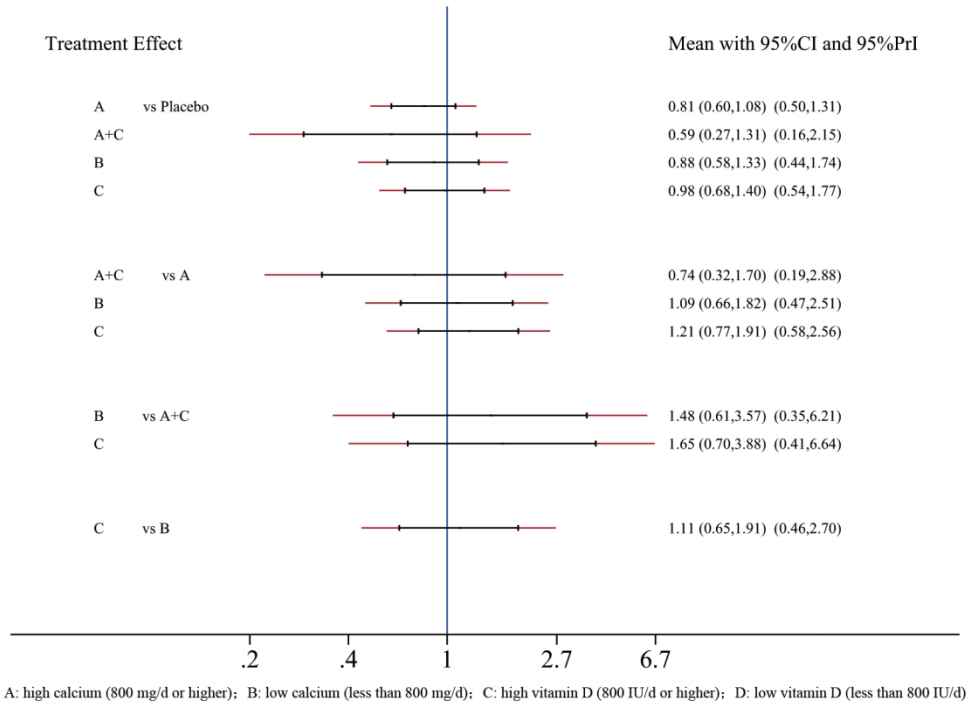
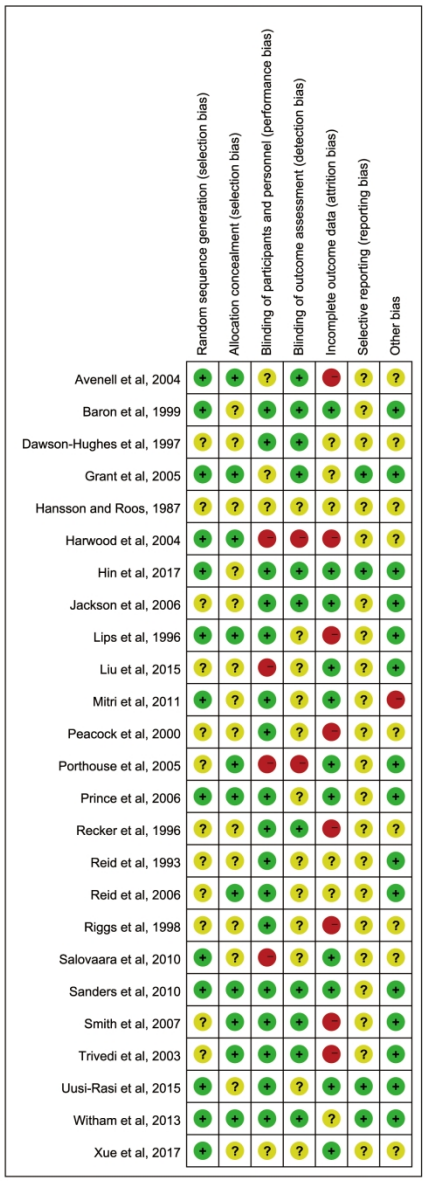


A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Avenell et al, 2004
Baron et al, 1999
Dawson-Hughes et al, 1997
Grant et al, 2005
Hansson and Roos, 1987
Harwood et al, 2004
Hin et al, 2017
Jackson et al, 2006
Lips et al, 1996
Liu et al, 2015
Mitri et al, 2011
Peacock et al, 2000
Porthouse et al, 2005
Prince et al, 2006
Recker et al, 1996
Reid et al, 1993
Reid et al, 2006
Riggs et al, 1998
Salovaara et al, 2010
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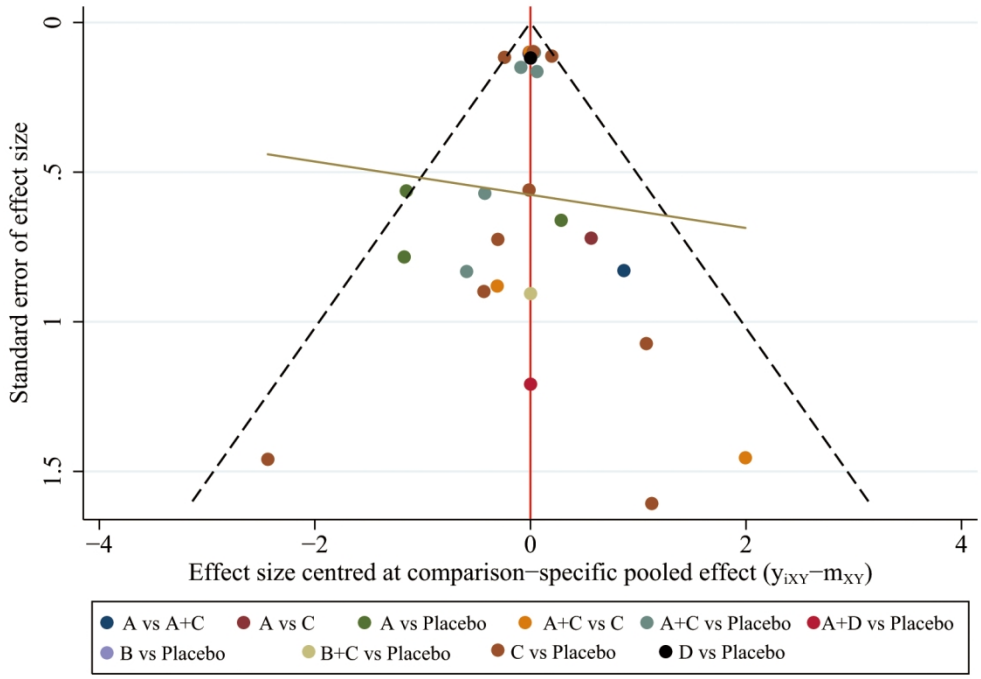
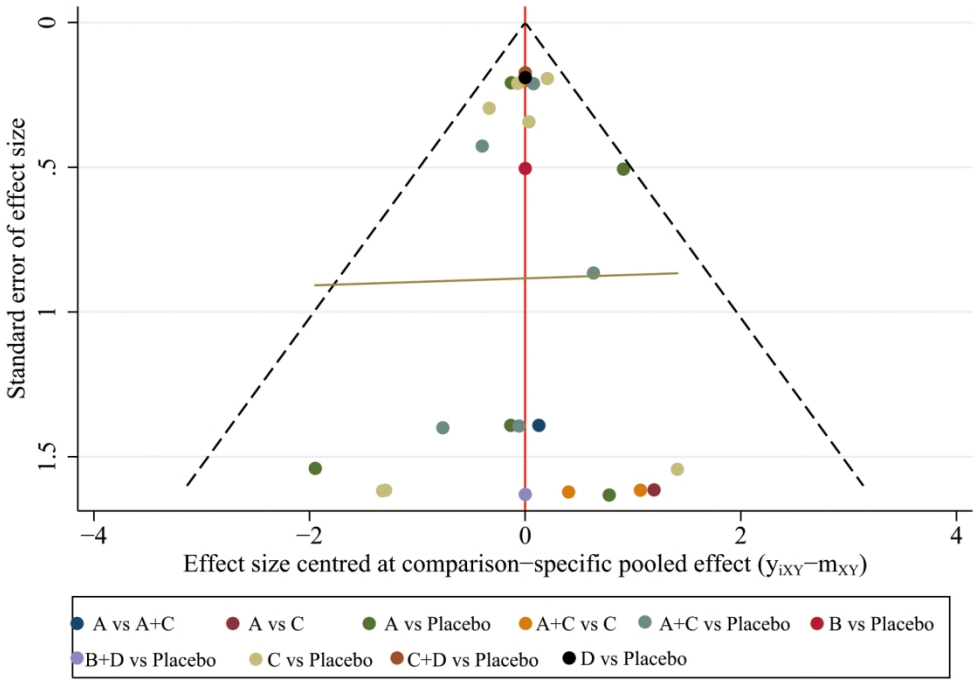
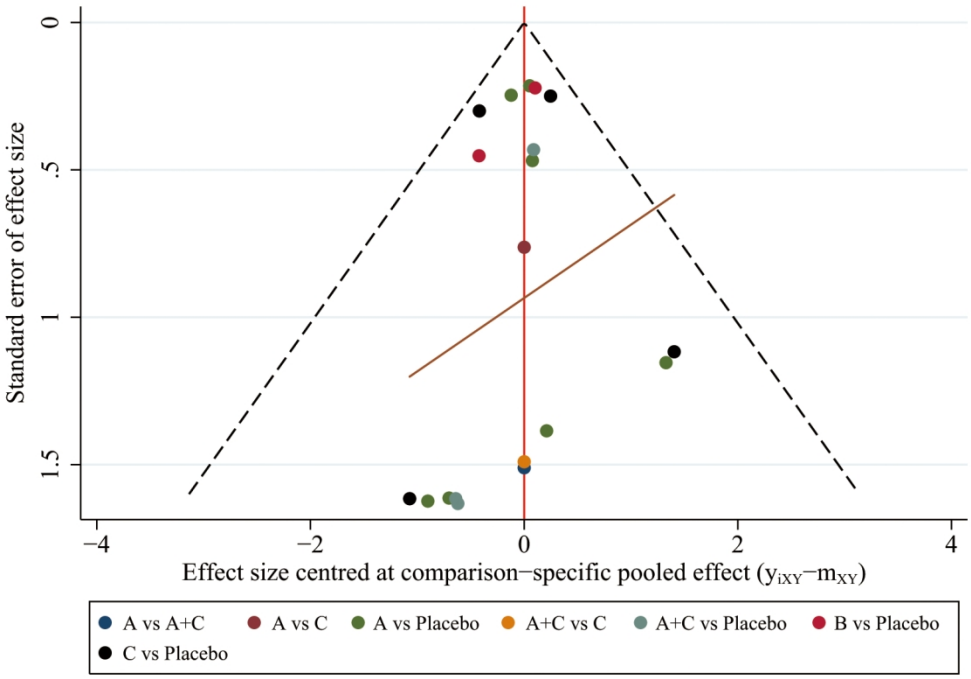
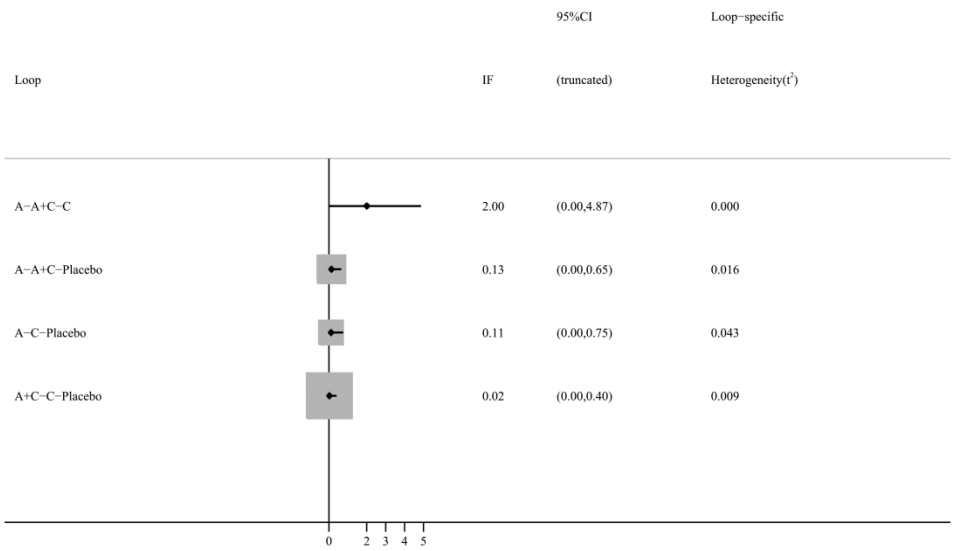
Smith et al, 2007
Trivedi et al, 2003
Uusi-Rasi et al, 2015
Witham et al, 2013
Xue et al, 2017


Standard error of effect size
0
.5
1
1.5
−4
−2
0
2
4
Effect size centred at comparison−specific pooled effect ($y_{iXY}-m_{XY}$)
A vs A+C
A vs C
A vs Placebo
A+C vs C
A+C vs Placebo
A+D vs Placebo
B vs Placebo
B+C vs Placebo
C vs Placebo
D vs Placebo


Standard error of effect size
0
.5
1
1.5
−4
−2
0
2
4
Effect size centred at comparison−specific pooled effect ($y_{iXY}-m_{XY}$)
A vs A+C
A vs C
A vs Placebo
A+C vs C
A+C vs Placebo
B vs Placebo
B+D vs Placebo
C vs Placebo
C+D vs Placebo
D vs Placebo


Standard error of effect size
0
.5
1
1.5
−4
−2
0
2
4
Effect size centred at comparison−specific pooled effect (y_{iXY}−m_{XY})
A vs A+C
A vs C
A vs Placebo
A+C vs C
A+C vs Placebo
B vs Placebo
C vs Placebo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IF
95%CI
(truncated)
Loop−specific
Heterogeneity(t^2)
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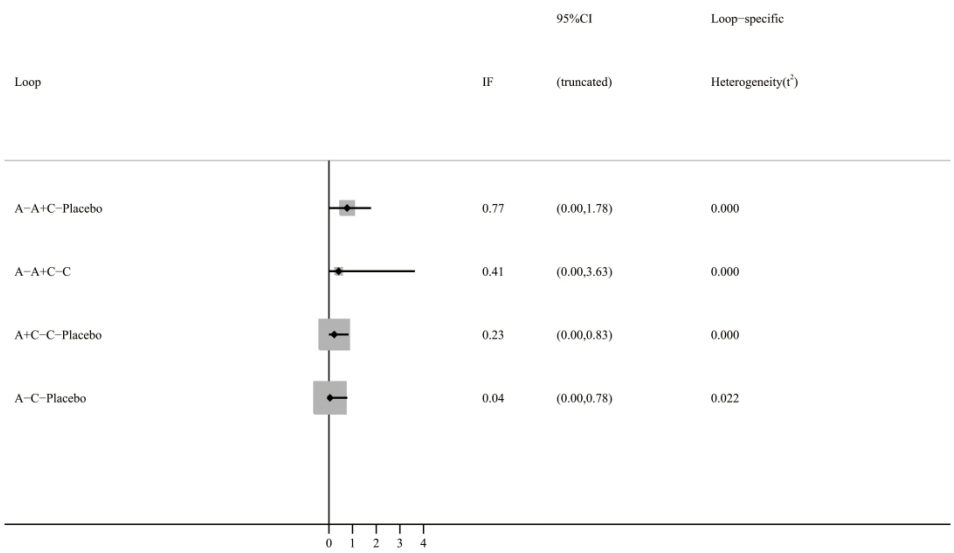
(0.00,4.87)
0.000
A−A+C−Placebo
0.13
(0.00,0.65)
0.016
A−C−Placebo
0.11
(0.00,0.75)
0.043
A+C−C−Placebo
0.02
(0.00,0.40)
0.009
0
2
3
4
5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A−A+C−C
0.41
(0.00,3.63)
0.000
A+C−C−Placebo
0.23
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0.000
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(0.00,0.78)
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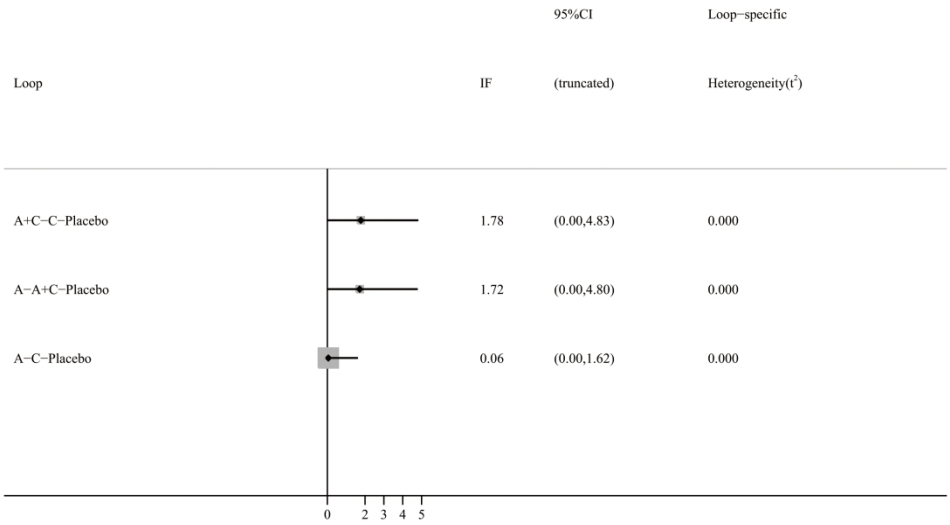
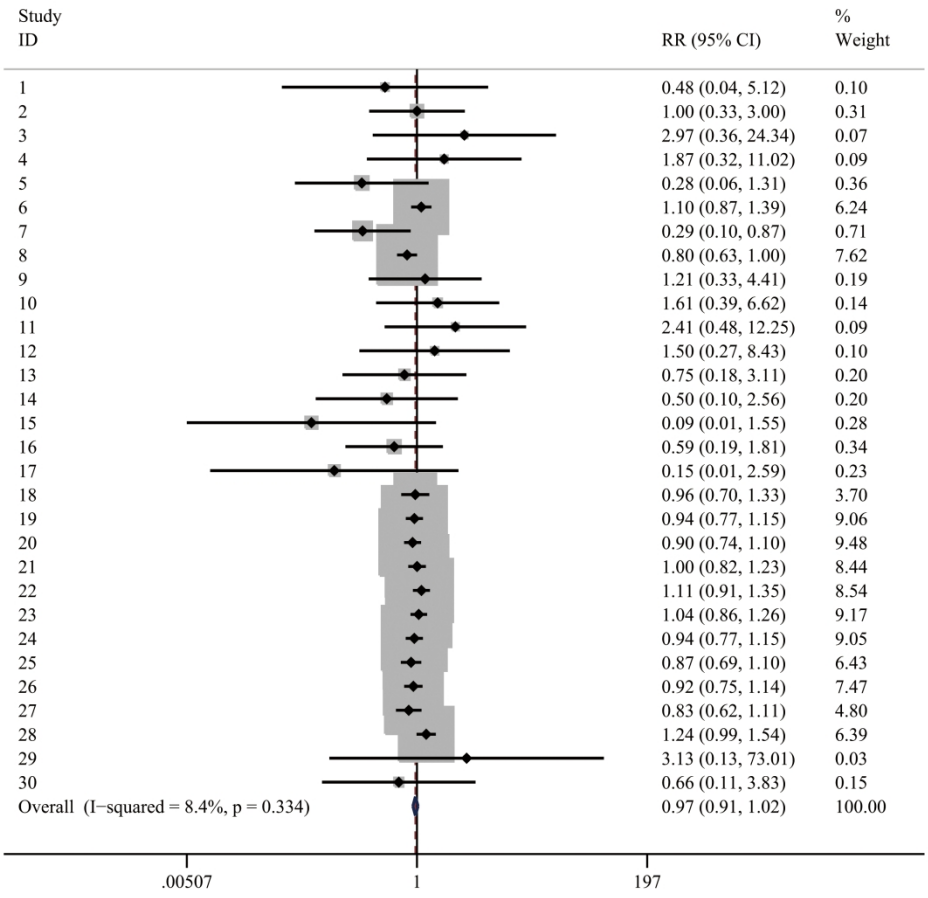
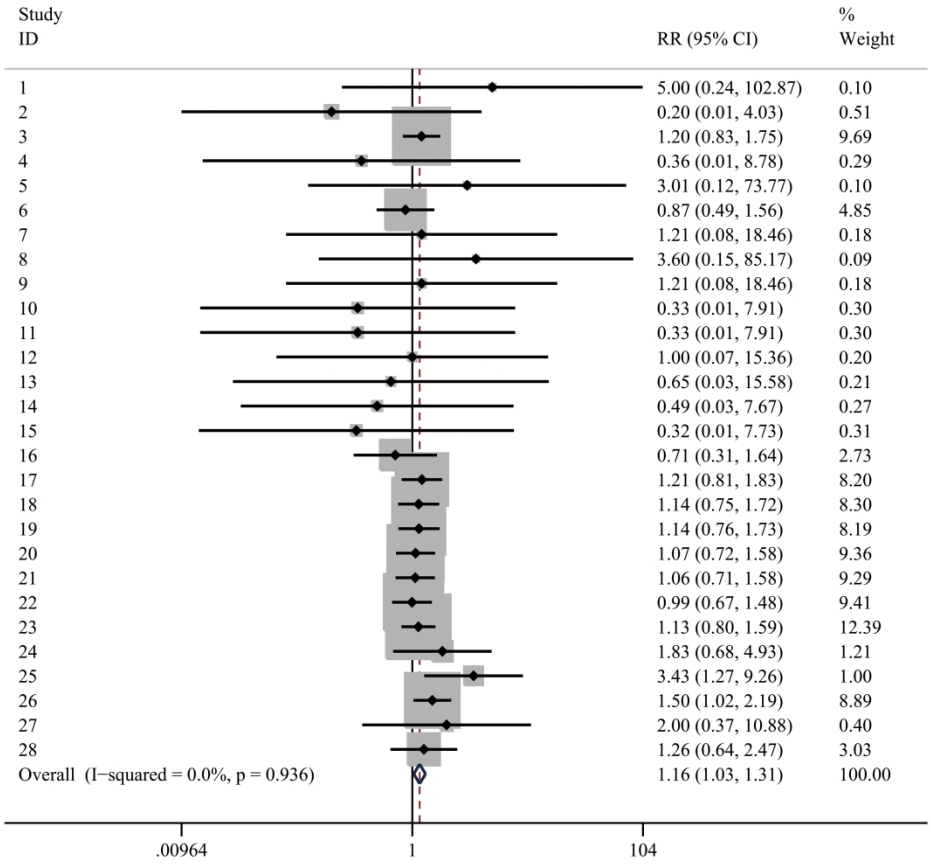
0
1
2
3
4



*** Loop(s) [A−A+C−C] are formed only by multi−arm trial(s) − Consistent by definition


Study ID
RR (95% CI)
% Weight
1 0.48 (0.04, 5.12) 0.10
2 1.00 (0.33, 3.00) 0.31
3 2.97 (0.36, 24.34) 0.07
4 1.87 (0.32, 11.02) 0.09
5 0.28 (0.06, 1.31) 0.36
6 1.10 (0.87, 1.39) 6.24
7 0.29 (0.10, 0.87) 0.71
8 0.80 (0.63, 1.00) 7.62
9 1.21 (0.33, 4.41) 0.19
10 1.61 (0.39, 6.62) 0.14
11 2.41 (0.48, 12.25) 0.09
12 1.50 (0.27, 8.43) 0.10
13 0.75 (0.18, 3.11) 0.20
14 0.50 (0.10, 2.56) 0.20
15 0.09 (0.01, 1.55) 0.28
16 0.59 (0.19, 1.81) 0.34
17 0.15 (0.01, 2.59) 0.23
18 0.96 (0.70, 1.33) 3.70
19 0.94 (0.77, 1.15) 9.06
20 0.90 (0.74, 1.10) 9.48
21 1.00 (0.82, 1.23) 8.44
22 1.11 (0.91, 1.35) 8.54
23 1.04 (0.86, 1.26) 9.17
24 0.94 (0.77, 1.15) 9.05
25 0.87 (0.69, 1.10) 6.43
26 0.92 (0.75, 1.14) 7.47
27 0.83 (0.62, 1.11) 4.80
28 1.24 (0.99, 1.54) 6.39
29 3.13 (0.13, 73.01) 0.03
30 0.66 (0.11, 3.83) 0.15
Overall (I−squared = 8.4%, p = 0.334) 0.97 (0.91, 1.02) 100.00
.00507
1
197


Study
ID
RR (95% CI)
%
Weight
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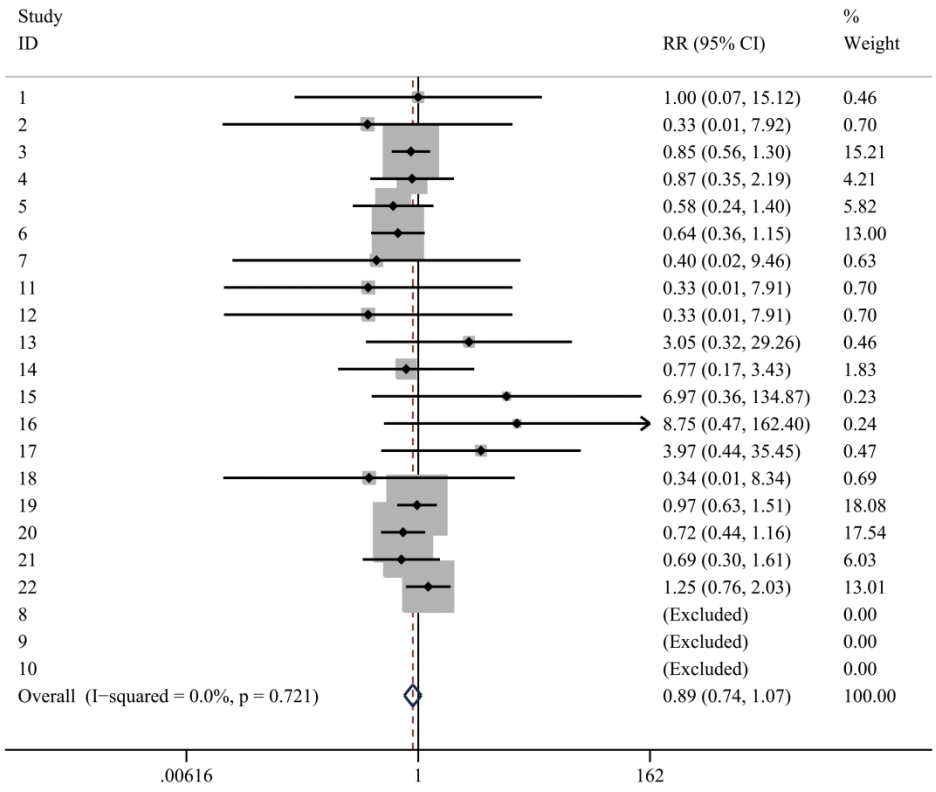
4 0.36 (0.01, 8.78) 0.29
5 3.01 (0.12, 73.77) 0.10
6 0.87 (0.49, 1.56) 4.85
7 1.21 (0.08, 18.46) 0.18
8 3.60 (0.15, 85.17) 0.09
9 1.21 (0.08, 18.46) 0.18
10 0.33 (0.01, 7.91) 0.30
11 0.33 (0.01, 7.91) 0.30
12 1.00 (0.07, 15.36) 0.20
13 0.65 (0.03, 15.58) 0.21
14 0.49 (0.03, 7.67) 0.27
15 0.32 (0.01, 7.73) 0.31
16 0.71 (0.31, 1.64) 2.73
17 1.21 (0.81, 1.83) 8.20
18 1.14 (0.75, 1.72) 8.30
19 1.14 (0.76, 1.73) 8.19
20 1.07 (0.72, 1.58) 9.36
21 1.06 (0.71, 1.58) 9.29
22 0.99 (0.67, 1.48) 9.41
23 1.13 (0.80, 1.59) 12.39
24 1.83 (0.68, 4.93) 1.21
25 3.43 (1.27, 9.26) 1.00
26 1.50 (1.02, 2.19) 8.89
27 2.00 (0.37, 10.88) 0.40
28 1.26 (0.64, 2.47) 3.03
Overall (I−squared = 0.0%, p = 0.936) 1.16 (1.03, 1.31) 100.00
.00964
1
104


Study
ID
RR (95% CI)
%
Weight
1 1.00 (0.07, 15.12) 0.46
2 0.33 (0.01, 7.92) 0.70
3 0.85 (0.56, 1.30) 15.21
4 0.87 (0.35, 2.19) 4.21
5 0.58 (0.24, 1.40) 5.82
6 0.64 (0.36, 1.15) 13.00
7 0.40 (0.02, 9.46) 0.63
11 0.33 (0.01, 7.91) 0.70
12 0.33 (0.01, 7.91) 0.70
13 3.05 (0.32, 29.26) 0.46
14 0.77 (0.17, 3.43) 1.83
15 6.97 (0.36, 134.87) 0.23
16 8.75 (0.47, 162.40) 0.24
17 3.97 (0.44, 35.45) 0.47
18 0.34 (0.01, 8.34) 0.69
19 0.97 (0.63, 1.51) 18.08
20 0.72 (0.44, 1.16) 17.54
21 0.69 (0.30, 1.61) 6.03
22 1.25 (0.76, 2.03) 13.01
8 (Excluded) 0.00
9 (Excluded) 0.00
10 (Excluded) 0.00
Overall (I−squared = 0.0%, p = 0.721) 0.89 (0.74, 1.07) 100.00
.00616
1
162

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Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials

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Primary Subject Heading:	Nutrition and metabolism
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Keywords:	Calcium, Vitamin D, Fractures, network meta-analysis

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Manuscripts

Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials

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Abstract

Objective Inconsistent findings in regard to association between different concentrations of vitamin D, calcium or their combination and the risk of fracture have been reported during the past decade in community-dwelling older people. This study was designed to compare the fracture risk using different concentrations of vitamin D, calcium or their combination.

Design A systematic review and network meta-analysis.

Data sources Randomized controlled trials in PubMed, Cochrane library, and EMBASE databases were systematically searched from the inception dates to December 31, 2017.

Outcomes Total fracture was defined as the primary outcome. Secondary outcomes were hip fracture and vertebral fracture. Due to the consistency of the original studies, a consistency model was adopted.

Results A total of 25 randomized controlled trials involving 43510 participants fulfilled the inclusion criteria. There was no evidence that the risk of total fracture was reduced by using different concentrations of vitamin D, calcium or their combination compared with placebo or no treatment. No significant associations were found between calcium, vitamin D, or combined calcium and vitamin D supplements and the incidence of hip, or vertebral fractures.

Conclusions The use of supplements that included calcium, vitamin D, or both was not found to be better than placebo or no treatment in terms of risk of fractures among community-dwelling older adults. It means the routine use of these supplements in community-dwelling older people should be treated more carefully.

Prospero registration number CRD42017079624

Keywords: Calcium; Vitamin D; Fractures; network meta-analysis

Strengths and limitations of this study

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- This systematic review and meta-analysis combined the evidence from randomized controlled trials.
- Our findings may not support the routine use of these supplements in community-dwelling older people.
- This work does not necessarily preclude any benefit of vitamin D and calcium supplementation in older, frail individuals.
- Potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence.

Introduction

Clinical fractures of the elderly represent a worldwide public health problem that leads to illness and social burden. The patients with osteoporosis in the European Union were estimated to be 27.5 million in 2010, and 3.5 million new fragility fractures were sustained[1]. In Asia, the average cost of osteoporotic fractures accounted for 18.95% of the countries' 2014 gross domestic product (GDP)/capita and increased annually[2-4]. The overall prevalence of osteoporosis or low bone mass in non-institutional population over the age of 50 in the USA was estimated at 10.3% and 43.9%, respectively, which means that 10.2 million elderly people had osteoporosis and 43.4 million people had low bone mass in 2010[5]. With the demographic trend of ageing and the predicted increase in life expectancy, the cost of fracture treatment is expected to rise.

Dietary allowances for calcium range from 700 to 1200 mg/d and vitamin D of 600-800 IU/d have long been recommended for the prevention of osteoporotic fractures in the elderly[6 7]. The supplements of calcium and vitamin D are commonly taken to maintain bone health.

However, the previous randomized controlled trials (RCT) and meta-analyses concerning vitamin D, calcium, or their combination for fractures yielded different efficacy outcomes. For instance, two meta-analyses demonstrated calcium or vitamin D supplementation alone has a small benefit on bone

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mineral density (BMD), but no clinically important to prevent fractures[8 9], while an updated meta-analysis and a pooled analysis found calcium plus vitamin D supplementation can significantly reduce hip fractures by 30% and total fractures by 15%[10 11]. Two RCTs reported that low dose of vitamin D supplementation (less than 800 IU/d) can reduce the incidence of falls[12] and may prevent fractures without adverse effects[13], but other RCTs showed no significant reduction in the incidence of hip or other peripheral fractures[14 15] and its possible effects were seen only in patients with initial calcium insufficiency. Based on the evidence from meta-analysis, Bischoff-Ferrari et al [16] illustrated that high-dose vitamin D supplementation (800 IU/d or higher) not only reduced the risk of falls and hip fractures, but also prevented non-vertebral fractures. In contrast, a study reported annual high-dose oral vitamin D resulted in an increased risk of falls and fractures [17]. On the other hand, low-dose calcium supplementation (less than 800mg/d) effectively led to a sustained reduction in the rate of bone loss [18] and turnover. Although it was also reported that the high dose of calcium (800 mg/d or higher) was associated with a lower risk of clinical fractures [19]. The high-dose calcium with high-dose vitamin D can't prevent fractures according to the evidence from reported RCT [20], but a meta-analysis supported their combination can prevent bone loss and significantly reduce the risk of hip fractures and all osteoporotic fractures [21]. Thus, it's challenging to conclude a dose-response relation between the intakes of vitamin D, calcium, or their combination and the main outcomes in these heterogeneous literatures.

Therefore, this study was designed to compare the fracture risk using different concentrations of vitamin D, calcium or their combination, and comprehensively evaluate the optimal concentration to guide clinical practice and public prevention in community-dwelling older people.

Methods

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Search strategy and selection criteria

This review and meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for network meta-analysis. Our meta-analysis was registered prospectively in PROSPERO (CRD42017079624) and the Checklist PRISMA 2009 (**Supplementary Table 1**) will be used and check our final reports [22].

We restricted our meta-analysis to the inclusion criteria should meet following details: (1) RCTs; (2) Interventions must be one of the following three: vitamin D only, calcium only, both vitamin D and calcium; (3) Complete outcome data of fracture; (4) Trials enrolling adults older than 50 years and living in their communities; (5) Only studies that lasted more than a year. Exclusion criteria were (1) Calcium or vitamin D combined with other therapies (eg: hormones, exercise); (2) Trials in which vitamin D analogues (eg: calcitriol) or hydroxylated vitamin D were used; (3) Trials in which dietary intake of calcium or vitamin D (eg: from milk) was evaluated; (4) Patients suffering from illness or long-term use of certain drugs affecting the stability of the calcium metabolism, such as metabolic bone disease, bone tumour, treatment of steroids and so on.

Participants must be randomly assigned to two or more following groups: (1) high calcium (800 mg/d or higher) only; (2) low calcium (less than 800 mg/d) only; (3) high vitamin D (800 IU/d or higher) only; (4) low vitamin D (less than 800 IU/d) only; (5) high calcium (800 mg/d or higher) + high vitamin D (800 IU/d or higher); (6) high calcium + low vitamin D (less than 800 IU/d); (7) low calcium (less than 800 mg/d) + high vitamin D; (8) low calcium + low vitamin D; (9) placebo. The interventions should be compared with placebo.

Two authors (ZHF and GZ) independently searched the electronic literature database of PubMed, Embase, Cochrane database on December 31, 2017 (detailed search strategies are reported

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in **supplementary eTable 1**). Related articles and reference lists were searched to avoid original miss. The reference studies of previous systematic reviews, meta-analysis, and included studies were manually searched to avoid initial miss. After 2 authors assessed the potentially eligible studies independently, any disagreement was discussed and resolved with the third independent author (QT).

Data collection and assessment of risk of bias

Two reviewers (ZHS and XBL) independently extracted data, and the third reviewer (LT) checked the consistency between them. A standard data extracted form was used at this stage, including the authors, publishing date, country, participant characteristics; doses of calcium, vitamin D, or their combination; dietary calcium intake; baseline serum 25-hydroxyvitamin D concentration; and trial duration. For continuous outcomes, the mean, SD (standard deviation) and participant number will be extracted. For dichotomous outcomes, we extracted the total numbers and the numbers of events of both groups. The data in other forms was recalculated when possible to enable pooled analysis.

We used the Cochrane risk of bias tool to assess risk bias of included studies. The tool has seven domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The classification of the judgment for each domain was low risk of bias, high risk of bias, or unclear risk of bias and two authors (ZHF and GZ) independently evaluated the risk of studies.

Data synthesis and statistical analysis

The data was extracted and input into the STATA software (version 12.0; StataCorp, College Station, TX, USA) for network meta-analysis. And we generated network plots for each outcome to illustrate which interventions had been compared directly in the included studies. Network meta-analysis is an extension of standard meta-analysis to compare multiple treatments based on

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randomized controlled trial evidence, which forms a connected network of comparisons. Treatment effect estimates from network meta-analysis exploit both the direct comparisons within trials and the indirect comparisons across trials. To choose the random effects or fixed effects model, we either make a judgement about what is most likely to be appropriate based on the assumptions of the different models or conduct both fixed or random effects and compare which seems to fit the data better[23]. Relative risk (RR) with 95% confidence intervals (CIs) was calculated for dichotomous outcomes while weighted mean difference (WMD) with 95% CIs for the continuous. Inconsistency refers to differences between direct and various indirect effect estimates for the same comparison. To assess inconsistency, we estimated the inconsistency factors in closed loop based on the method described by Chaimani et al[24]. The heterogeneity in each closed loop was estimated by utilizing inconsistency factor (IF). If the 95% confidence intervals (95% CI) of IF values are not truncated at zero, it suggests that the inconsistency among studies has statistical significance. We used the surface under the cumulative ranking probabilities (SUCRA) to indicate which treatment was the best one. The funnel plot was used to identify possible publication bias if the number of studies was larger than 10.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, and no patients were involved in developing plans for design or implementation of the study. Furthermore, no patients were asked to advice on interpretation or writing up of results. Since this meta-analysis used aggregated data from previous trials, it is unable to disseminate the results of the research to study participants directly.

Result

Data Retrieval

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In summary, a total of 7909 potential records were initially identified through PubMed (5187), Embase (2688), Cochrane Data base (34). Based on our review of the title and abstract, 99 full-text papers were reviewed and 25 studies[13 17 19 20 25-45] met inclusion criteria (**Figure 1)**.

Study and Patient Characteristics

The characteristics of all 25 included studies were summarized and shown in **supplementary Table 2**. And the detailed data of outcomes was collected in **supplementary Table 3**. The papers had similar distributions of sex, age, country, intervention and all of them were community-dwelling older people. Hansson et al[29] did not report the residential status of participants, although a previous meta-analysis classified this status as community. The trial by Hansson et al was included, but a sensitivity analysis was performed that excluded that trial (**supplementary Figure 1**).

Supplementary Figure 2 showed the assessment of the risk of bias. All studies were randomized; 17 were double-blind, placebo-controlled trials; 13 trials described an adequate random sequence generation process; and 11 trials described the methods used for allocation concealment. No obvious publication bias was reported according to the **supplementary Figure 3, supplementary Figure 4** and **supplementary Figure 5**.

Inconsistence and heterogeneity check

The statistical inconsistency between direct and indirect comparisons was generally low according to inconsistency test because the CI values included zero (**supplementary Figure 6, supplementary Figure 7, supplementary Figure 8**). Therefore, we adopted a consistency model in all three groups. Meanwhile, the global heterogeneity parameter I^2 values were 8.4%, 0% and 0% respectively, which indicated no obvious heterogeneity was observed in all these results (**supplementary Figure 9, supplementary Figure 10, supplementary Figure 11**).

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Primary outcome: total fracture

For estimating the vitamin D, calcium or their combination efficacy against total fractures, we looked at data from 24965 individuals from 18 studies[13 17 19 20 25 26 28 30 31 33-35 37 39 40 43-45]. Pooled estimates included 15 studies with one treatment, 1 study with two treatments, and 2 studies with three treatments.

The network plot of comparisons on total fractures was shown in **Figure 2A**. The forest plot for the network meta-analysis was shown in **Figure 3**. The RR values and 95% CIs are summarized in **Figure 3**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between interventions and placebo (P<0.05). So we didn't continue to make ranking graph of distribution of probabilities on total fractures.

Secondary outcomes: **hip fracture and vertebral fracture**

A total of 41845 individuals were included from 16 studies[13 17 19 20 25-28 30 32 33 37 39 40 42 43] for evaluate the drug efficacy against hip fractures. Pooled estimates included 13 studies with one treatment, 1 study with two treatments, and two studies with three treatments.

The network plot of comparisons on hip fractures was shown in **Figure 2B**. The forest plot for the network meta-analysis was shown in **Figure 4**. The RR values and 95% CIs are summarized in **Figure 4**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between drug experimental groups and placebo (P<0.05). So we didn't continue to make ranking graph of distribution of probabilities on total fractures.

A total of 17612 individuals were collected from 12 studies[13 17 19 20 25 28 29 36 38-41] involving vertebral

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fractures. Pooled estimates included 10 studies with one treatment, and two studies with three treatments.

The network plot of comparisons on vertebral fractures was shown in **Figure 2C**. The forest plot for the network meta-analysis was shown in **Figure 5**. The RR values and 95% CIs are summarized in **Figure 5**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between drug experimental groups and placebo ($P<0.05$). So we didn't continue to make ranking graph of distribution of probabilities on total fractures. In a separate sensitivity analysis, we excluded Hansson's study[29] (**supplementary Figure 1**). However, there was still no significant association of vitamin D, calcium or their combination with total fracture.

Discussion

Vitamin D supplementation and calcium are suggested as interventions to treat and prevent fracture. We found the previous meta-analyses and RCTs are critically inconsistent in efficacy of different doses of vitamin D with calcium on fractures.

Results of this meta-analysis showed that calcium, calcium plus vitamin D, and vitamin D supplementation alone were not significantly associated with a lower incidence of hip, vertebral, or total fractures in community-dwelling older adults. Sensitivity analyses that excluded low-quality trials and studies that exclusively enrolled patients with particular medical conditions did not alter these results.

A meta-analysis conducted by Jia-Guo Zhao et al[46] showed that no significant difference was found in the incidence of hip or other fractures, which was similar to our result. However, the object of Zhao's study was to investigate whether calcium, vitamin D, or combined calcium and vitamin D

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supplement are associated with a lower facture incidence while our study was designed to evaluate the optimal concentration of them. Meanwhile, in Zhao's meta-analysis, the participants of the included study reported by Massart[47] were adult maintenance hemodialysis patients, which may result in the imbalance of calcium in the body. Patients on hemodialysis may also be receiving 1,25-dihydroxyvitamin D, which may affect their response to vitamin D supplementation. So we did not include that trial in our network meta-analysis. What's more, we didn't include studies that lasted less than a year because we thought this time-frame was too short to see anti-fracture efficacy. And we suspected that a network meta-analysis might be a more suitable choice concerning all these different interventions mixed.

Bischoff-Ferrari et al [48] reported that high-dose vitamin D supplementation (800 IU/d or higher) played an important role in the reduction of the risk of falls and hip fractures, as well as prevented non-vertebral fractures in adults 65 years or older. However, their findings may have been influenced by the trial of Chapuy et al [49], which only enrolled participants living in an institution. What's more, differences in conclusions of previous meta-analyses and the current meta-analysis were due to the recently published trials which reported neutral or harmful associations of vitamin D supplementation and fracture incidence more and more. Study findings here indicated that vitamin D might result in a higher risk for hip fracture, but this conclusion did not reach statistical significance. This finding may be attributable to lack of statistical power in this meta-analysis.

Most recently there was a meta-analysis published in the Lancet by Bolland et al[50], whose findings suggested that vitamin D supplementation does not prevent fractures or falls, or have clinically meaningful effects on bone mineral density. Although it was similar to our study to some extent, they are really different. First, we only included community-dwelling older people. We found that some

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meta-analyses equated community-dwelling older people with those in nursing institution. The lack of exercise, dietary intake and exposure to sunlight made people in nursing institution turned more susceptible to the use of supplements including vitamin D, calcium or their combination. Although the studies involving participants living in nursing institution were only a small part, but it could change the whole outcomes and produce false positive results. We found only Avenell's study paid attention to this question when they conducted a subgroup analysis, but they did not discussed separately. Meanwhile, we only enrolled adults older than 50 years and trial duration more than 1 year to reduce the statistical heterogeneity in network meta-analysis. Furthermore, the current analyses included calcium supplementation, where the Bolland's study focused on vitamin D.

However, possible limitations of this study protocol include potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence. Some RCTs were of poor quality and, for example, used unclear allocation concealment. So we made a sensitivity analysis by excluding low-quality trials. Meanwhile, some study characteristics such as baseline serum 25-hydroxyvitamin D concentrations might be to contribute heterogeneity so future analyses are still needed to explore this potential heterogeneity. What's more, we combined bolus dosing by injection with oral supplements taken daily/monthly/yearly, which might have different effects on vitamin D status in the body. In addition, the report ignored the effect of treatment with vitamin D on plasma 25-hydroxy-vitamin D concentrations and sub-types of fracture, such as pathologic fractures; this work does not necessarily preclude any benefit of vitamin D and calcium supplementation in older, frail individuals.

Conclusions

In this meta-analysis of randomized clinical trials, we found that the use of different concentrations of vitamin D, calcium or their combination in community-dwelling older adults was not associated with a

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lower risk of fractures. Our findings may not support the routine use of these supplements in community-dwelling older people.

Contributors

ZCH and AMW conceived the study. The search strategy was developed by LT and XBL. ZHF, GZ and QT will complete electronic search, select publications and assess their eligibility. ZHS and XBL will extract information of the included studies after screening. JWX will check the data entry for accuracy and completeness. ZCH and LT will give advice for data analysis and presentation of study result. LYS and CMS contributed to the text revision. WFN and AMW supervised the overall conduct of the study. All the authors drafted and critically reviewed and approved the final manuscript.

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Conflicts of interest

None declared

Patient consent

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

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All data relevant to the study are included in the article or uploaded as supplementary information.

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Legends:

Figure 1. The selection of literature for included studies.

Figure 2. The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral

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fractures (C). A: high calcium (800 mg/d or higher)； B: low calcium (less than 800 mg/d)； C: high vitamin D (800 IU/d or higher)； D: low vitamin D (less than 800 IU/d)

Figure 3. The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher)； B: low calcium (less than 800 mg/d)； C: high vitamin D (800 IU/d or higher)； D: low vitamin D (less than 800 IU/d)

Figure 4. The forest plot for the risk of hip fractures. A: high calcium (800 mg/d or higher)； B: low calcium (less than 800 mg/d)； C: high vitamin D (800 IU/d or higher)； D: low vitamin D (less than 800 IU/d)

Figure 5. The forest plot for the risk of vertebral fractures. A: high calcium (800 mg/d or higher)； B: low calcium (less than 800 mg/d)； C: high vitamin D (800 IU/d or higher)； D: low vitamin D (less than 800 IU/d)

supplementary Figure 1. A sensitivity analysis excluded the trial of Hansson et al. A: high calcium (800 mg/d or higher)； B: low calcium (less than 800 mg/d)； C: high vitamin D (800 IU/d or higher)； D: low vitamin D (less than 800 IU/d)

supplementary Figure 2. Risk of Bias Assessment of All Included Studies

supplementary Figure 3. Publication bias for the total fractures. A: high calcium (800 mg/d or higher)；

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B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 4. Publication bias for the hip fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 5. Publication bias for the vertebral fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 6. Inconsistency test for the total fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 7. Inconsistency test for the hip fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 8. Inconsistency test for the vertebral fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

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supplementary Figure 9. Heterogeneity test for the total fractures.

supplementary Figure 10. Heterogeneity test for the hip fractures.

supplementary Figure 11. Heterogeneity test for the vertebral fractures.

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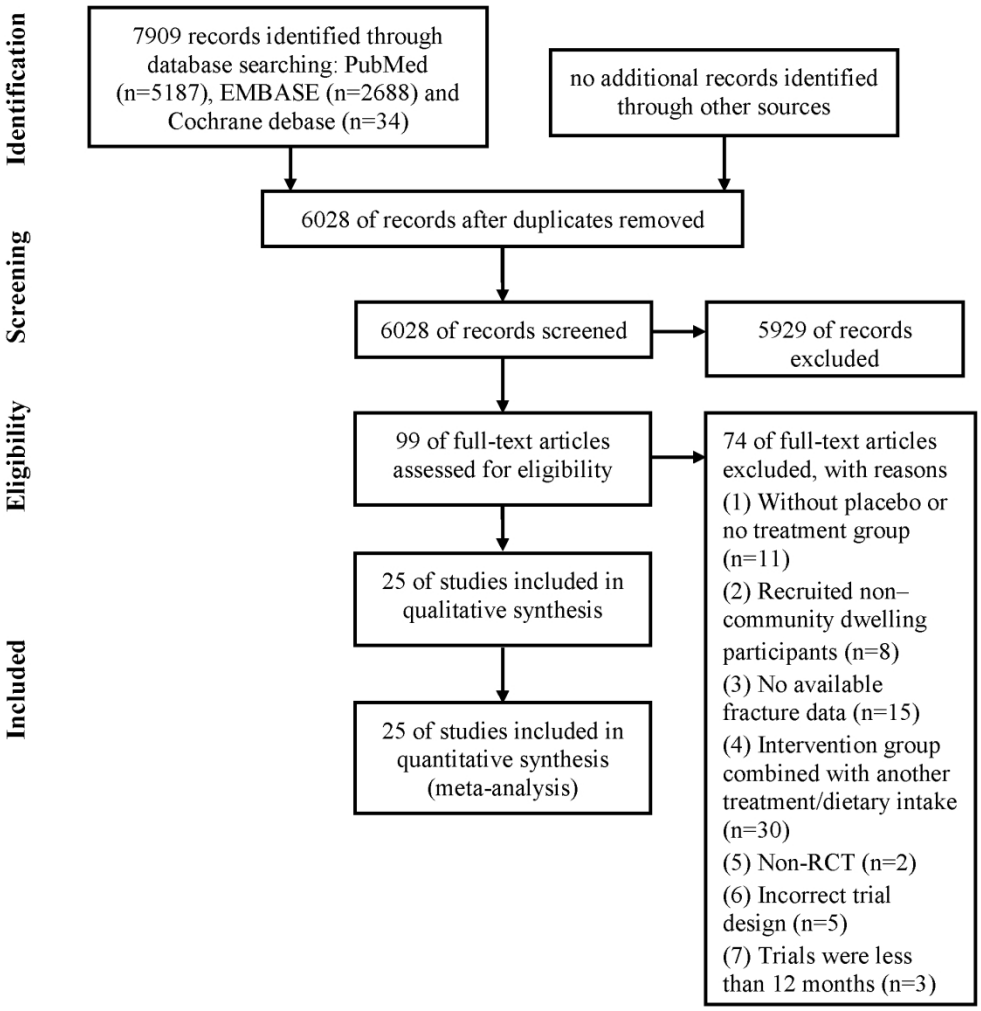

The selection of literature for included studies.

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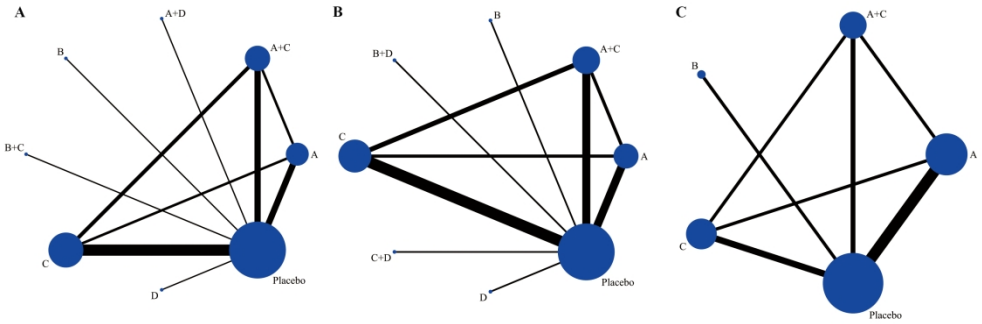

The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral fractures (C). A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)

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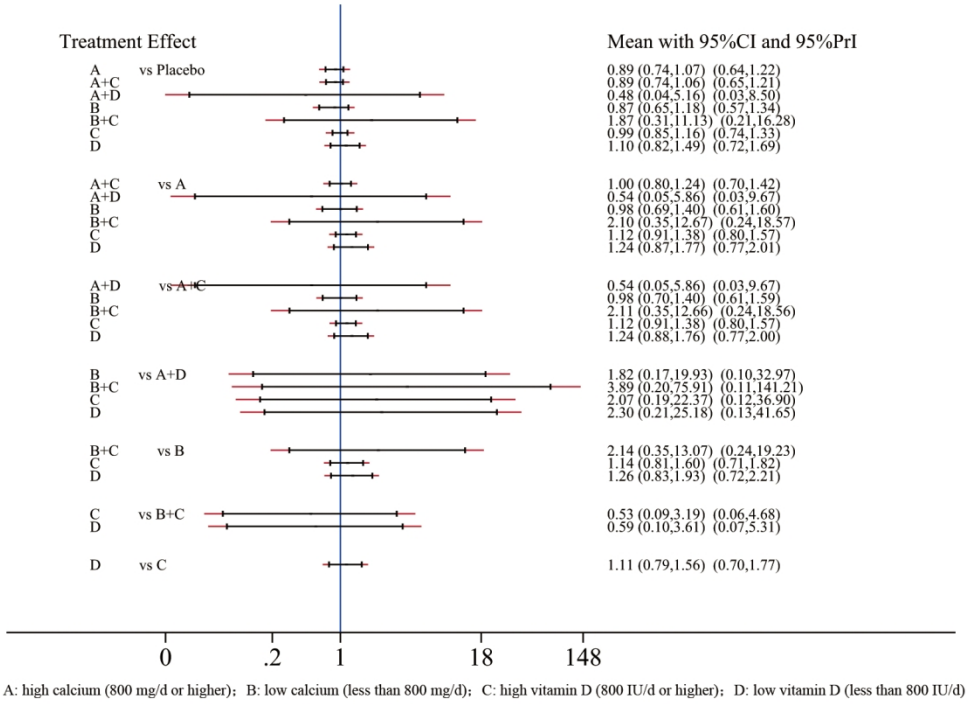
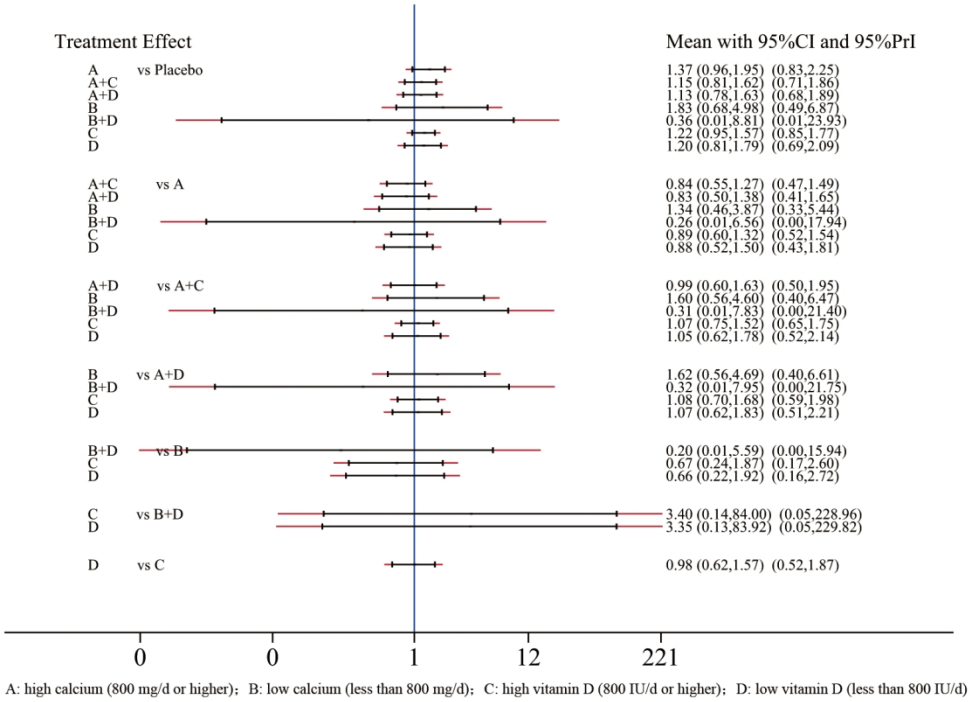
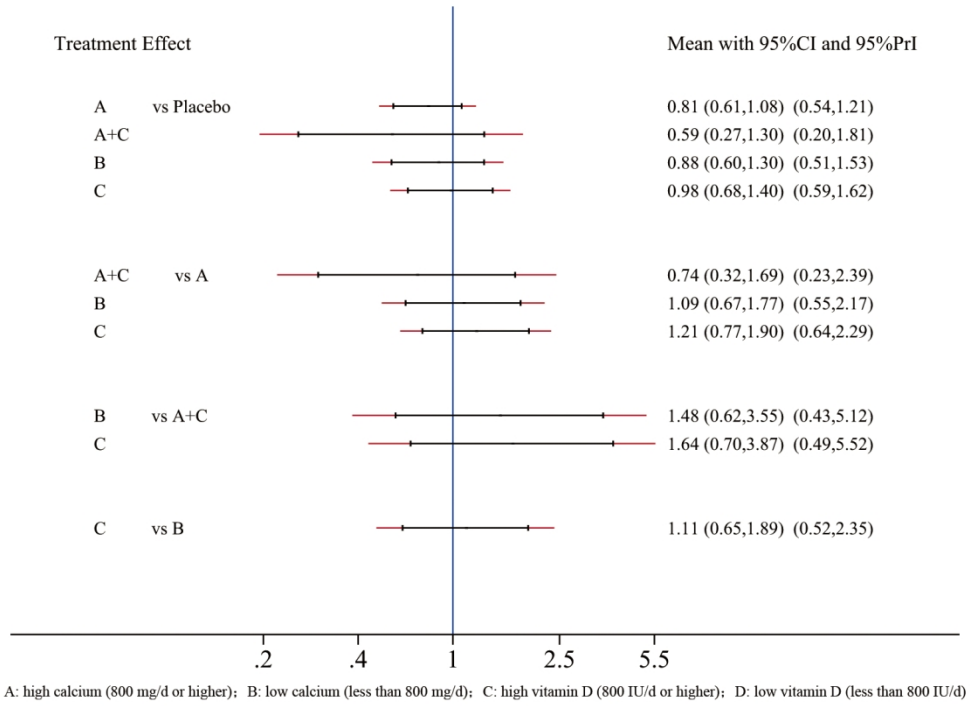


The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)



The forest plot for the risk of hip fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)



The forest plot for the risk of vertebral fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)

Supplementary eTable 1. Search Strategy for Each Database

Database	Search strategy
Pubmed	#1 "calcium"[MeSH Terms] OR "calcium"[All Fields]
	#2 "vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]
	#3 "fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields]
	#4 #1 or #2
	#5 #3 and #4

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Supplementary Table 1 - Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5

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Section/topic	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10

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Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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Source	Intervention	Women, No. (%)	Mean Age, y	Previous Fracture	Calcium Intake, mg/d	Baseline 25OHD, ng/mL	Treatment Duration
Avenell et al, 2004 (United Kingdom)	Calcium(1 g/d) (n = 29)	NA [a] (83)	78 [b]	Yes	NA	NA	3.8 y
	No treatment (n = 35)						
	D_3(800IU/d) (n = 35)	NA [a] (83)	78 [b]	Yes	NA	NA	3.8 y
	No treatment (n = 35)						
	Calcium (1g/d) + D_3 (800IU/d) (n = 35)	NA [a] (83)	78 [b]	Yes	NA	NA	3.8 y
	No treatment (n = 35)						
Baron et al, 1999 (United States)	Calcium: 1.2 g/d (n = 464)	258 (28)	61.0	NA	877	NA	4 y
	Placebo (n = 466)						
Dawson-Hughes et al, 1997 (United States)	Calcium (0.5g/d) + D_3 (700IU/d) (n = 187)	213 (54)	71.1	NA	729	29.6 [e]	3 y
	Placebo (n = 202)						
Grant et al, 2005 (United Kingdom)	Calcium(1 g/d) (n = 1311)	2241 (85)	77	Yes	NA	15.2 [e,f]	2-5 y
	Placebo (n = 1332)						
	D_3(800IU/d) (n = 1343)	2264 (85)	77	Yes	NA	15.2 [e,f]	2-5 y
	Placebo (n = 1332)						
	Calcium (1g/d) + D_3 (800IU/d) (n = 1306)	2232 (85)	77.5	Yes	NA	15.2 [e,f]	2-5 y
	Placebo (n = 1332)						
Hansson and Roos, 1987 (Sweden)	Calcium (1g/d) (n = 25)	50 (100)	65.9	Yes	NA	NA	3 y
	Placebo (n = 25)						
Harwood et al, 2004 (United Kingdom)	D_3 (300000 IU once) (n = 38)	75 (100)	80.5	Yes	NA	11.6	1 y
	No treatment (n = 37)						
	Calcium (1g/d) + D_2 (300000 IU once) (n = 36)	112 (100)	81.7	Yes	NA	11.9	1 y
	Calcium (1g/d) + D_3 (800IU/d) (n = 39)						
	No treatment (n = 37)						
Hin et al, 2017 (United Kingdom)	D_3(4000 IU/d)(n = 102)	150 (49)	71.7	Partial [c]	710	20.1	1 y
	D_3(2000 IU/d)(n = 102)						
	Placebo (n = 101)						
Jackson et al, 2006 (United States)	Calcium (1g/d) + D_3 (400 IU/d) (n = 4015)	7972 (100)	62.4	Partial [c]	1151	18.9 [e]	7 y

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	Placebo (n = 3957)						
Lips et al, 1996 (The Netherlands)	400 IU/d (n = 1291) Placebo (n = 1287)	1916 (74)	80.0	No hip fracture	868	10.6 [e]	3-4 y
Liu et al, 2015 (China)	Calcium (1.5g/d) + D_3 (600 IU/d) (n = 50) Placebo (n = 48)	98 (100)	62.1	No	1500	NA	1 y
Mitri et al, 2011 (United States)	D_3(2000 IU/d)(n = 23) Placebo (n = 24)	25 (53)	58.0	NA	926	25.3	4 mo
Peacock et al, 2000 (United States)	Calcium (0.75g/d) (n = 126) Placebo (n = 135)	187 (72)	73.8	Partial [c]	597	25.0	4 y
Porthouse et al, 2005 (United Kingdom)	Calcium (1g/d) + D_3 (800 IU/d) (n = 1321) No treatment (n = 1993)	3314 (100)	76.8	Partial [c]	1080	NA	1.5-3.5 y
Prince et al, 2006 (Australia)	Calcium (0.48g/d) (n = 730) Placebo (n = 730)	1460 (100)	75.2	Partial [c]	915	31.0 [e]	5 y
Recker et al, 1996 (United States)	Calcium (1.2 g/d) (n = 95) Placebo (n = 102)	197 (100)	73.5	Partial [c]	434	25.5 [e]	4 y
Reid et al, 1993 (New Zealand)	Calcium (1 g/d) (n = 68) Placebo (n = 67)	135 (100)	58	No vertebral fracture	750	37.5	4 y
Reid et al, 2006 (New Zealand)	Calcium (1 g/d) (n = 732) Placebo (n = 739)	1471 (100)	74.3	Partial [c]	857	20.7	5 y
Riggs et al, 1998 (United States)	Calcium (1.6 g/d) (n = 119) Placebo (n = 117)	236 (100)	66.2	No	714	30.1	4 y
Salovaara et al, 2010 (Finland)	Calcium(1g/d) + D_3 (800 IU/d) (n = 1718) No treatment (n = 1714)	3432 (100)	67.3	Partial [c]	957	19.8 [e]	3 y
Sanders et al, 2010 (Australia)	D_3 (500000 IU every year) (n = 1131) Placebo (n = 1127)	2258 (100)	76.1	Partial [c]	976	19.8 [e]	3-5 y
Smith et al, 2007 (United Kingdom)	D_3 (300000 IU every year) (n = 4727) Placebo (n = 4713)	5086 (54)	79.1	Partial [c]	625 [d]	22.6 [e]	3 y
Trivedi et al, 2003 (United Kingdom)	D_3 (100000 IU every 4 mo) (n = 1345) Placebo (n = 1341)	649 (24)	74.8	NA	742	NA	5 y
Yusi-Rasi et al, 2015	D_3 (800 IU/d) (n = 102)	204 (100)	73.9	NA	1082	26.7	2 y

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(Finland)	Placebo (n = 102)						
Witham et al, 2013 (United Kingdom)	D_3(100000 IU every 3 mo) (n = 80) Placebo (n = 79)	77 (49)	76.8	NA	1125	18.0	1 y
Xue et al, 2017 (China)	Calcium (0.6g/d) + D_3 (800 IU/d) (n = 139) Placebo (n = 173)	312 (100)	63.6	Partial [c]	NA	30.8	1 y

Abbreviation: 25OHD, 25-hydroxyvitamin D; NA, not available

[a] Women accounted for 83% of total participants in this trial, but detailed data not available for each group.

[b] Mean age is 78 y for total participants in this trial, but detailed data not available for each group.

[c] This trial reported partial participants with fracture history.

[d] Partial participants were assessed for dietary calcium intake.

[e] Partial participants received measurement of baseline 25OHD concentrations.

[f] The RECORD trial reported that the mean baseline 25OHD concentrations for a sample of 60 participants was 15.2 ng/mL, but detailed data were not available for each group.

supplementary Table 2. The characteristics of the included studies.

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Source	Treatment Duration	Intervention	No. of Participants		
			Total Fracture	Hip fracture	Vertebral Fracture
Avenell et al, 2004 (United Kingdom)	3.8 y	Calcium(1 g/d) (n = 29)	4	1	0
		D_3(800IU/d) (n = 35)	3	0	0
		Calcium (1g/d) + D_3 (800IU/d) (n = 35)	2	1	0
		No treatment (n = 35)	4	1	1
Baron et al, 1999 (United States)	4 y	Calcium: 1.2 g/d (n = 464)	4	1	
		Placebo (n = 466)	14	0	
Dawson-Hughes et al, 1997 (United States)	3 y	Calcium (0.5g/d) + D_3 (700IU/d) (n = 187)		0	
		Placebo (n = 202)		1	
Grant et al, 2005 (United Kingdom)	2-5 y	Calcium(1 g/d) (n = 1311)	166	49	3
		D_3(800IU/d) (n = 1343)	188	47	4
		Calcium (1g/d) + D_3 (800IU/d) (n = 1306)	165	46	0
		Placebo (n = 1332)	179	41	1
Hansson and Roos, 1987 (Sweden)	3 y	Calcium (1g/d) (n = 25)			1
		Placebo (n = 25)			1
Harwood et al, 2004 (United Kingdom)	1 y	D_3 (300000 IU once) (n = 38)	0	0	
		Calcium (1g/d) + D_2 (300000 IU once) (n = 36) Calcium (1g/d) + D_3 (800IU/d) (n = 39)	6	1	
		No treatment (n = 37)	5	1	
Hin et al, 2017 (United Kingdom)	1 y	D_3(4000 IU/d)(n = 102) D_3(2000 IU/d)(n = 102)	6		
		Placebo (n = 101)	1		
Jackson et al, 2006 (United States)	7 y	Calcium (1g/d) + D_3 (400 IU/d) (n = 4015)		70	
		Placebo (n = 3957)		61	

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Lips et al, 1996 (The Netherlands)	3-4 y	400 IU/d (n = 1291)	135	58	
		Placebo (n = 1287)	122	48	
Liu et al, 2015 (China)	1 y	Calcium (1.5g/d) + D_3 (600 IU/d) (n = 50)	1		
		Placebo (n = 48)	2		
Mitri et al, 2011 (United States)	4 mo	D_3(2000 IU/d)(n = 23)	1		
		Placebo (n = 24)	0		
Peacock et al, 2000 (United States)	4 y	Calcium (0.75g/d) (n = 126)			7
		Placebo (n = 135)			13
Porthouse et al, 2005 (United Kingdom)	1.5-3.5 y	Calcium (1g/d) + D_3 (800 IU/d) (n = 1321)	58	8	
		No treatment (n = 1993)	91	17	
Prince et al, 2006 (Australia)	5 y	Calcium (0.48g/d) (n = 730)	110	11	38
		Placebo (n = 730)	126	6	39
Recker et al, 1996 (United States)	4 y	Calcium (1.2 g/d) (n = 95)			27
		Placebo (n = 102)			34
Reid et al, 1993 (New Zealand)	4 y	Calcium (1 g/d) (n = 68)	2	0	0
		Placebo (n = 67)	7	2	1
Reid et al, 2006 (New Zealand)	5 y	Calcium (1 g/d) (n = 732)	134	17	27
		Placebo (n = 739)	147	5	38
Riggs et al, 1998 (United States)	4 y	Calcium (1.6 g/d) (n = 119)			8
		Placebo (n = 117)			9
Salovaara et al, 2010 (Finland)	3 y	Calcium(1g/d) + D_3 (800 IU/d) (n = 1718)	78	4	9
		No treatment (n = 1714)	94	2	13
Sanders et al, 2010 (Australia)	3-5 y	D_3 (500000 IU every year) (n = 1131)	155	19	35
		Placebo (n = 1127)	125	15	28
Smith et al, 2007 (United Kingdom)	3 y	D_3 (300000 IU every year) (n = 4727)		66	
		Placebo (n = 4713)		44	
Trivedi et al, 2003 (United Kingdom)	5 y	D_3 (100000 IU every 4 mo) (n = 1345)	119	21	18
		Placebo (n = 1341)	149	24	28

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Uusi-Rasi et al, 2015 (Finland)	2 y	D_3 (800 IU/d) (n = 102)	6	2
		Placebo (n = 102)	6	0
Witham et al, 2013 (United Kingdom)	1 y	D_3(100000 IU every 3 mo) (n = 80)	2	
		Placebo (n = 79)	3	
Xue et al, 2017 (China)	1 y	Calcium (0.6g/d) + D_3 (800 IU/d) (n = 139)	3	
		Placebo (n = 173)	2	

Supplementary Table 3. The detailed data of outcomes

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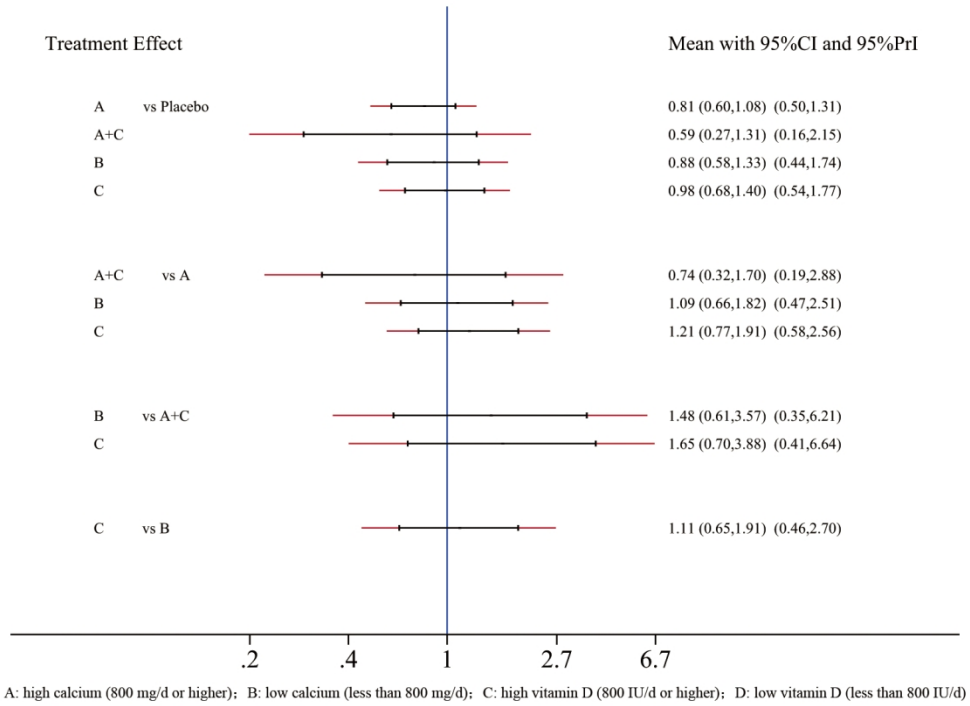
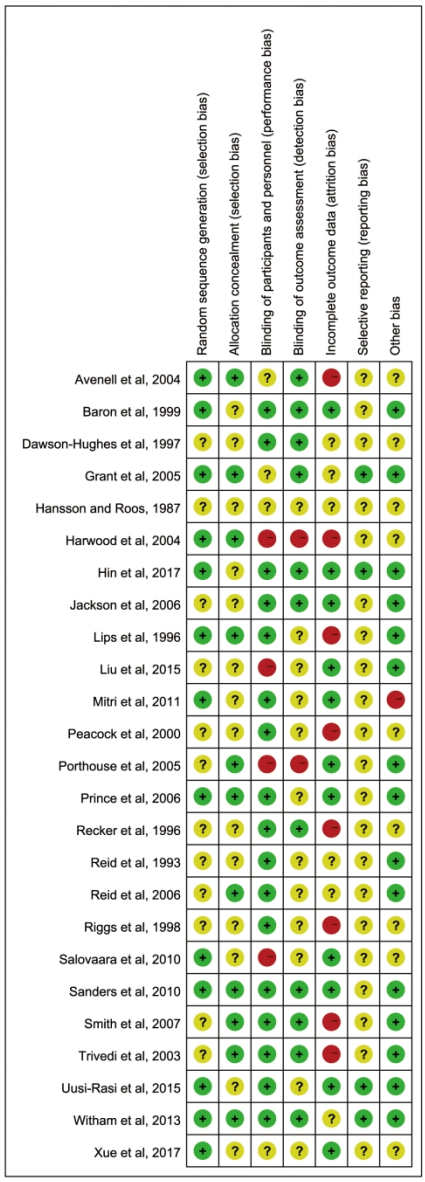
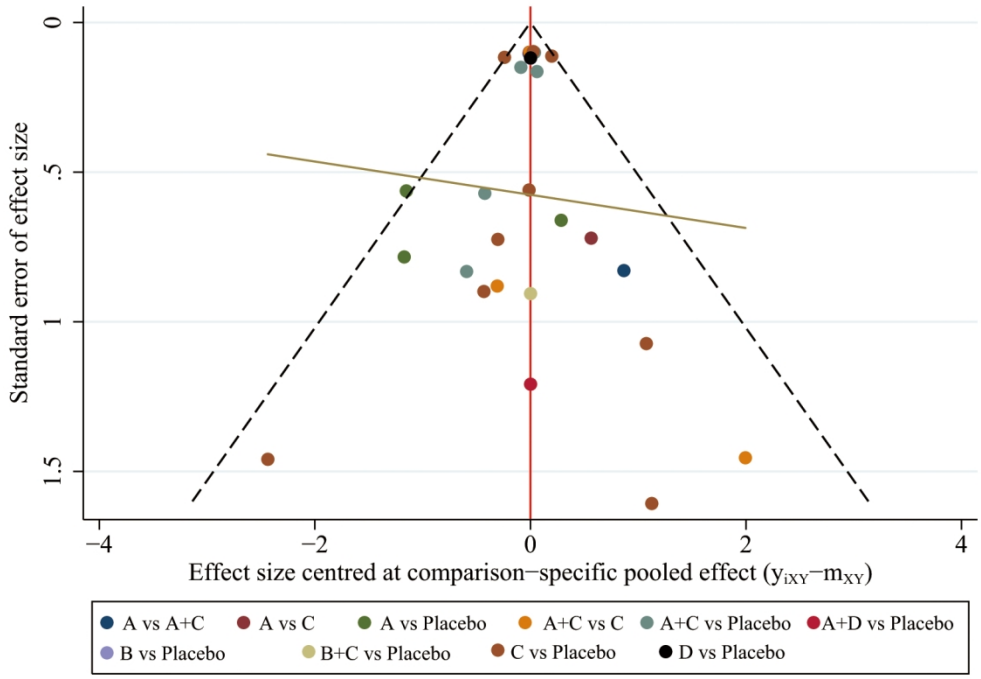
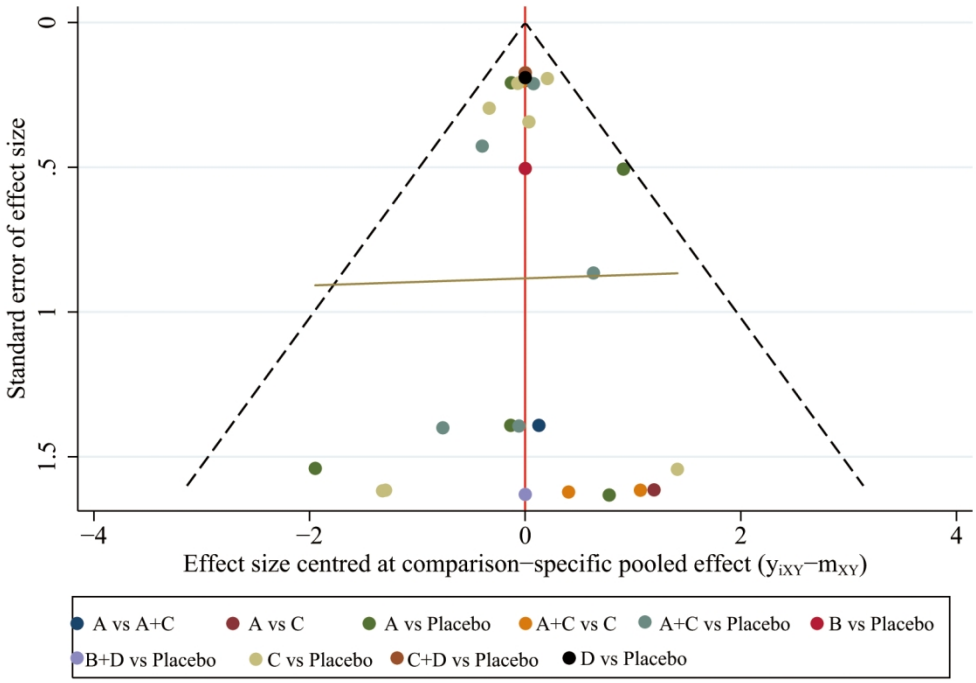
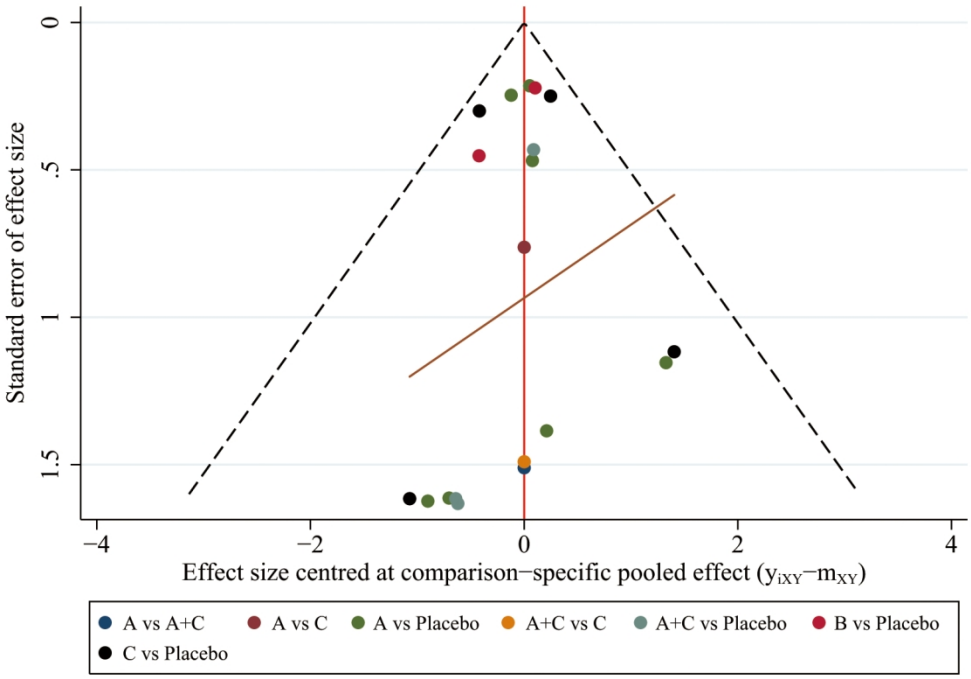


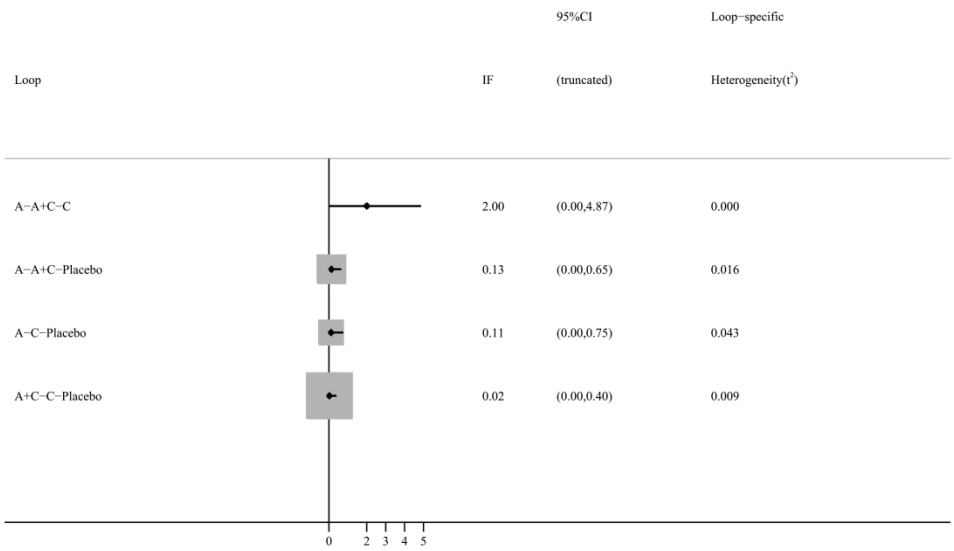
A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

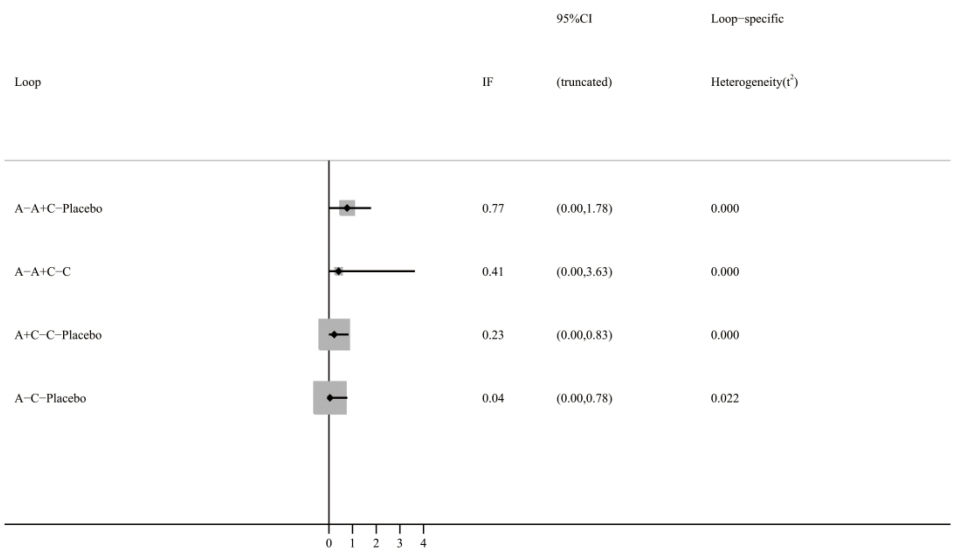

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Avenell et al, 2004
Baron et al, 1999
Dawson-Hughes et al, 1997
Grant et al, 2005
Hansson and Roos, 1987
Harwood et al, 2004
Hin et al, 2017
Jackson et al, 2006
Lips et al, 1996
Liu et al, 2015
Mitri et al, 2011
Peacock et al, 2000
Porthouse et al, 2005
Prince et al, 2006
Recker et al, 1996
Reid et al, 1993
Reid et al, 2006
Riggs et al, 1998
Salovaara et al, 2010
Sanders et al, 2010
Smith et al, 2007
Trivedi et al, 2003
Uusi-Rasi et al, 2015
Witham et al, 2013
Xue et al, 2017

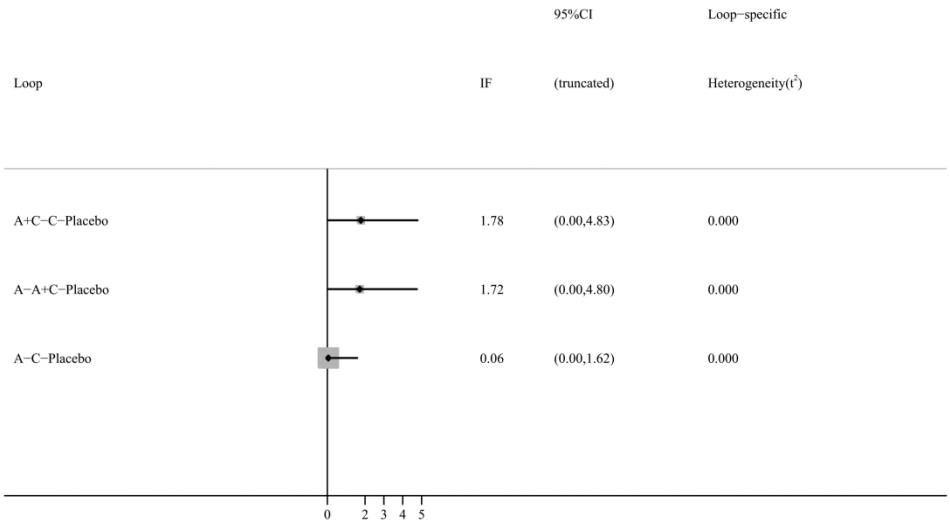

Standard error of effect size
0
.5
1
1.5
−4
−2
0
2
4
Effect size centred at comparison−specific pooled effect ($y_{iXY}-m_{XY}$)
A vs A+C
A vs C
A vs Placebo
A+C vs C
A+C vs Placebo
A+D vs Placebo
B vs Placebo
B+C vs Placebo
C vs Placebo
D vs Placebo


Standard error of effect size
0
.5
1
1.5
−4
−2
0
2
4
Effect size centred at comparison−specific pooled effect ($y_{iXY}-m_{XY}$)
A vs A+C
A vs C
A vs Placebo
A+C vs C
A+C vs Placebo
B vs Placebo
B+D vs Placebo
C vs Placebo
C+D vs Placebo
D vs Placebo

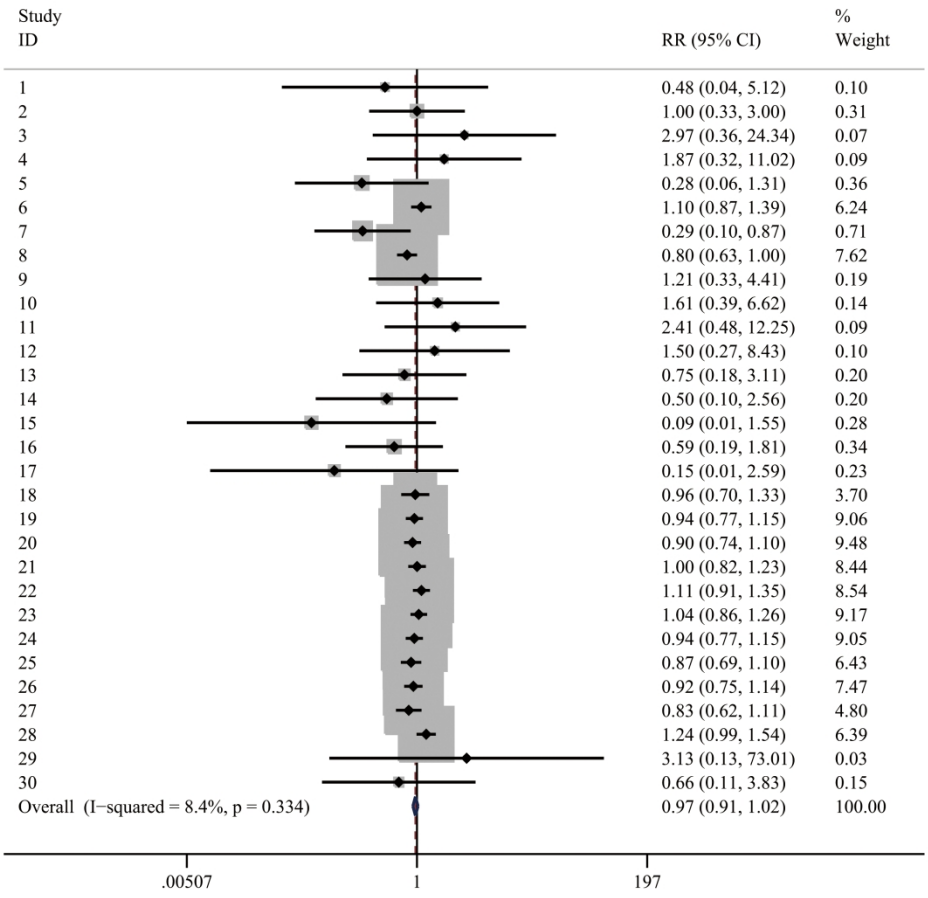

Standard error of effect size
0
.5
1
1.5
−4
−2
0
2
4
Effect size centred at comparison−specific pooled effect (y_{iXY}−m_{XY})
A vs A+C
A vs C
A vs Placebo
A+C vs C
A+C vs Placebo
B vs Placebo
C vs Placebo

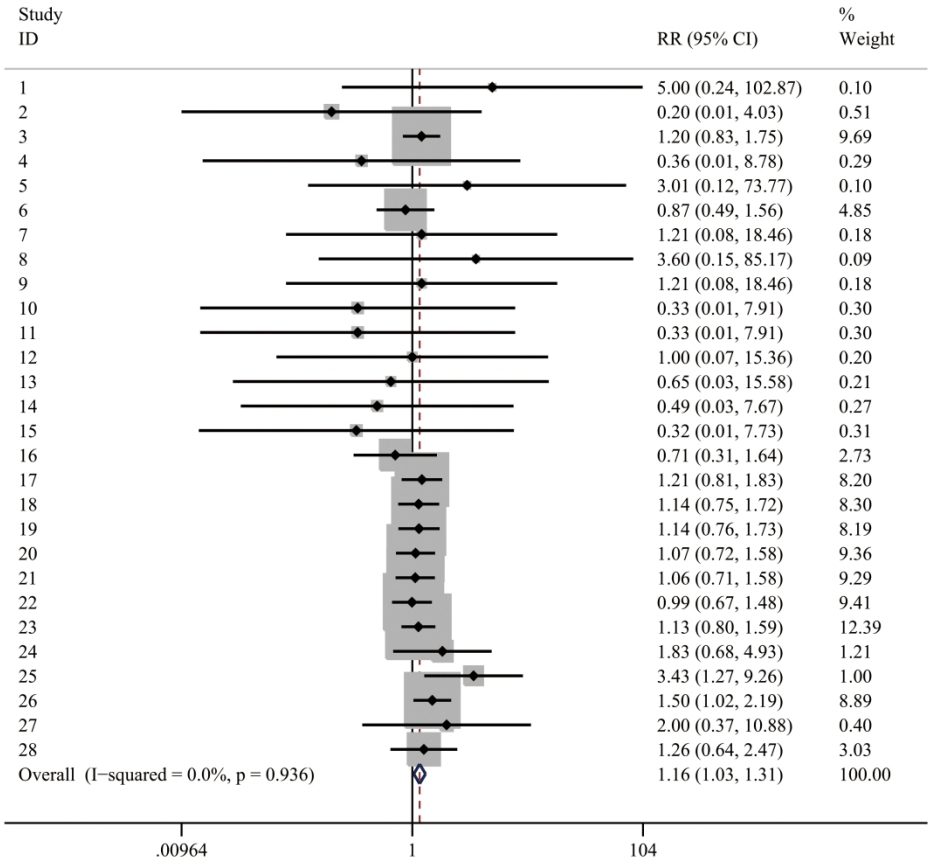

Loop
IF
95%CI
(truncated)
Loop−specific
Heterogeneity(t^2)
A−A+C−C
2.00
(0.00,4.87)
0.000
A−A+C−Placebo
0.13
(0.00,0.65)
0.016
A−C−Placebo
0.11
(0.00,0.75)
0.043
A+C−C−Placebo
0.02
(0.00,0.40)
0.009
0
2
3
4
5

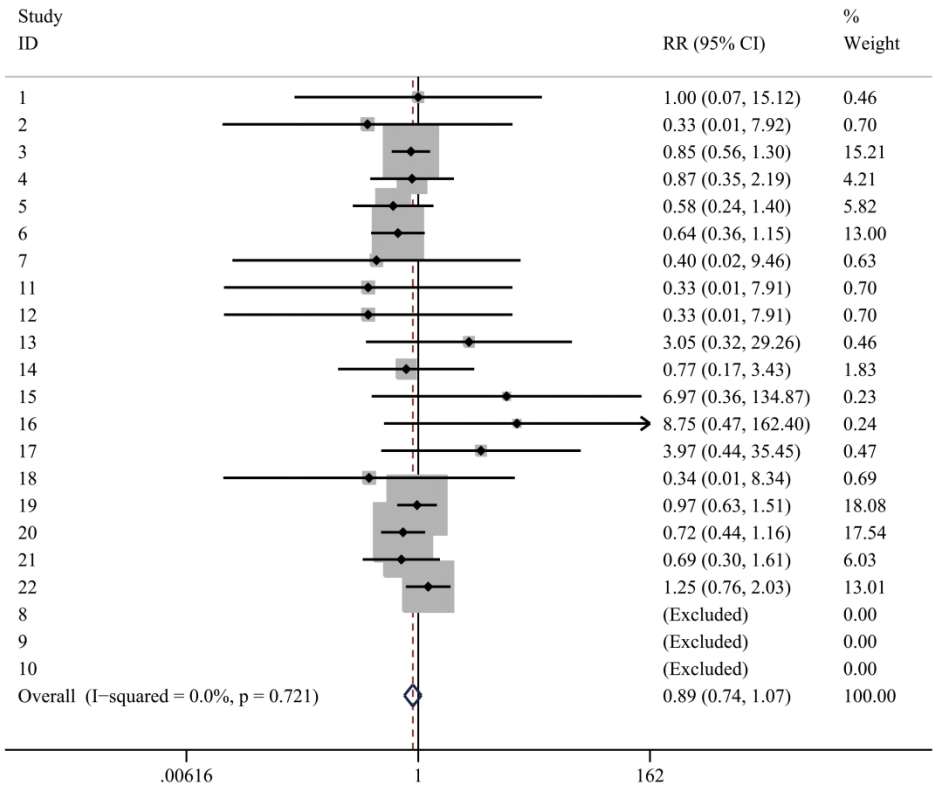

Loop
IF
95%CI
(truncated)
Loop−specific
Heterogeneity(t^2)
A−A+C−Placebo
0.77
(0.00,1.78)
0.000
A−A+C−C
0.41
(0.00,3.63)
0.000
A+C−C−Placebo
0.23
(0.00,0.83)
0.000
A−C−Placebo
0.04
(0.00,0.78)
0.022
0
1
2
3
4



*** Loop(s) [A−A+C−C] are formed only by multi−arm trial(s) − Consistent by definition


Study ID
RR (95% CI)
% Weight
1 0.48 (0.04, 5.12) 0.10
2 1.00 (0.33, 3.00) 0.31
3 2.97 (0.36, 24.34) 0.07
4 1.87 (0.32, 11.02) 0.09
5 0.28 (0.06, 1.31) 0.36
6 1.10 (0.87, 1.39) 6.24
7 0.29 (0.10, 0.87) 0.71
8 0.80 (0.63, 1.00) 7.62
9 1.21 (0.33, 4.41) 0.19
10 1.61 (0.39, 6.62) 0.14
11 2.41 (0.48, 12.25) 0.09
12 1.50 (0.27, 8.43) 0.10
13 0.75 (0.18, 3.11) 0.20
14 0.50 (0.10, 2.56) 0.20
15 0.09 (0.01, 1.55) 0.28
16 0.59 (0.19, 1.81) 0.34
17 0.15 (0.01, 2.59) 0.23
18 0.96 (0.70, 1.33) 3.70
19 0.94 (0.77, 1.15) 9.06
20 0.90 (0.74, 1.10) 9.48
21 1.00 (0.82, 1.23) 8.44
22 1.11 (0.91, 1.35) 8.54
23 1.04 (0.86, 1.26) 9.17
24 0.94 (0.77, 1.15) 9.05
25 0.87 (0.69, 1.10) 6.43
26 0.92 (0.75, 1.14) 7.47
27 0.83 (0.62, 1.11) 4.80
28 1.24 (0.99, 1.54) 6.39
29 3.13 (0.13, 73.01) 0.03
30 0.66 (0.11, 3.83) 0.15
Overall (I−squared = 8.4%, p = 0.334) 0.97 (0.91, 1.02) 100.00
.00507
1
197


Study
ID
RR (95% CI)
%
Weight
1 5.00 (0.24, 102.87) 0.10
2 0.20 (0.01, 4.03) 0.51
3 1.20 (0.83, 1.75) 9.69
4 0.36 (0.01, 8.78) 0.29
5 3.01 (0.12, 73.77) 0.10
6 0.87 (0.49, 1.56) 4.85
7 1.21 (0.08, 18.46) 0.18
8 3.60 (0.15, 85.17) 0.09
9 1.21 (0.08, 18.46) 0.18
10 0.33 (0.01, 7.91) 0.30
11 0.33 (0.01, 7.91) 0.30
12 1.00 (0.07, 15.36) 0.20
13 0.65 (0.03, 15.58) 0.21
14 0.49 (0.03, 7.67) 0.27
15 0.32 (0.01, 7.73) 0.31
16 0.71 (0.31, 1.64) 2.73
17 1.21 (0.81, 1.83) 8.20
18 1.14 (0.75, 1.72) 8.30
19 1.14 (0.76, 1.73) 8.19
20 1.07 (0.72, 1.58) 9.36
21 1.06 (0.71, 1.58) 9.29
22 0.99 (0.67, 1.48) 9.41
23 1.13 (0.80, 1.59) 12.39
24 1.83 (0.68, 4.93) 1.21
25 3.43 (1.27, 9.26) 1.00
26 1.50 (1.02, 2.19) 8.89
27 2.00 (0.37, 10.88) 0.40
28 1.26 (0.64, 2.47) 3.03
Overall (I−squared = 0.0%, p = 0.936) 1.16 (1.03, 1.31) 100.00
.00964
1
104


Study
ID
RR (95% CI)
%
Weight
1 1.00 (0.07, 15.12) 0.46
2 0.33 (0.01, 7.92) 0.70
3 0.85 (0.56, 1.30) 15.21
4 0.87 (0.35, 2.19) 4.21
5 0.58 (0.24, 1.40) 5.82
6 0.64 (0.36, 1.15) 13.00
7 0.40 (0.02, 9.46) 0.63
11 0.33 (0.01, 7.91) 0.70
12 0.33 (0.01, 7.91) 0.70
13 3.05 (0.32, 29.26) 0.46
14 0.77 (0.17, 3.43) 1.83
15 6.97 (0.36, 134.87) 0.23
16 8.75 (0.47, 162.40) 0.24
17 3.97 (0.44, 35.45) 0.47
18 0.34 (0.01, 8.34) 0.69
19 0.97 (0.63, 1.51) 18.08
20 0.72 (0.44, 1.16) 17.54
21 0.69 (0.30, 1.61) 6.03
22 1.25 (0.76, 2.03) 13.01
8 (Excluded) 0.00
9 (Excluded) 0.00
10 (Excluded) 0.00
Overall (I−squared = 0.0%, p = 0.721) 0.89 (0.74, 1.07) 100.00
.00616
1
162

BMJ Open

Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024595.R3
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Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their combination: a network meta-analysis of randomized controlled trials

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Abstract

Objective Inconsistent findings in regard to association between different concentrations of vitamin D, calcium or their combination and the risk of fracture have been reported during the past decade in community-dwelling older people. This study was designed to compare the fracture risk using different concentrations of vitamin D, calcium or their combination.

Design A systematic review and network meta-analysis.

Data sources Randomized controlled trials in PubMed, Cochrane library, and EMBASE databases were systematically searched from the inception dates to December 31, 2017.

Outcomes Total fracture was defined as the primary outcome. Secondary outcomes were hip fracture and vertebral fracture. Due to the consistency of the original studies, a consistency model was adopted.

Results A total of 25 randomized controlled trials involving 43510 participants fulfilled the inclusion criteria. There was no evidence that the risk of total fracture was reduced by using different concentrations of vitamin D, calcium or their combination compared with placebo or no treatment. No significant associations were found between calcium, vitamin D, or combined calcium and vitamin D supplements and the incidence of hip, or vertebral fractures.

Conclusions The use of supplements that included calcium, vitamin D, or both was not found to be better than placebo or no treatment in terms of risk of fractures among community-dwelling older adults. It means the routine use of these supplements in community-dwelling older people should be treated more carefully.

Prospero registration number CRD42017079624

Keywords: Calcium; Vitamin D; Fractures; network meta-analysis

Strengths and limitations of this study

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- This systematic review and meta-analysis combined the evidence from randomized controlled trials.
- Our findings may not support the routine use of these supplements in community-dwelling older people.
- This work does not necessarily preclude any benefit of vitamin D and calcium supplementation in older, frail individuals.
- Potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence.

Introduction

Clinical fractures of the elderly represent a worldwide public health problem that leads to illness and social burden. The patients with osteoporosis in the European Union were estimated to be 27.5 million in 2010, and 3.5 million new fragility fractures were sustained[1]. In Asia, the average cost of osteoporotic fractures accounted for 18.95% of the countries' 2014 gross domestic product (GDP)/capita and increased annually[2-4]. The overall prevalence of osteoporosis or low bone mass in non-institutional population over the age of 50 in the USA was estimated at 10.3% and 43.9%, respectively, which means that 10.2 million elderly people had osteoporosis and 43.4 million people had low bone mass in 2010[5]. With the demographic trend of ageing and the predicted increase in life expectancy, the cost of fracture treatment is expected to rise.

Dietary allowances for calcium range from 700 to 1200 mg/d and vitamin D of 600-800 IU/d have long been recommended for the prevention of osteoporotic fractures in the elderly[6 7]. The supplements of calcium and vitamin D are commonly taken to maintain bone health.

However, the previous randomized controlled trials (RCT) and meta-analyses concerning vitamin D, calcium, or their combination for fractures yielded different efficacy outcomes. For instance, two meta-analyses demonstrated calcium or vitamin D supplementation alone has a small benefit on bone

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mineral density (BMD), but no clinically important to prevent fractures[8 9], while an updated meta-analysis and a pooled analysis found calcium plus vitamin D supplementation can significantly reduce hip fractures by 30% and total fractures by 15%[10 11]. Two RCTs reported that low dose of vitamin D supplementation (less than 800 IU/d) can reduce the incidence of falls[12] and may prevent fractures without adverse effects[13], but other RCTs showed no significant reduction in the incidence of hip or other peripheral fractures[14 15] and its possible effects were seen only in patients with initial calcium insufficiency. Based on the evidence from meta-analysis, Bischoff-Ferrari et al [16] illustrated that high-dose vitamin D supplementation (800 IU/d or higher) not only reduced the risk of falls and hip fractures, but also prevented non-vertebral fractures. In contrast, a study reported annual high-dose oral vitamin D resulted in an increased risk of falls and fractures [17]. On the other hand, low-dose calcium supplementation (less than 800mg/d) effectively led to a sustained reduction in the rate of bone loss [18] and turnover. Although it was also reported that the high dose of calcium (800 mg/d or higher) was associated with a lower risk of clinical fractures [19]. The high-dose calcium with high-dose vitamin D can't prevent fractures according to the evidence from reported RCT [20], but a meta-analysis supported their combination can prevent bone loss and significantly reduce the risk of hip fractures and all osteoporotic fractures [21]. Thus, it's challenging to conclude a dose-response relation between the intakes of vitamin D, calcium, or their combination and the main outcomes in these heterogeneous literatures.

Therefore, this study was designed to compare the fracture risk using different concentrations of vitamin D, calcium or their combination, and comprehensively evaluate the optimal concentration to guide clinical practice and public prevention in community-dwelling older people.

Methods

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Search strategy and selection criteria

This review and meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) extension statement for network meta-analysis. Our meta-analysis was registered prospectively in PROSPERO (CRD42017079624) and the Checklist PRISMA 2009 (**Supplementary Table 1**) will be used and check our final reports [22].

We restricted our meta-analysis to the inclusion criteria should meet following details: (1) RCTs; (2) Interventions must be one of the following three: vitamin D only, calcium only, both vitamin D and calcium; (3) Complete outcome data of fracture; (4) Trials enrolling adults older than 50 years and living in their communities; (5) Only studies that lasted more than a year. Exclusion criteria were (1) Calcium or vitamin D combined with other therapies (eg: hormones, exercise); (2) Trials in which vitamin D analogues (eg: calcitriol) or hydroxylated vitamin D were used; (3) Trials in which dietary intake of calcium or vitamin D (eg: from milk) was evaluated; (4) Patients suffering from illness or long-term use of certain drugs affecting the stability of the calcium metabolism, such as metabolic bone disease, bone tumour, treatment of steroids and so on.

Participants must be randomly assigned to two or more following groups: (1) high calcium (800 mg/d or higher) only; (2) low calcium (less than 800 mg/d) only; (3) high vitamin D (800 IU/d or higher) only; (4) low vitamin D (less than 800 IU/d) only; (5) high calcium (800 mg/d or higher) + high vitamin D (800 IU/d or higher); (6) high calcium + low vitamin D (less than 800 IU/d); (7) low calcium (less than 800 mg/d) + high vitamin D; (8) low calcium + low vitamin D; (9) placebo. The interventions should be compared with placebo.

Two authors (ZHF and GZ) independently searched the electronic literature database of PubMed, Embase, Cochrane database on December 31, 2017 (detailed search strategies are reported in

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supplementary Table 2). Related articles and reference lists were searched to avoid original miss. The reference studies of previous systematic reviews, meta-analysis, and included studies were manually searched to avoid initial miss. After 2 authors assessed the potentially eligible studies independently, any disagreement was discussed and resolved with the third independent author (QT).

Data collection and assessment of risk of bias

Two reviewers (ZHS and XBL) independently extracted data, and the third reviewer (LT) checked the consistency between them. A standard data extracted form was used at this stage, including the authors, publishing date, country, participant characteristics; doses of calcium, vitamin D, or their combination; dietary calcium intake; baseline serum 25-hydroxyvitamin D concentration; and trial duration. For continuous outcomes, the mean, SD (standard deviation) and participant number will be extracted. For dichotomous outcomes, we extracted the total numbers and the numbers of events of both groups. The data in other forms was recalculated when possible to enable pooled analysis.

We used the Cochrane risk of bias tool to assess risk bias of included studies. The tool has seven domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. The classification of the judgment for each domain was low risk of bias, high risk of bias, or unclear risk of bias and two authors (ZHF and GZ) independently evaluated the risk of studies.

Data synthesis and statistical analysis

The data was extracted and input into the STATA software (version 12.0; StataCorp, College Station, TX, USA) for network meta-analysis. And we generated network plots for each outcome to illustrate which interventions had been compared directly in the included studies. Network meta-analysis is an extension of standard meta-analysis to compare multiple treatments based on

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randomized controlled trial evidence, which forms a connected network of comparisons. Treatment effect estimates from network meta-analysis exploit both the direct comparisons within trials and the indirect comparisons across trials. To choose the random effects or fixed effects model, we either make a judgement about what is most likely to be appropriate based on the assumptions of the different models or conduct both fixed or random effects and compare which seems to fit the data better[23]. Relative risk (RR) with 95% confidence intervals (CIs) was calculated for dichotomous outcomes while weighted mean difference (WMD) with 95% CIs for the continuous. Inconsistency refers to differences between direct and various indirect effect estimates for the same comparison. To assess inconsistency, we estimated the inconsistency factors in closed loop based on the method described by Chaimani et al[24]. The heterogeneity in each closed loop was estimated by utilizing inconsistency factor (IF). If the 95% confidence intervals (95% CI) of IF values are not truncated at zero, it suggests that the inconsistency among studies has statistical significance. We used the surface under the cumulative ranking probabilities (SUCRA) to indicate which treatment was the best one. The funnel plot was used to identify possible publication bias if the number of studies was larger than 10.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, and no patients were involved in developing plans for design or implementation of the study. Furthermore, no patients were asked to advice on interpretation or writing up of results. Since this meta-analysis used aggregated data from previous trials, it is unable to disseminate the results of the research to study participants directly.

Result

Data Retrieval

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In summary, a total of 7909 potential records were initially identified through PubMed (5187), Embase (2688), Cochrane Data base (34). Based on our review of the title and abstract, 99 full-text papers were reviewed and 25 studies[13 17 19 20 25-45] met inclusion criteria (**Figure 1)**.

Study and Patient Characteristics

The characteristics of all 25 included studies were summarized and shown in **supplementary Table 3**. And the detailed data of outcomes was collected in **supplementary Table 4**. The papers had similar distributions of sex, age, country, intervention and all of them were community-dwelling older people. Hansson et al[29] did not report the residential status of participants, although a previous meta-analysis classified this status as community. The trial by Hansson et al was included, but a sensitivity analysis was performed that excluded that trial (**supplementary Figure 1**).

Supplementary Figure 2 showed the assessment of the risk of bias. All studies were randomized; 17 were double-blind, placebo-controlled trials; 13 trials described an adequate random sequence generation process; and 11 trials described the methods used for allocation concealment. No obvious publication bias was reported according to the **supplementary Figure 3, supplementary Figure 4** and **supplementary Figure 5**.

Inconsistence and heterogeneity check

The statistical inconsistency between direct and indirect comparisons was generally low according to inconsistency test because the CI values included zero (**supplementary Figure 6, supplementary Figure 7, supplementary Figure 8**). Therefore, we adopted a consistency model in all three groups. Meanwhile, we adopted the fixed effects models and the heterogeneity parameter I^2 values were 8.4%, 0% and 0% respectively, which indicated no obvious heterogeneity was observed in all these results (**supplementary Figure 9, supplementary Figure 10, supplementary Figure 11**).

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Primary outcome: total fracture

For estimating the vitamin D, calcium or their combination efficacy against total fractures, we looked at data from 24965 individuals from 18 studies[13 17 19 20 25 26 28 30 31 33-35 37 39 40 43-45]. Pooled estimates included 15 studies with one treatment, 1 study with two treatments, and 2 studies with three treatments.

The network plot of comparisons on total fractures was shown in **Figure 2A**. The forest plot for the network meta-analysis was shown in **Figure 3**. The RR values and 95% CIs are summarized in **Figure 3**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between interventions and placebo (P<0.05). So we didn't continue to make ranking graph of distribution of probabilities on total fractures.

Secondary outcomes: **hip fracture and vertebral fracture**

A total of 41845 individuals were included from 16 studies[13 17 19 20 25-28 30 32 33 37 39 40 42 43] for evaluate the drug efficacy against hip fractures. Pooled estimates included 13 studies with one treatment, 1 study with two treatments, and two studies with three treatments.

The network plot of comparisons on hip fractures was shown in **Figure 2B**. The forest plot for the network meta-analysis was shown in **Figure 4**. The RR values and 95% CIs are summarized in **Figure 4**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between drug experimental groups and placebo (P<0.05). So we didn't continue to make ranking graph of distribution of probabilities on total fractures.

A total of 17612 individuals were collected from 12 studies[13 17 19 20 25 28 29 36 38-41] involving vertebral

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fractures. Pooled estimates included 10 studies with one treatment, and two studies with three treatments.

The network plot of comparisons on vertebral fractures was shown in **Figure 2C**. The forest plot for the network meta-analysis was shown in **Figure 5**. The RR values and 95% CIs are summarized in **Figure 5**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their combination that remained in the main network. Neither do the statistical differences between drug experimental groups and placebo ($P<0.05$). So we didn't continue to make ranking graph of distribution of probabilities on total fractures. In a separate sensitivity analysis, we excluded Hansson's study[29] (**supplementary Figure 1**). However, there was still no significant association of vitamin D, calcium or their combination with total fracture.

Discussion

Vitamin D supplementation and calcium are suggested as interventions to treat and prevent fracture. We found the previous meta-analyses and RCTs are critically inconsistent in efficacy of different doses of vitamin D with calcium on fractures.

Results of this meta-analysis showed that calcium, calcium plus vitamin D, and vitamin D supplementation alone were not significantly associated with a lower incidence of hip, vertebral, or total fractures in community-dwelling older adults. Sensitivity analyses that excluded low-quality trials and studies that exclusively enrolled patients with particular medical conditions did not alter these results.

A meta-analysis conducted by Jia-Guo Zhao et al[46] showed that no significant difference was found in the incidence of hip or other fractures, which was similar to our result. However, the object of Zhao's study was to investigate whether calcium, vitamin D, or combined calcium and vitamin D

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supplement are associated with a lower facture incidence while our study was designed to evaluate the optimal concentration of them. Meanwhile, in Zhao's meta-analysis, the participants of the included study reported by Massart[47] were adult maintenance hemodialysis patients, which may result in the imbalance of calcium in the body. Patients on hemodialysis may also be receiving 1,25-dihydroxyvitamin D, which may affect their response to vitamin D supplementation. So we did not include that trial in our network meta-analysis. What's more, we didn't include studies that lasted less than a year because we thought this time-frame was too short to see anti-fracture efficacy. And we suspected that a network meta-analysis might be a more suitable choice concerning all these different interventions mixed.

Bischoff-Ferrari et al [48] reported that high-dose vitamin D supplementation (800 IU/d or higher) played an important role in the reduction of the risk of falls and hip fractures, as well as prevented non-vertebral fractures in adults 65 years or older. However, their findings may have been influenced by the trial of Chapuy et al [49], which only enrolled participants living in an institution. What's more, differences in conclusions of previous meta-analyses and the current meta-analysis were due to the recently published trials which reported neutral or harmful associations of vitamin D supplementation and fracture incidence more and more. Study findings here indicated that vitamin D might result in a higher risk for hip fracture, but this conclusion did not reach statistical significance. This finding may be attributable to lack of statistical power in this meta-analysis.

Most recently there was a meta-analysis published in the Lancet by Bolland et al[50], whose findings suggested that vitamin D supplementation does not prevent fractures or falls, or have clinically meaningful effects on bone mineral density. Although it was similar to our study to some extent, they are really different. First, we only included community-dwelling older people. We found that some

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meta-analyses equated community-dwelling older people with those in nursing institution. The lack of exercise, dietary intake and exposure to sunlight made people in nursing institution turned more susceptible to the use of supplements including vitamin D, calcium or their combination. Although the studies involving participants living in nursing institution were only a small part, but it could change the whole outcomes and produce false positive results. We found only Avenell's study paid attention to this question when they conducted a subgroup analysis, but they did not discussed separately. Meanwhile, we only enrolled adults older than 50 years and trial duration more than 1 year to reduce the statistical heterogeneity in network meta-analysis. Furthermore, the current analyses included calcium supplementation, where the Bolland's study focused on vitamin D.

However, possible limitations of this study protocol include potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence. Some RCTs were of poor quality and, for example, used unclear allocation concealment. So we made a sensitivity analysis by excluding low-quality trials. Meanwhile, some study characteristics such as baseline serum 25-hydroxyvitamin D concentrations might be to contribute heterogeneity so future analyses are still needed to explore this potential heterogeneity. What's more, we combined bolus dosing by injection with oral supplements taken daily/monthly/yearly, which might have different effects on vitamin D status in the body. In addition, the report ignored the effect of treatment with vitamin D on plasma 25-hydroxy-vitamin D concentrations and sub-types of fracture, such as pathologic fractures; this work does not necessarily preclude any benefit of vitamin D and calcium supplementation in older, frail individuals.

Conclusions

In this meta-analysis of randomized clinical trials, we found that the use of different concentrations of vitamin D, calcium or their combination in community-dwelling older adults was not associated with a

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lower risk of fractures. Our findings may not support the routine use of these supplements in community-dwelling older people.

Contributors

ZCH and AMW conceived the study. The search strategy was developed by LT and XBL. ZHF, GZ and QT will complete electronic search, select publications and assess their eligibility. ZHS and XBL will extract information of the included studies after screening. JWX will check the data entry for accuracy and completeness. ZCH and LT will give advice for data analysis and presentation of study result. LYS and CMS contributed to the text revision. WFN and AMW supervised the overall conduct of the study. All the authors drafted and critically reviewed and approved the final manuscript.

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Conflicts of interest

None declared

Patient consent

Not required.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

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All data relevant to the study are included in the article or uploaded as supplementary information.

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Legends:

Figure 1. The selection of literature for included studies.

Figure 2. The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral

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fractures (C). A: high calcium (800 mg/d or higher)； B: low calcium (less than 800 mg/d)； C: high vitamin D (800 IU/d or higher)； D: low vitamin D (less than 800 IU/d)

Figure 3. The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher)； B: low calcium (less than 800 mg/d)； C: high vitamin D (800 IU/d or higher)； D: low vitamin D (less than 800 IU/d)

Figure 4. The forest plot for the risk of hip fractures. A: high calcium (800 mg/d or higher)； B: low calcium (less than 800 mg/d)； C: high vitamin D (800 IU/d or higher)； D: low vitamin D (less than 800 IU/d)

Figure 5. The forest plot for the risk of vertebral fractures. A: high calcium (800 mg/d or higher)； B: low calcium (less than 800 mg/d)； C: high vitamin D (800 IU/d or higher)； D: low vitamin D (less than 800 IU/d)

supplementary Figure 1. A sensitivity analysis excluded the trial of Hansson et al. A: high calcium (800 mg/d or higher)； B: low calcium (less than 800 mg/d)； C: high vitamin D (800 IU/d or higher)； D: low vitamin D (less than 800 IU/d)

supplementary Figure 2. Risk of Bias Assessment of All Included Studies

supplementary Figure 3. Publication bias for the total fractures. A: high calcium (800 mg/d or higher)；

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B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 4. Publication bias for the hip fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 5. Publication bias for the vertebral fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 6. Inconsistency test for the total fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 7. Inconsistency test for the hip fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

supplementary Figure 8. Inconsistency test for the vertebral fractures. A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

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supplementary Figure 9. Heterogeneity test for the total fractures. A: the result of random effects model; B: the result of fixed effects model.

supplementary Figure 10. Heterogeneity test for the hip fractures. A: the result of random effects model; B: the result of fixed effects model.

supplementary Figure 11. Heterogeneity test for the vertebral fractures. A: the result of random effects model; B: the result of fixed effects model.

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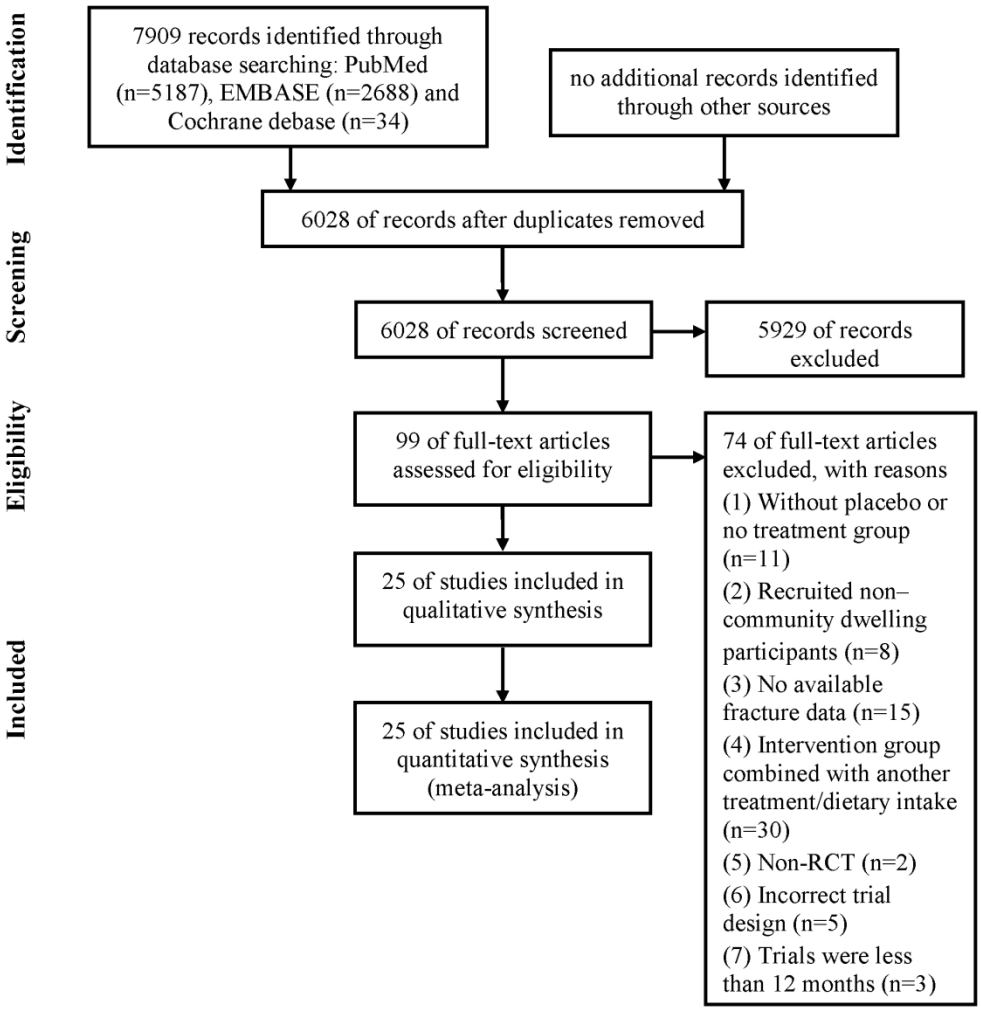

The selection of literature for included studies.

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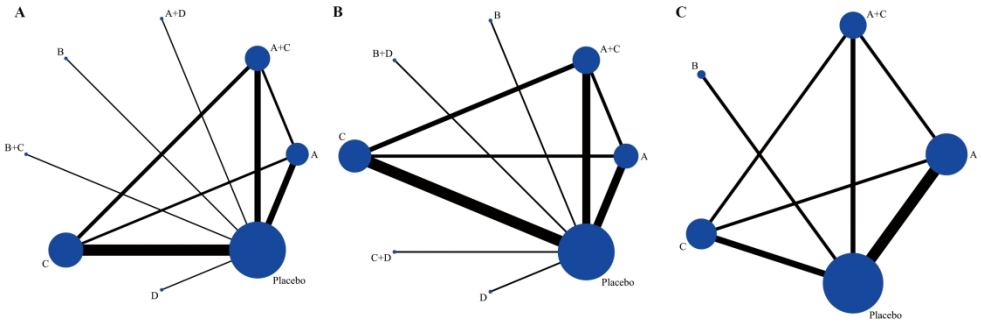

The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral fractures (C). A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)

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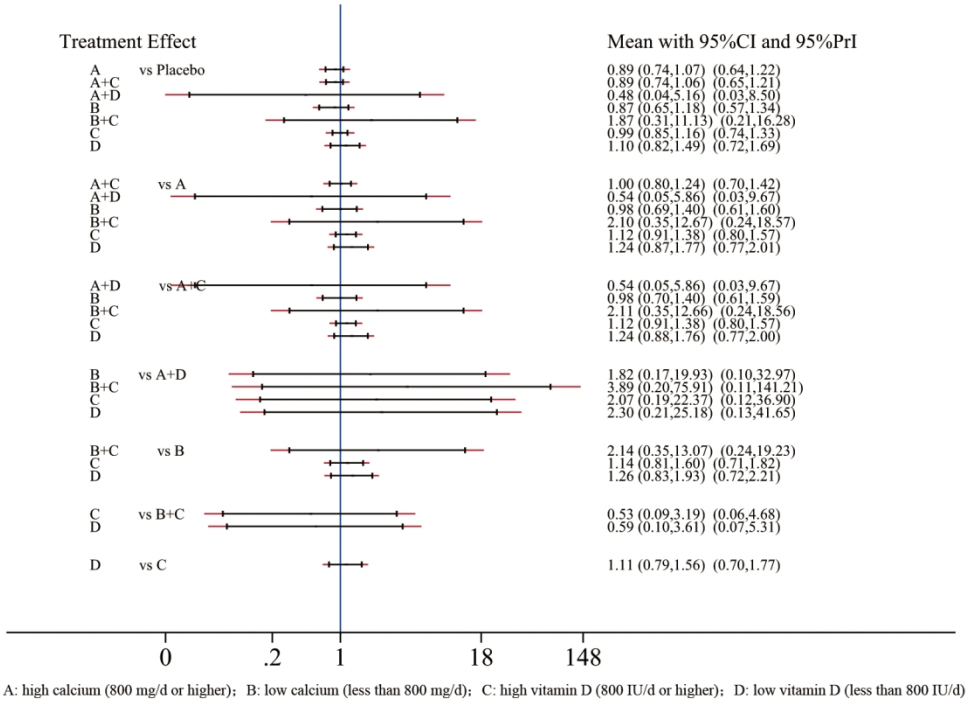
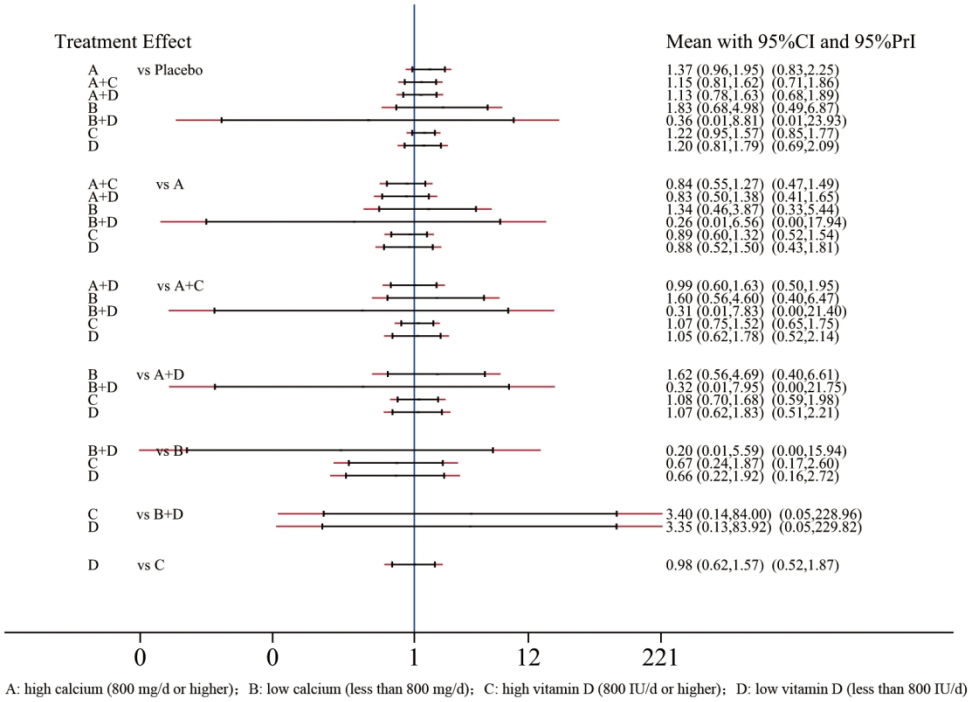
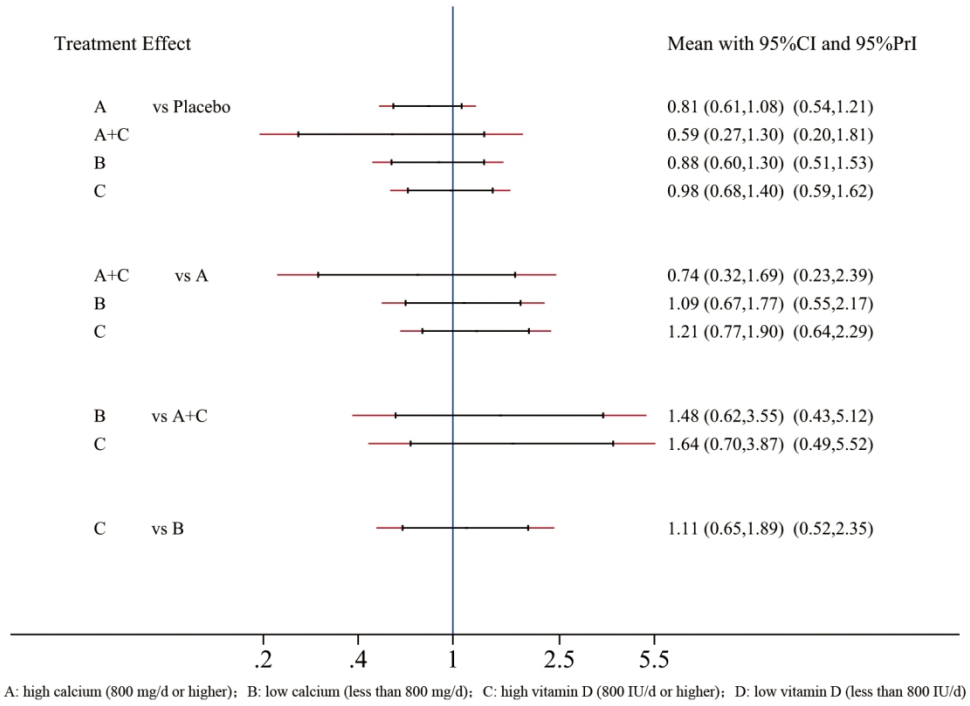


The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)



The forest plot for the risk of hip fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)



The forest plot for the risk of vertebral fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)

Supplementary Table 1 - Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5

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Section/topic	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10

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Section/topic	#	Checklist item	Reported on page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).	10-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

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Supplementary Table 2. Search Strategy for Each Database

Database	Search strategy
Pubmed	#1 "calcium"[MeSH Terms] OR "calcium"[All Fields]
	#2 "vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]
	#3 "fractures, bone"[MeSH Terms] OR ("fractures"[All Fields] AND "bone"[All Fields]) OR "bone fractures"[All Fields] OR "fracture"[All Fields]
	#4 #1 or #2
	#5 #3 and #4

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Source	Intervention	Women, No. (%)	Mean Age, y	Previous Fracture	Calcium Intake, mg/d	Baseline 25OHD, ng/mL	Treatment Duration
Avenell et al, 2004 (United Kingdom)	Calcium(1 g/d) (n = 29)	NA [a] (83)	78 [b]	Yes	NA	NA	3.8 y
	No treatment (n = 35)						
	D_3(800IU/d) (n = 35)	NA [a] (83)	78 [b]	Yes	NA	NA	3.8 y
	No treatment (n = 35)						
	Calcium (1g/d) + D_3 (800IU/d) (n = 35)	NA [a] (83)	78 [b]	Yes	NA	NA	3.8 y
	No treatment (n = 35)						
Baron et al, 1999 (United States)	Calcium: 1.2 g/d (n = 464)	258 (28)	61.0	NA	877	NA	4 y
	Placebo (n = 466)						
Dawson-Hughes et al, 1997 (United States)	Calcium (0.5g/d) + D_3 (700IU/d) (n = 187)	213 (54)	71.1	NA	729	29.6 [e]	3 y
	Placebo (n = 202)						
Grant et al, 2005 (United Kingdom)	Calcium(1 g/d) (n = 1311)	2241 (85)	77	Yes	NA	15.2 [e,f]	2-5 y
	Placebo (n = 1332)						
	D_3(800IU/d) (n = 1343)	2264 (85)	77	Yes	NA	15.2 [e,f]	2-5 y
	Placebo (n = 1332)						
	Calcium (1g/d) + D_3 (800IU/d) (n = 1306)	2232 (85)	77.5	Yes	NA	15.2 [e,f]	2-5 y
	Placebo (n = 1332)						
Hansson and Roos, 1987 (Sweden)	Calcium (1g/d) (n = 25)	50 (100)	65.9	Yes	NA	NA	3 y
	Placebo (n = 25)						
Harwood et al, 2004 (United Kingdom)	D_3 (300000 IU once) (n = 38)	75 (100)	80.5	Yes	NA	11.6	1 y
	No treatment (n = 37)						
	Calcium (1g/d) + D_2 (300000 IU once) (n = 36)	112 (100)	81.7	Yes	NA	11.9	1 y
	Calcium (1g/d) + D_3 (800IU/d) (n = 39)						
	No treatment (n = 37)						
Hin et al, 2017 (United Kingdom)	D_3(4000 IU/d)(n = 102)	150 (49)	71.7	Partial [c]	710	20.1	1 y
	D_3(2000 IU/d)(n = 102)						
	Placebo (n = 101)						
Jackson et al, 2006 (United States)	Calcium (1g/d) + D_3 (400 IU/d) (n = 4015)	7972 (100)	62.4	Partial [c]	1151	18.9 [e]	7 y

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	Placebo (n = 3957)						
Lips et al, 1996 (The Netherlands)	400 IU/d (n = 1291) Placebo (n = 1287)	1916 (74)	80.0	No hip fracture	868	10.6 [e]	3-4 y
Liu et al, 2015 (China)	Calcium (1.5g/d) + D_3 (600 IU/d) (n = 50) Placebo (n = 48)	98 (100)	62.1	No	1500	NA	1 y
Mitri et al, 2011 (United States)	D_3(2000 IU/d)(n = 23) Placebo (n = 24)	25 (53)	58.0	NA	926	25.3	4 mo
Peacock et al, 2000 (United States)	Calcium (0.75g/d) (n = 126) Placebo (n = 135)	187 (72)	73.8	Partial [c]	597	25.0	4 y
Porthouse et al, 2005 (United Kingdom)	Calcium (1g/d) + D_3 (800 IU/d) (n = 1321) No treatment (n = 1993)	3314 (100)	76.8	Partial [c]	1080	NA	1.5-3.5 y
Prince et al, 2006 (Australia)	Calcium (0.48g/d) (n = 730) Placebo (n = 730)	1460 (100)	75.2	Partial [c]	915	31.0 [e]	5 y
Recker et al, 1996 (United States)	Calcium (1.2 g/d) (n = 95) Placebo (n = 102)	197 (100)	73.5	Partial [c]	434	25.5 [e]	4 y
Reid et al, 1993 (New Zealand)	Calcium (1 g/d) (n = 68) Placebo (n = 67)	135 (100)	58	No vertebral fracture	750	37.5	4 y
Reid et al, 2006 (New Zealand)	Calcium (1 g/d) (n = 732) Placebo (n = 739)	1471 (100)	74.3	Partial [c]	857	20.7	5 y
Riggs et al, 1998 (United States)	Calcium (1.6 g/d) (n = 119) Placebo (n = 117)	236 (100)	66.2	No	714	30.1	4 y
Salovaara et al, 2010 (Finland)	Calcium(1g/d) + D_3 (800 IU/d) (n = 1718) No treatment (n = 1714)	3432 (100)	67.3	Partial [c]	957	19.8 [e]	3 y
Sanders et al, 2010 (Australia)	D_3 (500000 IU every year) (n = 1131) Placebo (n = 1127)	2258 (100)	76.1	Partial [c]	976	19.8 [e]	3-5 y
Smith et al, 2007 (United Kingdom)	D_3 (300000 IU every year) (n = 4727) Placebo (n = 4713)	5086 (54)	79.1	Partial [c]	625 [d]	22.6 [e]	3 y
Trivedi et al, 2003 (United Kingdom)	D_3 (100000 IU every 4 mo) (n = 1345) Placebo (n = 1341)	649 (24)	74.8	NA	742	NA	5 y
Yusi-Rasi et al, 2015	D_3 (800 IU/d) (n = 102)	204 (100)	73.9	NA	1082	26.7	2 y

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(Finland)	Placebo (n = 102)						
Witham et al, 2013 (United Kingdom)	D_3(100000 IU every 3 mo) (n = 80)	77 (49)	76.8	NA	1125	18.0	1 y
	Placebo (n = 79)						
Xue et al, 2017 (China)	Calcium (0.6g/d) + D_3 (800 IU/d) (n = 139)	312 (100)	63.6	Partial [c]	NA	30.8	1 y
	Placebo (n = 173)						

Abbreviation: 25OHD, 25-hydroxyvitamin D; NA, not available

[a] Women accounted for 83% of total participants in this trial, but detailed data not available for each group.

[b] Mean age is 78 y for total participants in this trial, but detailed data not available for each group.

[c] This trial reported partial participants with fracture history.

[d] Partial participants were assessed for dietary calcium intake.

[e] Partial participants received measurement of baseline 25OHD concentrations.

[f] The RECORD trial reported that the mean baseline 25OHD concentrations for a sample of 60 participants was 15.2 ng/mL, but detailed data were not available for each group.

supplementary Table 3. The characteristics of the included studies.

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Source	Treatment Duration	Intervention	No. of Participants		
			Total Fracture	Hip fracture	Vertebral Fracture
Avenell et al, 2004 (United Kingdom)	3.8 y	Calcium(1 g/d) (n = 29)	4	1	0
		D_3(800IU/d) (n = 35)	3	0	0
		Calcium (1g/d) + D_3 (800IU/d) (n = 35)	2	1	0
		No treatment (n = 35)	4	1	1
Baron et al, 1999 (United States)	4 y	Calcium: 1.2 g/d (n = 464)	4	1	
		Placebo (n = 466)	14	0	
Dawson-Hughes et al, 1997 (United States)	3 y	Calcium (0.5g/d) + D_3 (700IU/d) (n = 187)		0	
		Placebo (n = 202)		1	
Grant et al, 2005 (United Kingdom)	2-5 y	Calcium(1 g/d) (n = 1311)	166	49	3
		D_3(800IU/d) (n = 1343)	188	47	4
		Calcium (1g/d) + D_3 (800IU/d) (n = 1306)	165	46	0
		Placebo (n = 1332)	179	41	1
Hansson and Roos, 1987 (Sweden)	3 y	Calcium (1g/d) (n = 25)			1
		Placebo (n = 25)			1
Harwood et al, 2004 (United Kingdom)	1 y	D_3 (300000 IU once) (n = 38)	0	0	
		Calcium (1g/d) + D_2 (300000 IU once) (n = 36) Calcium (1g/d) + D_3 (800IU/d) (n = 39)	6	1	
		No treatment (n = 37)	5	1	
Hin et al, 2017 (United Kingdom)	1 y	D_3(4000 IU/d)(n = 102) D_3(2000 IU/d)(n = 102)	6		
		Placebo (n = 101)	1		
Jackson et al, 2006 (United States)	7 y	Calcium (1g/d) + D_3 (400 IU/d) (n = 4015)		70	
		Placebo (n = 3957)		61	

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Lips et al, 1996 (The Netherlands)	3-4 y	400 IU/d (n = 1291)	135	58	
		Placebo (n = 1287)	122	48	
Liu et al, 2015 (China)	1 y	Calcium (1.5g/d) + D_3 (600 IU/d) (n = 50)	1		
		Placebo (n = 48)	2		
Mitri et al, 2011 (United States)	4 mo	D_3(2000 IU/d)(n = 23)	1		
		Placebo (n = 24)	0		
Peacock et al, 2000 (United States)	4 y	Calcium (0.75g/d) (n = 126)			7
		Placebo (n = 135)			13
Porthouse et al, 2005 (United Kingdom)	1.5-3.5 y	Calcium (1g/d) + D_3 (800 IU/d) (n = 1321)	58	8	
		No treatment (n = 1993)	91	17	
Prince et al, 2006 (Australia)	5 y	Calcium (0.48g/d) (n = 730)	110	11	38
		Placebo (n = 730)	126	6	39
Recker et al, 1996 (United States)	4 y	Calcium (1.2 g/d) (n = 95)			27
		Placebo (n = 102)			34
Reid et al, 1993 (New Zealand)	4 y	Calcium (1 g/d) (n = 68)	2	0	0
		Placebo (n = 67)	7	2	1
Reid et al, 2006 (New Zealand)	5 y	Calcium (1 g/d) (n = 732)	134	17	27
		Placebo (n = 739)	147	5	38
Riggs et al, 1998 (United States)	4 y	Calcium (1.6 g/d) (n = 119)			8
		Placebo (n = 117)			9
Salovaara et al, 2010 (Finland)	3 y	Calcium(1g/d) + D_3 (800 IU/d) (n = 1718)	78	4	9
		No treatment (n = 1714)	94	2	13
Sanders et al, 2010 (Australia)	3-5 y	D_3 (500000 IU every year) (n = 1131)	155	19	35
		Placebo (n = 1127)	125	15	28
Smith et al, 2007 (United Kingdom)	3 y	D_3 (300000 IU every year) (n = 4727)		66	
		Placebo (n = 4713)		44	
Trivedi et al, 2003 (United Kingdom)	5 y	D_3 (100000 IU every 4 mo) (n = 1345)	119	21	18
		Placebo (n = 1341)	149	24	28

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Uusi-Rasi et al, 2015 (Finland)	2 y	D_3 (800 IU/d) (n = 102)	6	2
		Placebo (n = 102)	6	0
Witham et al, 2013 (United Kingdom)	1 y	D_3(100000 IU every 3 mo) (n = 80)	2	
		Placebo (n = 79)	3	
Xue et al, 2017 (China)	1 y	Calcium (0.6g/d) + D_3 (800 IU/d) (n = 139)	3	
		Placebo (n = 173)	2	

Supplementary Table 4. The detailed data of outcomes

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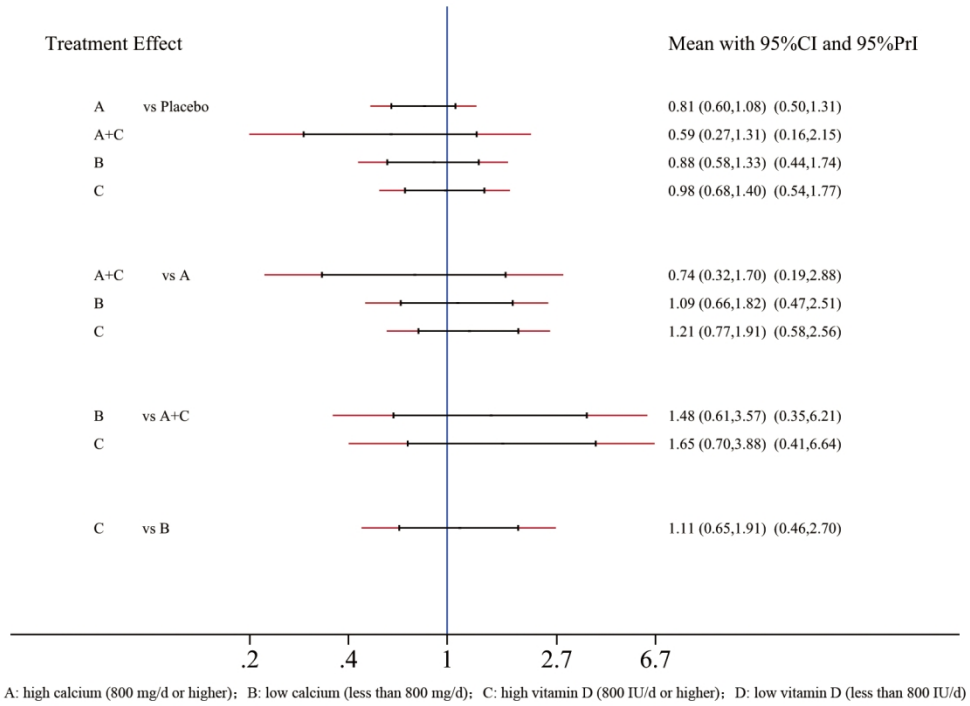
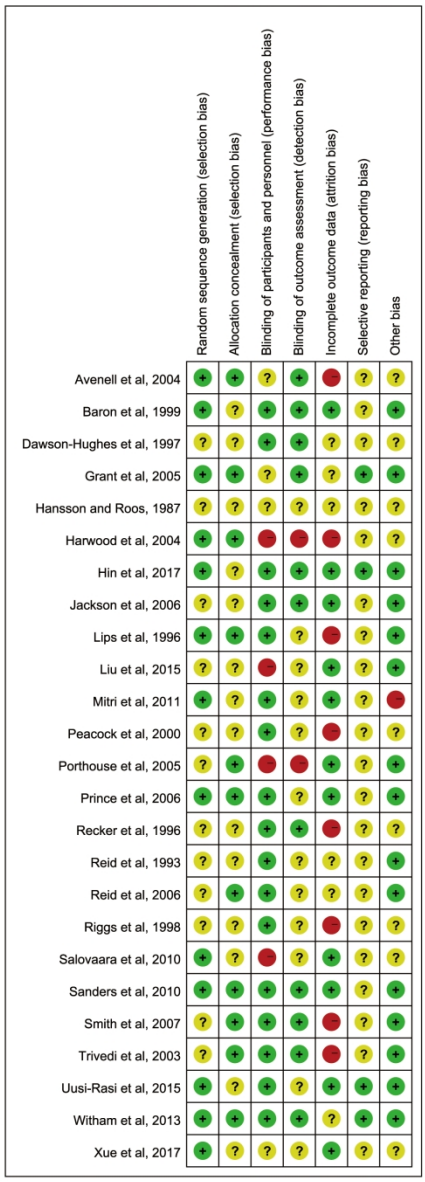
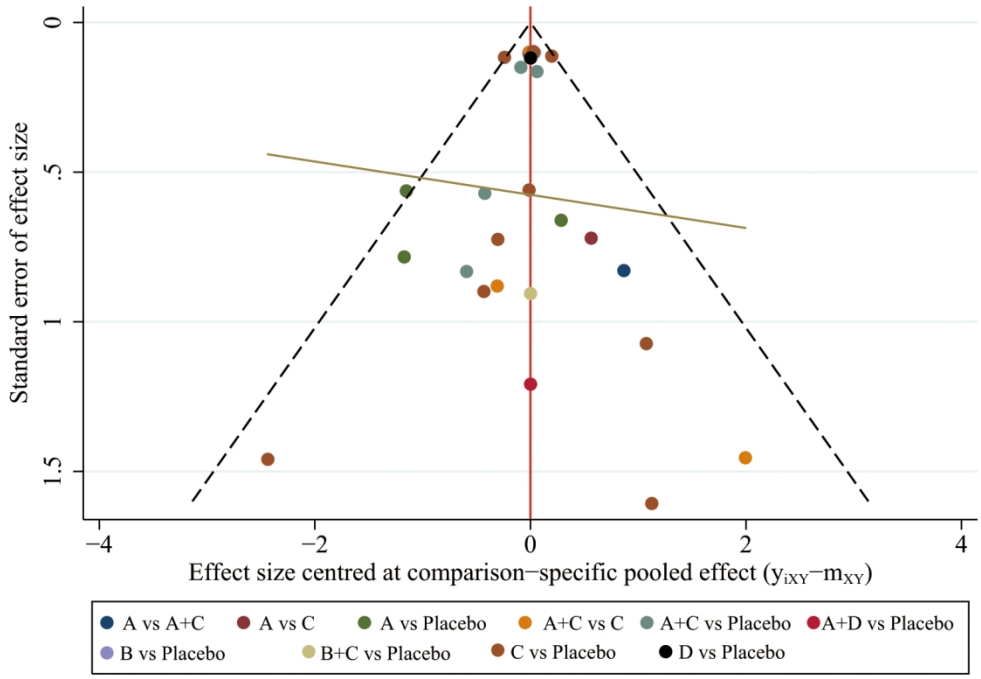
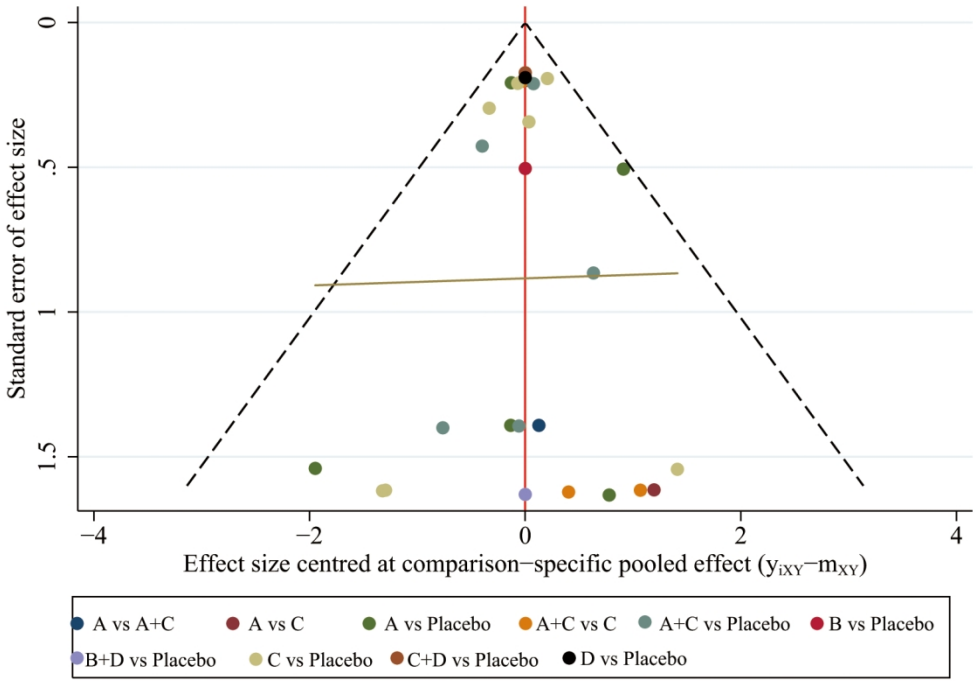
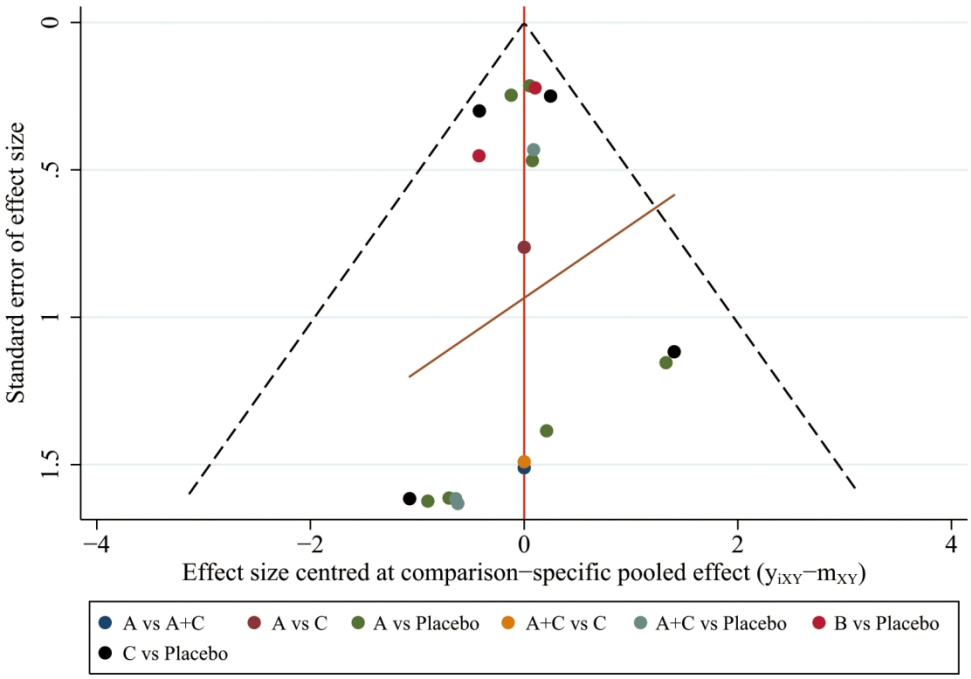


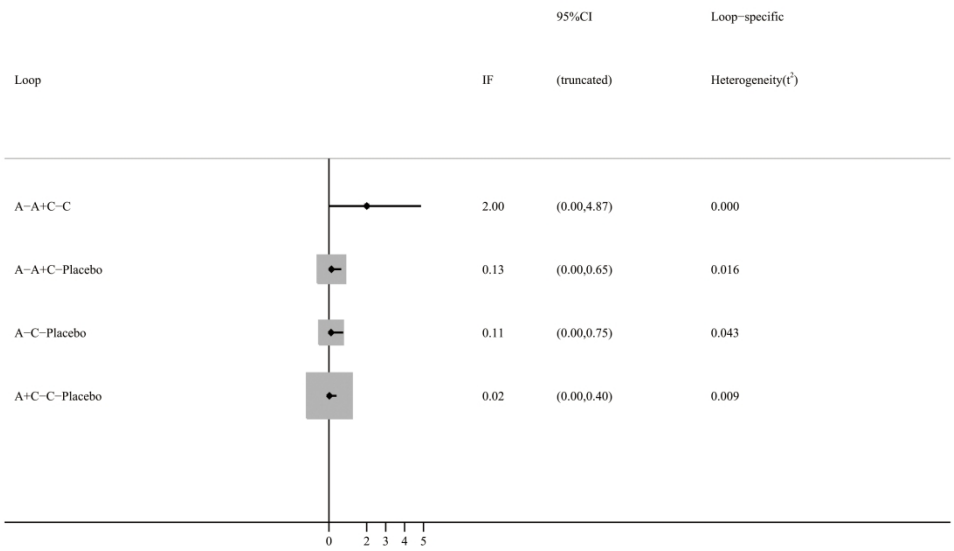
A: high calcium (800 mg/d or higher)；B: low calcium (less than 800 mg/d)；C: high vitamin D (800 IU/d or higher)；D: low vitamin D (less than 800 IU/d)

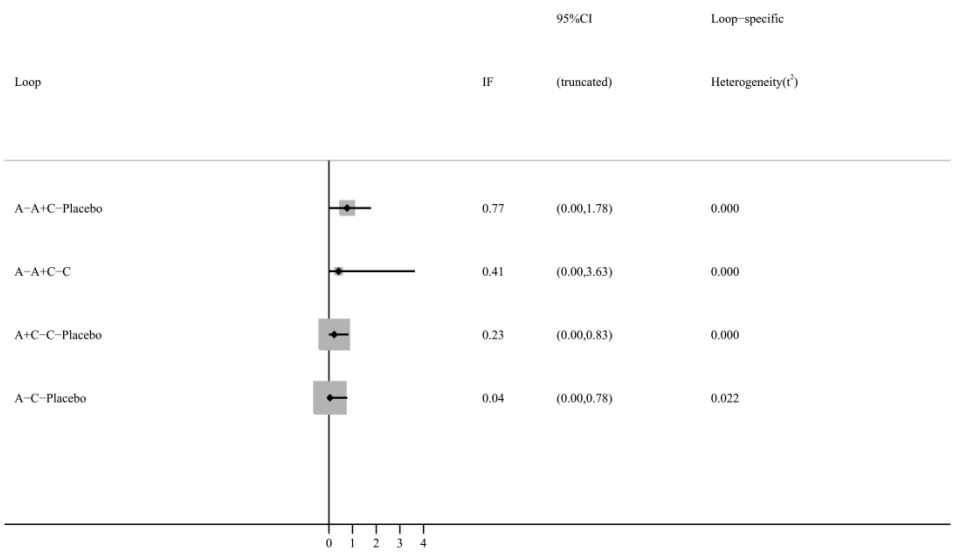

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Avenell et al, 2004
Baron et al, 1999
Dawson-Hughes et al, 1997
Grant et al, 2005
Hansson and Roos, 1987
Harwood et al, 2004
Hin et al, 2017
Jackson et al, 2006
Lips et al, 1996
Liu et al, 2015
Mitri et al, 2011
Peacock et al, 2000
Porthouse et al, 2005
Prince et al, 2006
Recker et al, 1996
Reid et al, 1993
Reid et al, 2006
Riggs et al, 1998
Salovaara et al, 2010
Sanders et al, 2010
Smith et al, 2007
Trivedi et al, 2003
Uusi-Rasi et al, 2015
Witham et al, 2013
Xue et al, 2017

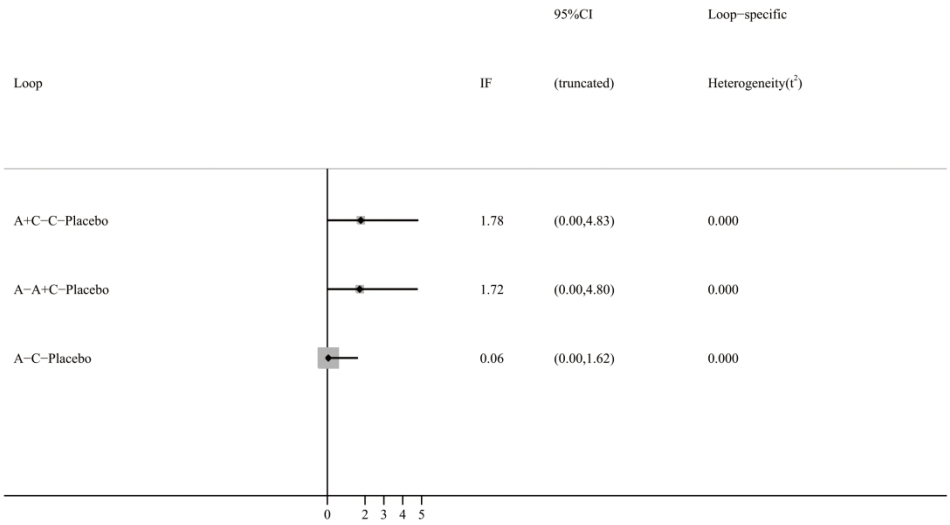

Standard error of effect size
0
.5
1
1.5
−4
−2
0
2
4
Effect size centred at comparison−specific pooled effect ($y_{iXY}-m_{XY}$)
A vs A+C
A vs C
A vs Placebo
A+C vs C
A+C vs Placebo
A+D vs Placebo
B vs Placebo
B+C vs Placebo
C vs Placebo
D vs Placebo


Standard error of effect size
0
.5
1
1.5
−4
−2
0
2
4
Effect size centred at comparison−specific pooled effect ($y_{iXY}-m_{XY}$)
A vs A+C
A vs C
A vs Placebo
A+C vs C
A+C vs Placebo
B vs Placebo
B+D vs Placebo
C vs Placebo
C+D vs Placebo
D vs Placebo

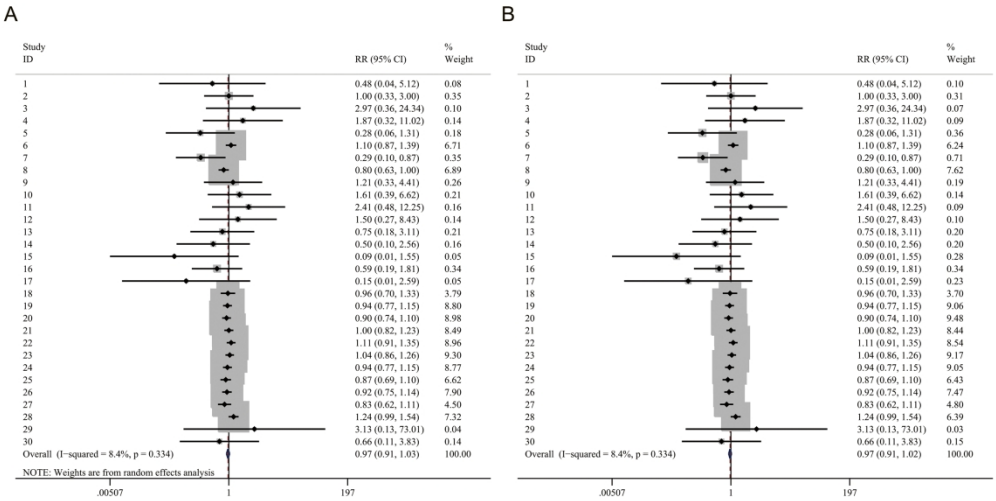

Standard error of effect size
0
.5
1
1.5
−4
−2
0
2
4
Effect size centred at comparison−specific pooled effect (y_{iXY}−m_{XY})
A vs A+C
A vs C
A vs Placebo
A+C vs C
A+C vs Placebo
B vs Placebo
C vs Placebo


Loop
IF
95%CI
(truncated)
Loop−specific
Heterogeneity(t^2)
A−A+C−C
2.00
(0.00,4.87)
0.000
A−A+C−Placebo
0.13
(0.00,0.65)
0.016
A−C−Placebo
0.11
(0.00,0.75)
0.043
A+C−C−Placebo
0.02
(0.00,0.40)
0.009
0
2
3
4
5

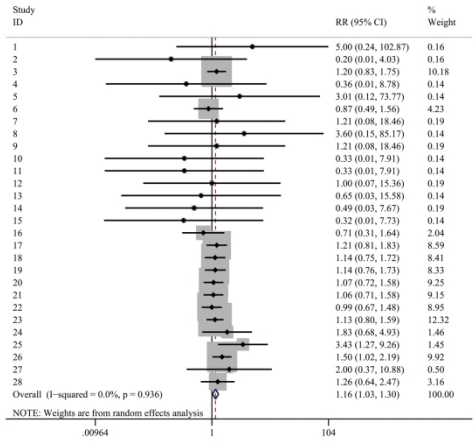

Loop
IF
95%CI
(truncated)
Loop−specific
Heterogeneity(t^2)
A−A+C−Placebo
0.77
(0.00,1.78)
0.000
A−A+C−C
0.41
(0.00,3.63)
0.000
A+C−C−Placebo
0.23
(0.00,0.83)
0.000
A−C−Placebo
0.04
(0.00,0.78)
0.022
0
1
2
3
4



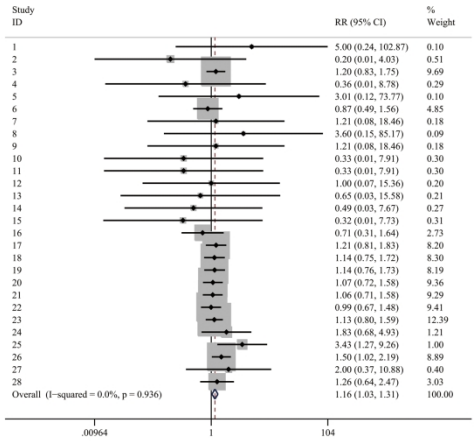
*** Loop(s) [A−A+C−C] are formed only by multi−arm trial(s) − Consistent by definition


A
Study ID
RR (95% CI)
% Weight
1 0.48 (0.04, 5.12) 0.08
2 1.00 (0.33, 3.00) 0.35
3 2.97 (0.36, 24.34) 0.10
4 1.87 (0.32, 11.02) 0.14
5 0.28 (0.06, 1.31) 0.18
6 1.10 (0.87, 1.39) 6.71
7 0.29 (0.10, 0.87) 0.35
8 0.80 (0.63, 1.00) 6.89
9 1.21 (0.33, 4.41) 0.26
10 1.61 (0.39, 6.62) 0.21
11 2.41 (0.48, 12.25) 0.16
12 1.50 (0.27, 8.43) 0.14
13 0.75 (0.18, 3.11) 0.21
14 0.50 (0.10, 2.56) 0.16
15 0.09 (0.01, 1.55) 0.05
16 0.59 (0.19, 1.81) 0.34
17 0.15 (0.01, 2.59) 0.05
18 0.96 (0.70, 1.33) 3.79
19 0.94 (0.77, 1.15) 8.80
20 0.90 (0.74, 1.10) 8.98
21 1.00 (0.82, 1.23) 8.49
22 1.11 (0.91, 1.35) 8.96
23 1.04 (0.86, 1.26) 9.30
24 0.94 (0.77, 1.15) 8.77
25 0.87 (0.69, 1.10) 6.62
26 0.92 (0.75, 1.14) 7.90
27 0.83 (0.62, 1.11) 4.50
28 1.24 (0.99, 1.54) 7.32
29 3.13 (0.13, 73.01) 0.04
30 0.66 (0.11, 3.83) 0.14
Overall (I−squared = 8.4%, p = 0.334) 0.97 (0.91, 1.03) 100.00
NOTE: Weights are from random effects analysis
.00507
1
197
B
Study ID
RR (95% CI)
% Weight
1 0.48 (0.04, 5.12) 0.10
2 1.00 (0.33, 3.00) 0.31
3 2.97 (0.36, 24.34) 0.07
4 1.87 (0.32, 11.02) 0.09
5 0.28 (0.06, 1.31) 0.36
6 1.10 (0.87, 1.39) 6.24
7 0.29 (0.10, 0.87) 0.71
8 0.80 (0.63, 1.00) 7.62
9 1.21 (0.33, 4.41) 0.19
10 1.61 (0.39, 6.62) 0.14
11 2.41 (0.48, 12.25) 0.09
12 1.50 (0.27, 8.43) 0.10
13 0.75 (0.18, 3.11) 0.20
14 0.50 (0.10, 2.56) 0.20
15 0.09 (0.01, 1.55) 0.28
16 0.59 (0.19, 1.81) 0.34
17 0.15 (0.01, 2.59) 0.23
18 0.96 (0.70, 1.33) 3.70
19 0.94 (0.77, 1.15) 9.06
20 0.90 (0.74, 1.10) 9.48
21 1.00 (0.82, 1.23) 8.44
22 1.11 (0.91, 1.35) 8.54
23 1.04 (0.86, 1.26) 9.17
24 0.94 (0.77, 1.15) 9.05
25 0.87 (0.69, 1.10) 6.43
26 0.92 (0.75, 1.14) 7.47
27 0.83 (0.62, 1.11) 4.80
28 1.24 (0.99, 1.54) 6.39
29 3.13 (0.13, 73.01) 0.03
30 0.66 (0.11, 3.83) 0.15
Overall (I−squared = 8.4%, p = 0.334) 0.97 (0.91, 1.02) 100.00
.00507
1
197

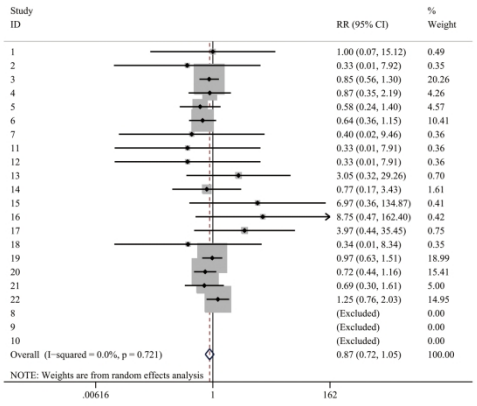
A


Study ID
RR (95% CI)
% Weight
1 5.00 (0.24, 102.87) 0.16
2 0.20 (0.01, 4.03) 0.16
3 1.20 (0.83, 1.75) 10.18
4 0.36 (0.01, 8.78) 0.14
5 3.01 (0.12, 73.77) 0.14
6 0.87 (0.49, 1.56) 4.23
7 1.21 (0.08, 18.46) 0.19
8 3.60 (0.15, 85.17) 0.14
9 1.21 (0.08, 18.46) 0.19
10 0.33 (0.01, 7.91) 0.14
11 0.33 (0.01, 7.91) 0.14
12 1.00 (0.07, 15.36) 0.19
13 0.65 (0.03, 15.58) 0.14
14 0.49 (0.03, 7.67) 0.19
15 0.32 (0.01, 7.73) 0.14
16 0.71 (0.31, 1.64) 2.04
17 1.21 (0.81, 1.83) 8.59
18 1.14 (0.75, 1.72) 8.41
19 1.14 (0.76, 1.73) 8.33
20 1.07 (0.72, 1.58) 9.25
21 1.06 (0.71, 1.58) 9.15
22 0.99 (0.67, 1.48) 8.95
23 1.13 (0.80, 1.59) 12.32
24 1.83 (0.68, 4.93) 1.46
25 3.43 (1.27, 9.26) 1.45
26 1.50 (1.02, 2.19) 9.92
27 2.00 (0.37, 10.88) 0.50
28 1.26 (0.64, 2.47) 3.16
Overall (I−squared = 0.0%, p = 0.936) 1.16 (1.03, 1.30) 100.00
NOTE: Weights are from random effects analysis
.00964
1
104

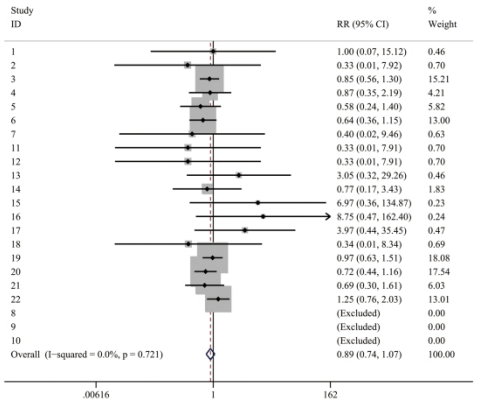
B


Study ID
RR (95% CI)
% Weight
1 5.00 (0.24, 102.87) 0.10
2 0.20 (0.01, 4.03) 0.51
3 1.20 (0.83, 1.75) 9.69
4 0.36 (0.01, 8.78) 0.29
5 3.01 (0.12, 73.77) 0.10
6 0.87 (0.49, 1.56) 4.85
7 1.21 (0.08, 18.46) 0.18
8 3.60 (0.15, 85.17) 0.09
9 1.21 (0.08, 18.46) 0.18
10 0.33 (0.01, 7.91) 0.30
11 0.33 (0.01, 7.91) 0.30
12 1.00 (0.07, 15.36) 0.20
13 0.65 (0.03, 15.58) 0.21
14 0.49 (0.03, 7.67) 0.27
15 0.32 (0.01, 7.73) 0.31
16 0.71 (0.31, 1.64) 2.73
17 1.21 (0.81, 1.83) 8.20
18 1.14 (0.75, 1.72) 8.30
19 1.14 (0.76, 1.73) 8.19
20 1.07 (0.72, 1.58) 9.36
21 1.06 (0.71, 1.58) 9.29
22 0.99 (0.67, 1.48) 9.41
23 1.13 (0.80, 1.59) 12.39
24 1.83 (0.68, 4.93) 1.21
25 3.43 (1.27, 9.26) 1.00
26 1.50 (1.02, 2.19) 8.89
27 2.00 (0.37, 10.88) 0.40
28 1.26 (0.64, 2.47) 3.03
Overall (I−squared = 0.0%, p = 0.936) 1.16 (1.03, 1.31) 100.00
.00964
1
104

A


Study ID
RR (95% CI)
% Weight
1 1.00 (0.07, 15.12) 0.49
2 0.33 (0.01, 7.92) 0.35
3 0.85 (0.56, 1.30) 20.26
4 0.87 (0.35, 2.19) 4.26
5 0.58 (0.24, 1.40) 4.57
6 0.64 (0.36, 1.15) 10.41
7 0.40 (0.02, 9.46) 0.36
11 0.33 (0.01, 7.91) 0.36
12 0.33 (0.01, 7.91) 0.36
13 3.05 (0.32, 29.26) 0.70
14 0.77 (0.17, 3.43) 1.61
15 6.97 (0.36, 134.87) 0.41
16 8.75 (0.47, 162.40) 0.42
17 3.97 (0.44, 35.45) 0.75
18 0.34 (0.01, 8.34) 0.35
19 0.97 (0.63, 1.51) 18.99
20 0.72 (0.44, 1.16) 15.41
21 0.69 (0.30, 1.61) 5.00
22 1.25 (0.76, 2.03) 14.95
8 (Excluded) 0.00
9 (Excluded) 0.00
10 (Excluded) 0.00
Overall (I−squared = 0.0%, p = 0.721) 0.87 (0.72, 1.05) 100.00
NOTE: Weights are from random effects analysis
.00616
1
162

B


Study ID
RR (95% CI)
% Weight
1 1.00 (0.07, 15.12) 0.46
2 0.33 (0.01, 7.92) 0.70
3 0.85 (0.56, 1.30) 15.21
4 0.87 (0.35, 2.19) 4.21
5 0.58 (0.24, 1.40) 5.82
6 0.64 (0.36, 1.15) 13.00
7 0.40 (0.02, 9.46) 0.63
11 0.33 (0.01, 7.91) 0.70
12 0.33 (0.01, 7.91) 0.70
13 3.05 (0.32, 29.26) 0.46
14 0.77 (0.17, 3.43) 1.83
15 6.97 (0.36, 134.87) 0.23
16 8.75 (0.47, 162.40) 0.24
17 3.97 (0.44, 35.45) 0.47
18 0.34 (0.01, 8.34) 0.69
19 0.97 (0.63, 1.51) 18.08
20 0.72 (0.44, 1.16) 17.54
21 0.69 (0.30, 1.61) 6.03
22 1.25 (0.76, 2.03) 13.01
8 (Excluded) 0.00
9 (Excluded) 0.00
10 (Excluded) 0.00
Overall (I−squared = 0.0%, p = 0.721) 0.89 (0.74, 1.07) 100.00
.00616
1
162