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

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4 **1 Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their**
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6 **2 combination: a network meta-analysis of randomized controlled trials**
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23 **Abstract**

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

28 **Design** A systematic review and network meta-analysis.

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

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

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

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

43 **Prospero registration number** CRD42017079624

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

45 **Strengths and limitations of this study**

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

54 **Introduction**

55 Clinical fractures of the elderly represent a worldwide public health problem that leads to illness and
56 social burden. The patients with osteoporosis in the EU were estimated to be 27.5 million in 2010, and
57 3.5 million new fragility fractures were sustained¹. In Asia, the average cost of osteoporotic fractures
58 accounted for 18.95% of the countries' 2014 GDP/capita and increased annually²⁻⁴. The overall
59 prevalence of osteoporosis or low bone mass in non-institutional population over the age of 50 in the
60 USA was estimated at 10.3% and 43.9%, respectively, which means that 10.2 million elderly people
61 had osteoporosis and 43.4 million people had low bone mass in 2010⁵. With the demographic trend of
62 ageing and the predicted increase in life expectancy, the cost of fracture treatment is expected to rise.

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

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

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4 67 for fractures yielded different efficacy outcomes. For instance, two meta-analyses demonstrated
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6 68 calcium or vitamin D supplementation alone has a small benefit on bone mineral density (BMD), but
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8 69 no clinically important to prevent fractures^{8,9}, while an updated meta-analysis and a pooled analysis
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11 70 found calcium plus vitamin D supplementation can significantly reduce hip fractures by 30% and total
12
13 71 fractures by 15%^{10,11}. Two RCTs reported that low dose of vitamin D supplementation (less than 800
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15 72 IU/d) can reduce the incidence of falls¹² and may prevent fractures without adverse effects¹³, but other
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18 73 RCTs showed no significant reduction in the incidence of hip or other peripheral fractures^{14,15} and its
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21 74 possible effects were seen only in patients with initial calcium insufficiency. What's more,
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23 75 Bischoff-Ferrari et al¹⁶ illustrated that high-dose vitamin D supplementation (800 IU/d or higher) not
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25 76 only reduced the risk of falls and hip fractures, but also prevented non-vertebral fractures. In contrast, a
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27
28 77 study reported annual high-dose oral vitamin D resulted in an increased risk of falls and fractures¹⁷. On
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30
31 78 the other hand, low-dose calcium supplementation (less than 800mg/d) effectively led to a sustained
32
33 79 reduction in the rate of bone loss¹⁸ and turnover. Although it was also reported that the high dose of
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35 80 calcium (800 mg/d or higher) was associated with a lower risk of clinical fractures¹⁹. The high-dose
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38 81 calcium with high-dose vitamin D can't prevent fractures according to the evidence from reported RCT
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40 82 ²⁰, but a meta-analysis supported their combination can prevent bone loss and significantly reduce the
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43 83 risk of hip fractures and all osteoporotic fractures²¹. Thus, it's a challenging to conclude a
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45 84 dose-response relation between the intakes of vitamin D, calcium, or their combination and the main
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48 85 outcomes in these heterogeneous literatures.

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50 86 Therefore, this study was designed to compare the fracture risk using different concentrations of
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52 87 vitamin D, calcium or their combination, and comprehensively evaluate the optimal concentration to
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55 88 guide clinical practice and public prevention in community-dwelling older people.

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89 **Methods**

90 **Search strategy and selection criteria**

91 This review and meta-analysis is based on the Preferred Reporting Items for Systematic Reviews and
92 Meta-Analysis (PRISMA) extension statement for network meta-analysis. Our meta-analysis was
93 registered prospectively in PROSPERO (CRD42017079624) and the Checklist PRISMA 2009
94 (**Supplementary Table 1**) will be used and check our final reports²².

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

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

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4 111 Two authors independently searched the electronic literature database of PubMed, Embase,
5
6 112 Cochrane database on December 31, 2017. Related articles and reference lists were searched to avoid
7
8 113 original miss. The reference studies of previous systematic reviews, meta-analysis, and included studies
9
10
11 114 were manually searched to avoid initial miss. After 2 authors assessed the potentially eligible studies
12
13 115 independently, any disagreement was discussed and resolved with the third independent author.

16 116 **Data collection and assessment of risk of bias**

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18 117 Two reviewers independently extracted data, and the third reviewer checked the consistency between
19
20 118 them. A standard data extracted form was used at this stage, including the authors, publishing date,
21
22
23 119 country, participant characteristics; doses of calcium, vitamin D, or their combination; dietary calcium
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25 120 intake; baseline serum 25-hydroxyvitamin D concentration; and trial duration. For continuous
26
27
28 121 outcomes, the mean, SD (standard deviation) and participant number will be extracted. For
29
30 122 dichotomous outcomes, we extracted the total numbers and the numbers of events of both groups. The
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33 123 data in other forms was recalculated when possible to enable pooled analysis.

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35 124 We used the Cochrane risk of bias tool to assess risk bias of included studies. The tool has seven
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38 125 domains including random sequence generation, allocation concealment, blinding of participants and
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40 126 personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias.
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43 127 The classification of the judgment for each domain was low risk of bias, high risk of bias, or unclear
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45 128 risk of bias and two authors independently evaluated the risk of studies.

47 129 **Data synthesis and statistical analysis**

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49
50 130 The data was extracted and input into the STATA software (version 12.0; StataCorp, College Station,
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52 131 TX, USA) for network meta-analysis. And we generated network plots for each outcome to illustrate
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55 132 which interventions had been compared directly in the included studies. Network meta-analysis is an

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4 133 extension of standard meta-analysis to compare multiple treatments based on randomized controlled
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6 134 trial evidence, which forms a connected network of comparisons. Treatment effect estimates from
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8 135 network meta-analysis exploit both the direct comparisons within trials and the indirect comparisons
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11 136 across trials. Relative risk (RR) was calculated for dichotomous outcomes while weighted mean
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13 137 difference (WMD) for the continuous both with 95%CI for direct comparisons or 95%CrI for indirect
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16 138 comparisons. Our network was a closed triangular circular network including both direct and indirect
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18 139 evidences. The model (which was proposed by Anna Chaimani, downloaded from www.mtm.uoi.gr)
19
20 140 we used was fit for all kinds of networks. To the only one triangular circular, we used ifplot command
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22
23 141 proposed by Anna Chaimani to evaluate the consistency of direct and indirect estimates. Then the
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25 142 operational model was chosen according to the inconsistency test, which was the basis of forest maps'
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28 143 calculation. We used the surface under the cumulative ranking probabilities (SUCRA) to indicate which
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30 144 treatment was the best one. The funnel plot was used to identify possible publication bias if the number
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33 145 of studies was larger than 10.

34 35 146 **Patient and public involvement**

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37 147 No patients were involved in setting the research question or the outcome measures, and no patients
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40 148 were involved in developing plans for design or implementation of the study. Furthermore, no patients
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43 149 were asked to advice on interpretation or writing up of results. Since this meta-analysis used
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45 150 aggregated data from previous trials, it is unable to disseminate the results of the research to study
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48 151 participants directly.

49 50 152 **Result**

51 52 153 **Data Retrieval**

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55 154 In summary, a total of 7909 potential records were initially identified through PubMed (5187),
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4 155 Embase (2688), Cochrane Data base (34). Based on our review of the title and abstract, 99 full-text
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6 156 papers were reviewed and 29 studies met inclusion criteria (**Figure 1**).

8 157 **Study and Patient Characteristics**

10 158 The characteristics of all 29 included studies were summarized and shown in **supplementary Table**

12
13 159 **2**. And the detailed data of outcomes was collected in **supplementary Table 3**. The papers had similar

14
15 160 distributions of sex, age, country, intervention and all of them were community-dwelling older people.

16
17 161 Hansson et al²³ did not report the residential status of participants, although a previous meta-analysis

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19 162 classified this status as community²⁴. The trial by Hansson et al²³ was included, but a sensitivity

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21 163 analysis was performed that excluded that trial (**supplementary Figure 1**). Inkovaara et al²⁵ did not

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23 164 report whether the data represent the number of fractures or participants with fracture. The trial by

24
25 165 Massart et al²⁶ was included, which adult maintenance hemodialysis patients were the participants. We

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27 166 suspected that the maintenance hemodialysis or the underlying disease might result in the imbalance of

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29 167 calcium in the body. Patients on haemodialysis may also be receiving 1,25-dihydroxyvitamin D, which

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31 168 may affect their response to vitamin D supplementation. The data were included, but a sensitivity

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33 169 analysis was performed that excluded both of two trials (**supplementary Figure 2**).

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35 170 **supplementary Figure 3 and supplementary Figure 4** showed the assessment of the risk of bias.

36
37 171 All studies were randomized; 21 were double-blind, placebo-controlled trials; 16 trials described an

38
39 172 adequate random sequence generation process; and 13 trials described the methods used for allocation

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41 173 concealment. Only one study showed low quality²⁵, so we also made a sensitivity analysis by excluding

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43 174 that trial (**supplementary Figure 2**). No obvious publication bias was reported according to the

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45 175 **supplementary Figure 5, supplementary Figure 6 and supplementary Figure 7**.

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47 176 **Primary outcome: total fracture**

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4 177 For estimating the vitamin D, calcium or their combination efficacy against total fractures, we
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6 178 looked at data from 27102 individuals from 22 studies. Pooled estimates included 18 studies with one
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8 179 treatment, 1 study with two treatments, and 3 studies with three treatments.

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11 180 The inconsistency between direct and indirect evidence based on both comparisons of consistency
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13 181 and inconsistency model was found according to inconsistency test (**supplementary Figure 8**), so we
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15 182 adopted an inconsistency model to deal with this problem.

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18 183 The network plot of comparisons on total fractures was shown in **Figure 2A**. The forest plot for the
19
20 184 network meta-analysis was shown in **Figure 3A**. We also made ranking graph of distribution of
21
22 185 probabilities on total fractures in **supplementary Figure 9**. The direct and indirect comparisons
23
24 186 indicated no differences among the vitamin D, calcium or their combination that remained in the main
25
26 187 network. Neither do the statistical differences between interventions and placebo. Based on SUCRA,
27
28 188 high calcium plus low vitamin D group (0.726) ranked the first, the second was high calcium plus high
29
30 189 vitamin D group (0.642) and the last was low calcium plus high vitamin D group (0.217). In a separate
31
32 190 sensitivity analysis, we excluded Inkovaara's ²⁵ and Massart's ²⁶ studies (**supplementary Figure 2**).
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34 191 However, there was still no significant association of vitamin D, calcium or their combination with
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36 192 total fracture.

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

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42 194 A total of 42531 individuals were included from 17 studies for evaluate the drug efficacy against hip
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44 195 fractures. Pooled estimates included 14 studies with one treatment, 1 study with two treatments, and
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46 196 two studies with three treatments.

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52 197 We adopted an inconsistency model to deal with this problem according to inconsistency test
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54 198 (**supplementary Figure 10**). The network plot of comparisons on hip fractures was shown in **Figure**

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4 199 **2B.** The forest plot for the network meta-analysis was shown in **Figure 3B**. We also made ranking
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6 200 graph of distribution of probabilities on hip fractures in **supplementary Figure 11**. The direct and
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8 201 indirect comparisons indicated no differences among the vitamin D, calcium or their combination that
9
10 202 remained in the main network. Neither do the statistical differences between drug experimental groups
11
12 203 and placebo. Based on SUCRA, high calcium plus high vitamin D group (0.791) ranked the first, the
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14 204 second was placebo or no treatment group (0.6753) and the last was high calcium group (0.198).

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18 205 A total of 17612 individuals were collected from 12 studies involving vertebral fractures. Pooled
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20 206 estimates included 10 studies with one treatment, and two studies with three treatments.

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23 207 We adopted an inconsistency model to deal with this problem according to inconsistency test
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25 208 (**supplementary Figure 12**). The network plot of comparisons on vertebral fractures was shown in
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27
28 209 **Figure 2C**. The forest plot for the network meta-analysis was shown in **Figure 3C**. We also made
29
30 210 ranking graph of distribution of probabilities on vertebral fractures in **supplementary Figure 13**. The
31
32 211 direct and indirect comparisons indicated no differences among the vitamin D, calcium or their
33
34 212 combination that remained in the main network. Neither do the statistical differences between drug
35
36 213 experimental groups and placebo. Based on SUCRA, high calcium plus high vitamin D group (0.825)
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38 214 ranked the first, the second was high calcium group (0.649) and the last was high vitamin D group
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40 215 (0.186). In a separate sensitivity analysis, we excluded Hansson's study²³ (**supplementary Figure 1**).
41
42 216 However, there was still no significant association of vitamin D, calcium or their combination with
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44 217 total fracture.

45 218 **Discussion**

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48 219 Vitamin D supplementation and calcium are suggested as interventions to treat and prevent fracture.
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50 220 We found the previous meta-analyses and RCTs are critically inconsistent in efficacy of different doses
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4 221 of vitamin D with calcium on fractures.

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6 222 Results of this meta-analysis showed that calcium, calcium plus vitamin D, and vitamin D
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8 223 supplementation alone were not significantly associated with a lower incidence of hip, vertebral, or
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10 224 total fractures in community-dwelling older adults. Sensitivity analyses that excluded low-quality trials
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12 225 and studies that exclusively enrolled patients with particular medical conditions did not alter these
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14 226 results.

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17
18 227 A meta-analysis conducted by Jia-Guo Zhao et al²⁷ showed that no significant difference was found
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20 228 in the incidence of hip or other fractures, which was similar to our result. However, it did not focus on
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22 229 the effect of different concentrations of vitamin D, calcium or their combination and we supposed that
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24 230 a network meta-analysis might be more reasonable. And in this meta-analysis the participants of the
25
26 231 included study reported by Massart²⁶ were adult maintenance hemodialysis patients, which may
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28 232 resulted in the imbalance of calcium in the body. Patients on haemodialysis may also be receiving
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30 233 1,25-dihydroxyvitamin D, which may affect their response to vitamin D supplementation. And we
31
32 234 suspected that a network meta-analysis might be a more suitable choice concerning all these different
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34 235 interventions mixed.

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37
38 236 Bischoff-Ferrari et al²⁸ reported that high-dose vitamin D supplementation (800 IU/d or higher)
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40 237 played an important role in the reduction of the risk of falls and hip fractures, as well as prevented
41
42 238 non-vertebral fractures in adults 65 years or older. However, their findings may have been influenced
43
44 239 by the trial of Chapuy et al²⁹, which only enrolled participants living in an institution. What's more,
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46 240 differences in conclusions of previous meta-analyses and the current meta-analysis were due to the
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48 241 recently published trials which reported neutral or harmful associations of vitamin D supplementation
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50 242 and fracture incidence more and more. Study findings here indicated that vitamin D might result in a
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4 243 higher risk for hip fracture, but this conclusion did not reach statistical significance. This finding may
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6 244 be attributable to lack of statistical power in this meta-analysis.

7
8 245 However, possible limitations of this study protocol include potential missing data and meta-biases,
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10 246 heterogeneity, which may limit the quality of evidence. Some RCTs were of poor quality and, for
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12 247 example, used unclear allocation concealment. So we made a sensitivity analysis by excluding
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14 248 low-quality trials. And some study characteristics such as sex, baseline serum 25-hydroxyvitamin D
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16 249 concentrations, duration of follow-up, performance bias and detection bias might be potential obstacles
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18 250 to the outcomes of our article, but we performed some subgroup analyses before statistical analysis and
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20 251 found no statistical differences between these subgroups. What's more, we combined bolus dosing by
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22 252 injection with oral supplements taken daily/monthly/yearly, which might have different effects on
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24 253 vitamin D status in the body. In addition, this work does not necessarily preclude any benefit of vitamin
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26 254 D and calcium supplementation in older, frail individuals.

27 28 29 30 31 32 33 255 **Conclusions**

34
35 256 In this meta-analysis of randomized clinical trials, we found that the use of different concentrations of
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37 257 vitamin D, calcium or their combination in community-dwelling older adults was not associated with a
38
39 258 lower risk of fractures. Our findings may not support the routine use of these supplements in
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41 259 community-dwelling older people.

42 43 44 45 260 **Contributors**

46
47 261 ZCH and AMW conceived the study. The search strategy was developed by LT and XBL. ZHF, GZ
48
49 262 and QT will complete electronic search, select publications and assess their eligibility. ZHS and XBL
50
51 263 will extract information of the included studies after screening. JWX will check the data entry for
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53 264 accuracy and completeness. ZCH and LT will give advice for data analysis and presentation of study
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4 265 result. WFN and AMW supervised the overall conduct of the study. All the authors drafted and
5
6 266 critically reviewed and approved the final manuscript.
7

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17
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19
20 272 (Y20170389). The funders had no role in the design, execution, or writing of the study.
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23 273 **Conflicts of interest**

24
25 274 None declared
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28 275 **Patient consent**

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30 276 Not required.
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33 277 **Provenance and peer review**

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35 278 Not commissioned; externally peer reviewed.
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38 279 **Data sharing statement**

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40 280 No additional data are available.
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8 377 vitamin D (800 IU/d or higher); D=low vitamin D (less than 800 IU/d)
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13 378 **Figure 3.** The forest plot for the risk of total fractures (A), hip fractures (B) and vertebral fractures (C).
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23 381 **supplementary Figure 1.** A sensitivity analysis excluded the trial of Hansson et al. A=high calcium
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43 387 **supplementary Figure 3.** Risk of Bias Assessment of All Included Studies
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52 389 **supplementary Figure 5.** Publication bias for the total fractures. A=high calcium (800 mg/d or higher);
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18 395 **supplementary Figure 7.** Publication bias for the vertebral fractures. A=high calcium (800 mg/d or
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28 398 **supplementary Figure 8.** Inconsistency test for the total fractures. A=high calcium (800 mg/d or
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38 401 **supplementary Figure 9.** Ranking graph of distribution of probabilities for total fractures. A=high
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48 404 **supplementary Figure 10.** Inconsistency test for the hip fractures. A=high calcium (800 mg/d or
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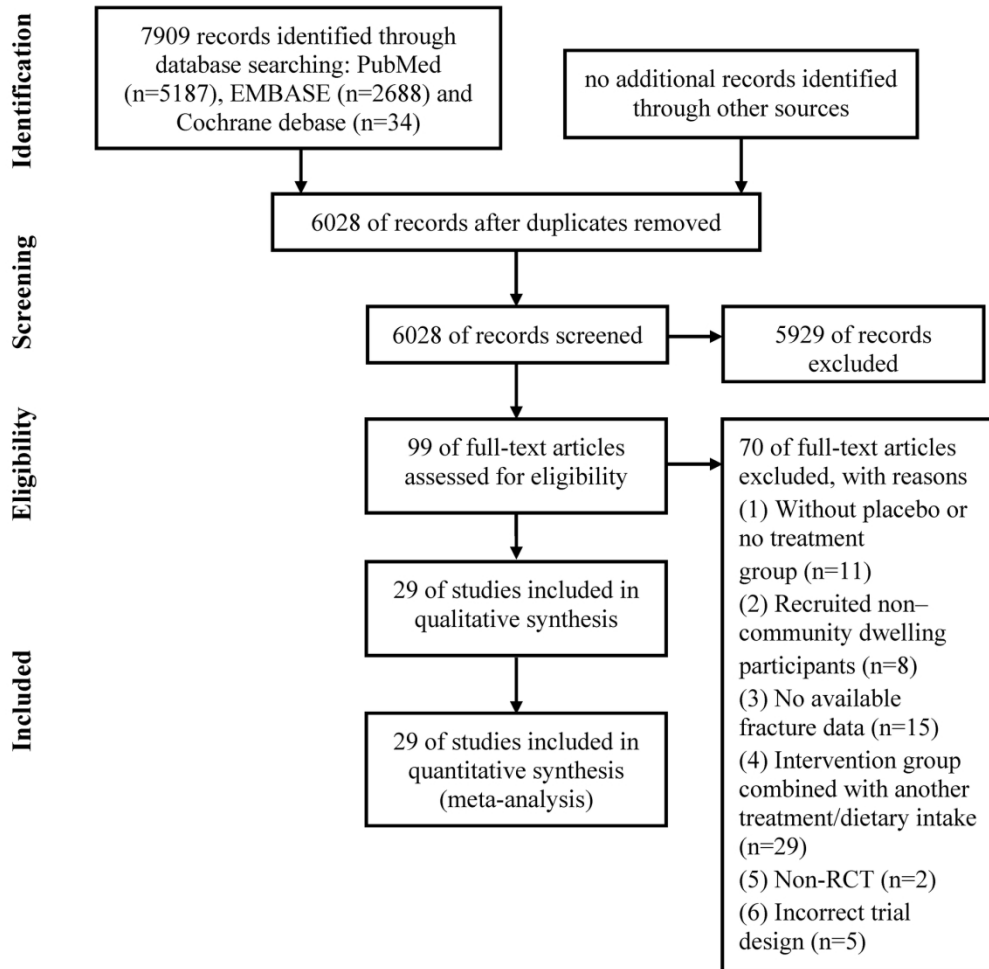
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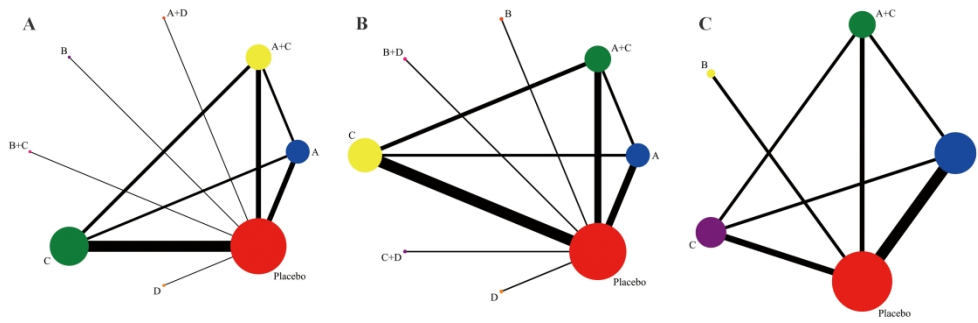
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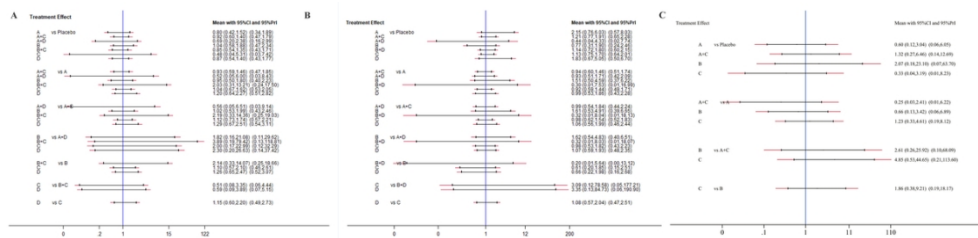
The selection of literature for included studies

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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)

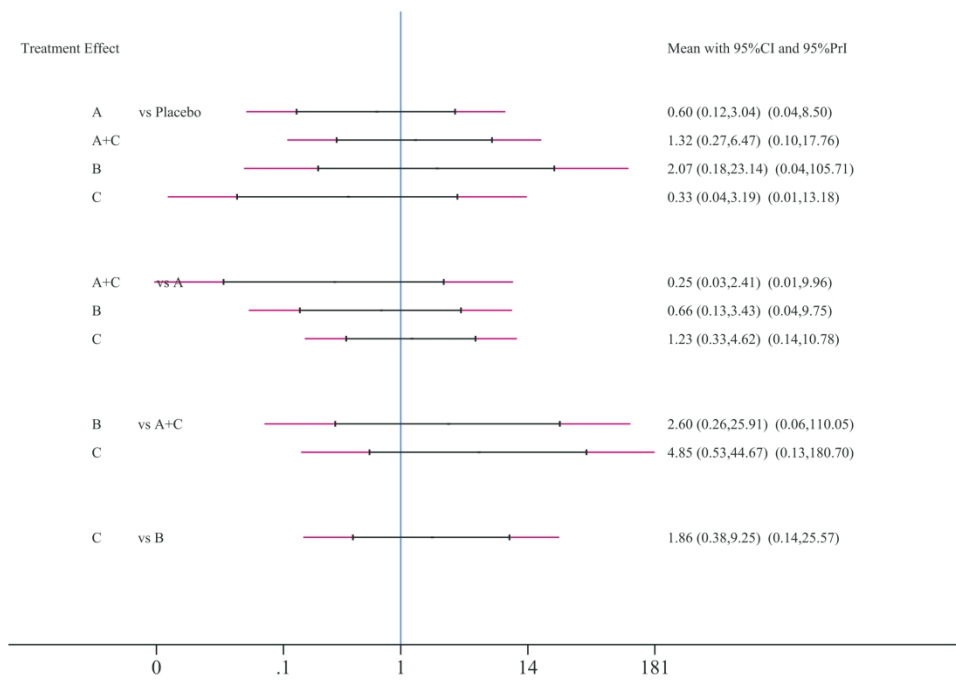
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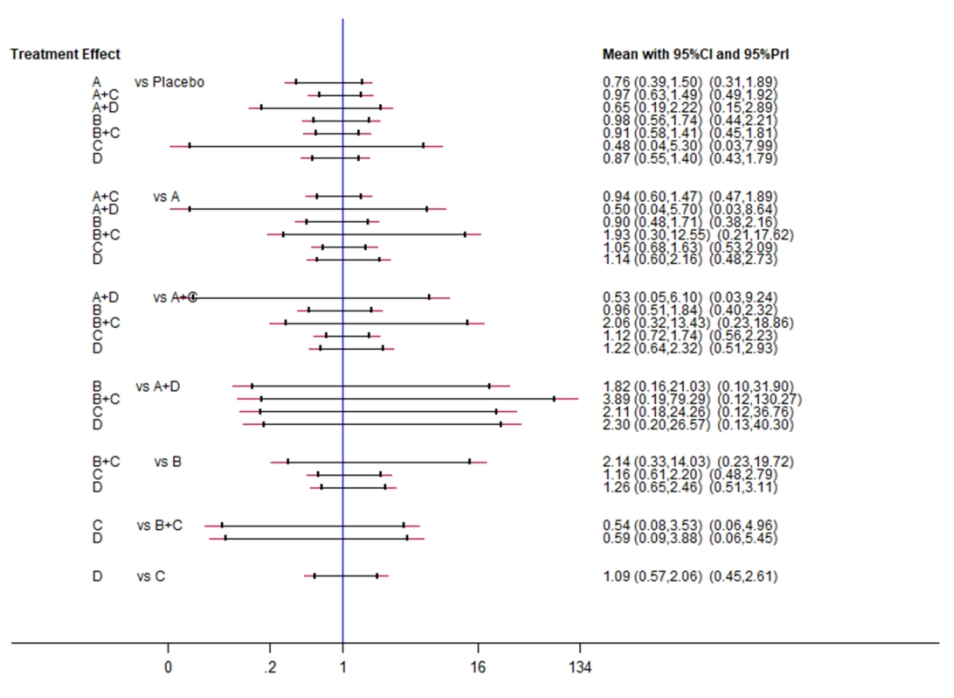
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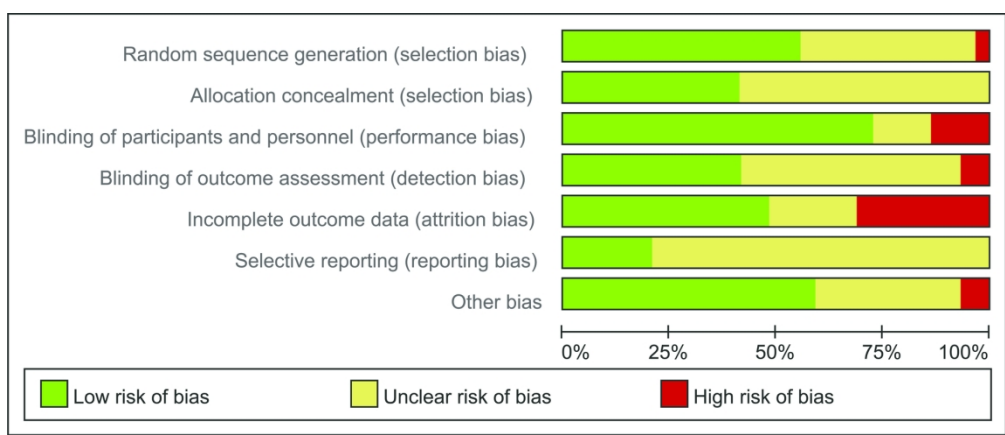


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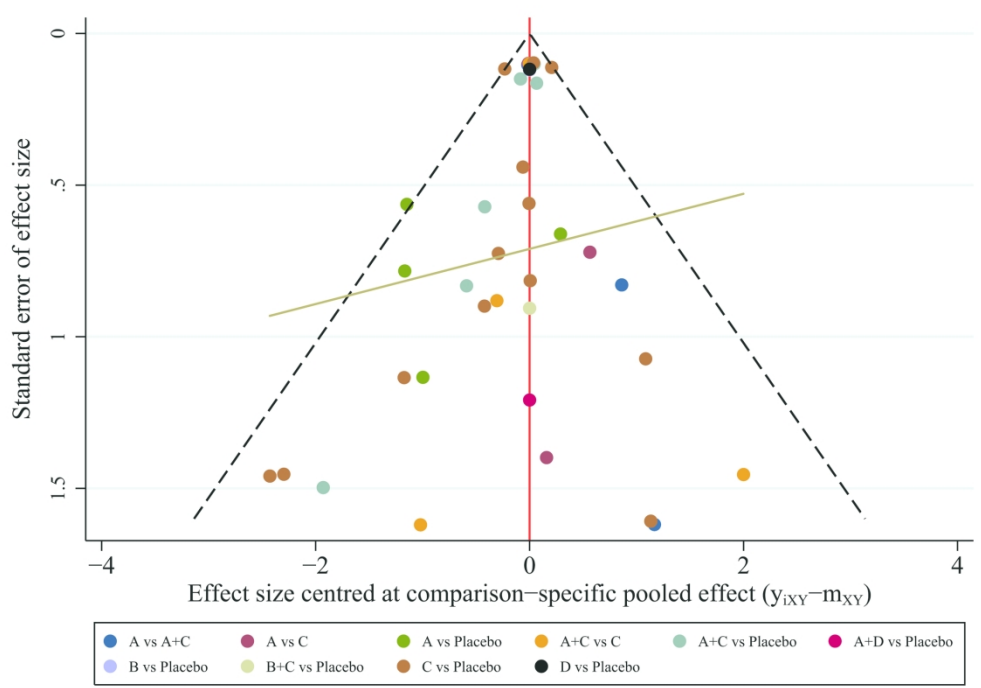
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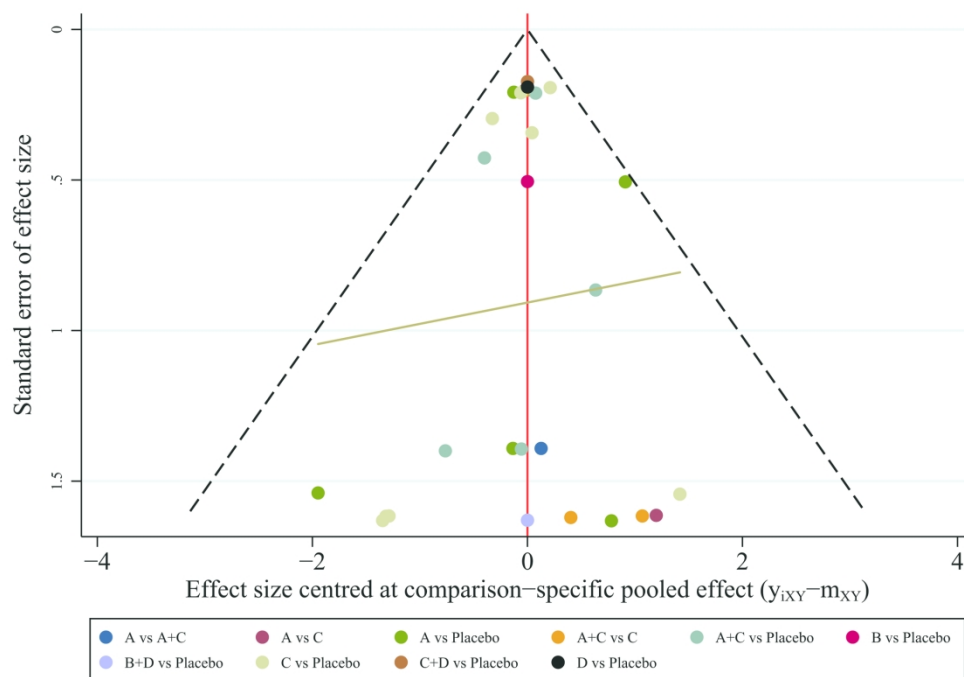
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Uusi-Rasi et al, 2015	+	?	?	?	+	+	+
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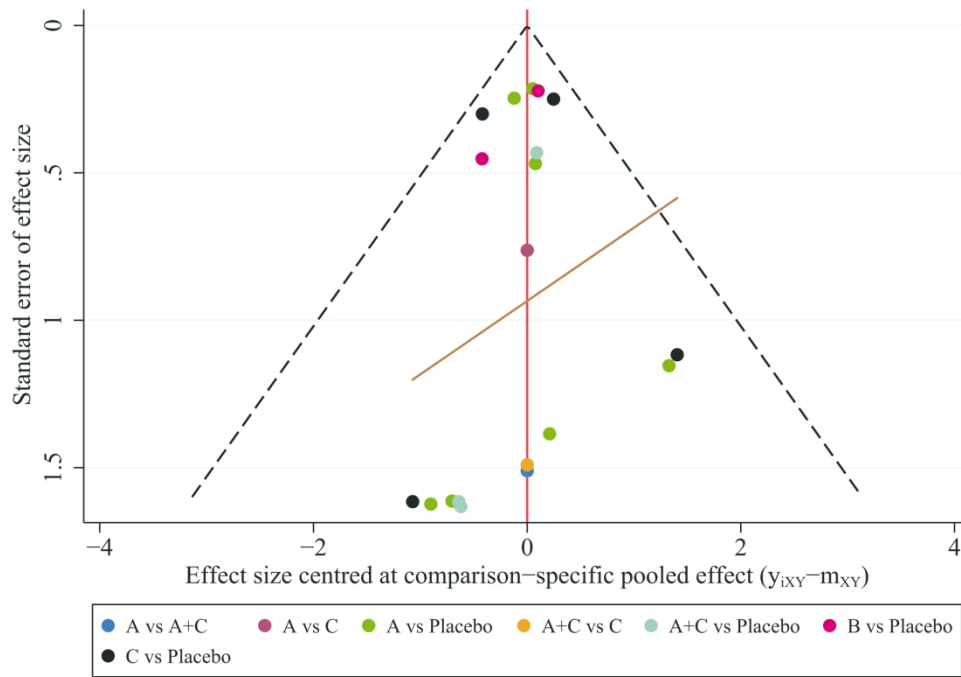
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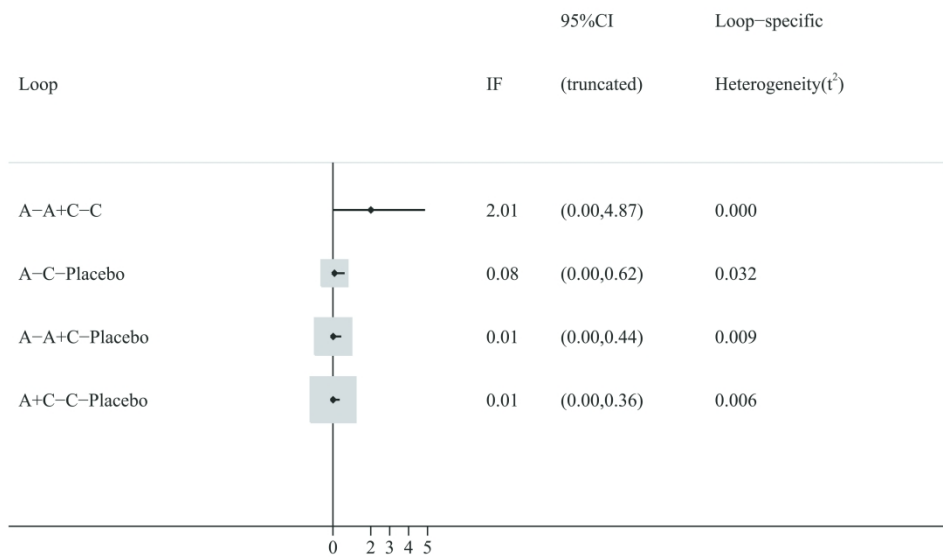


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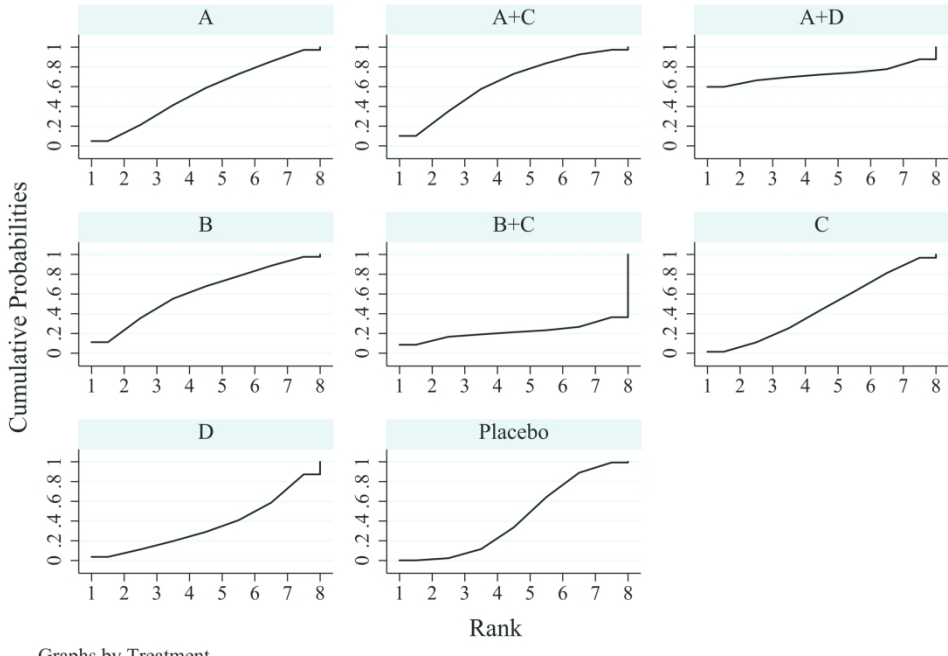
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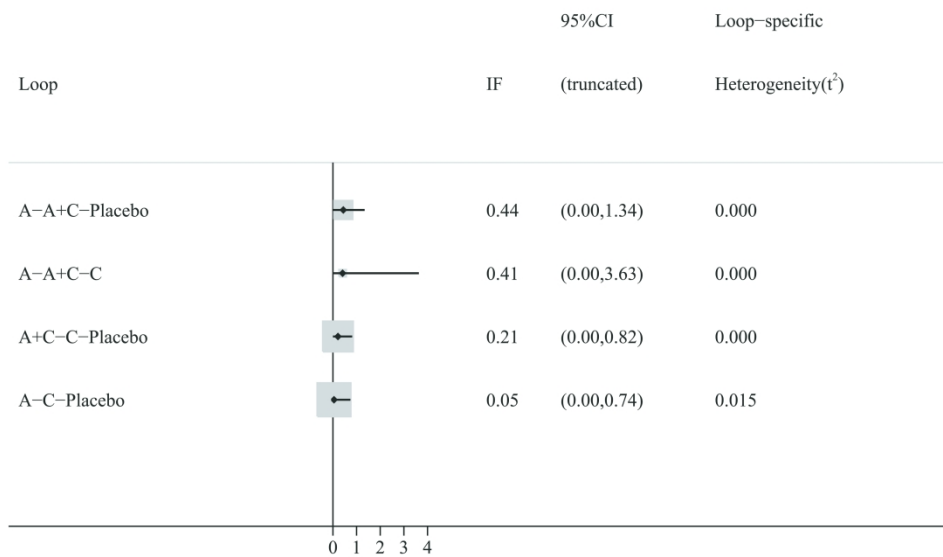
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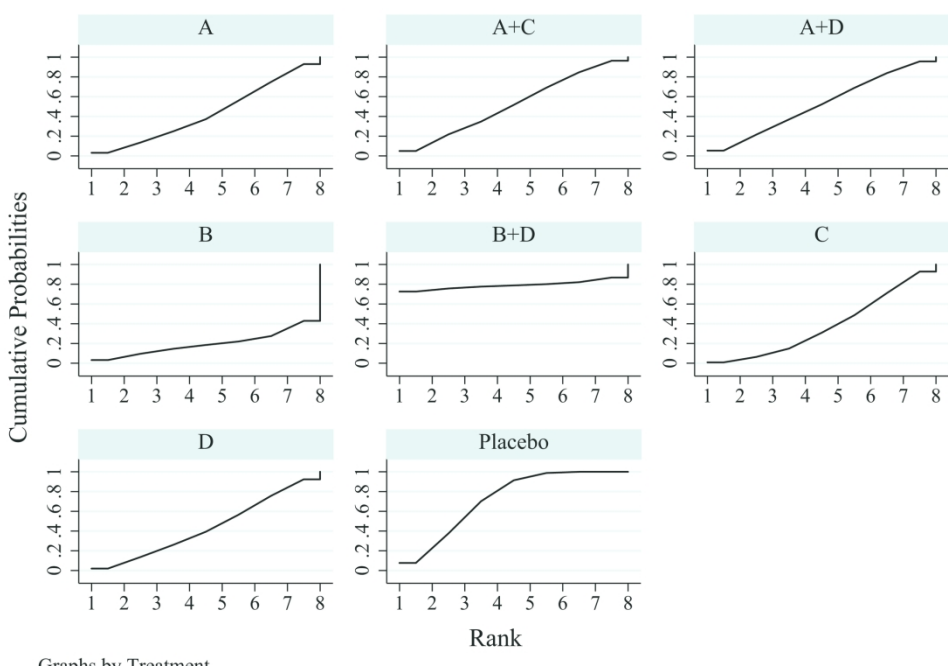
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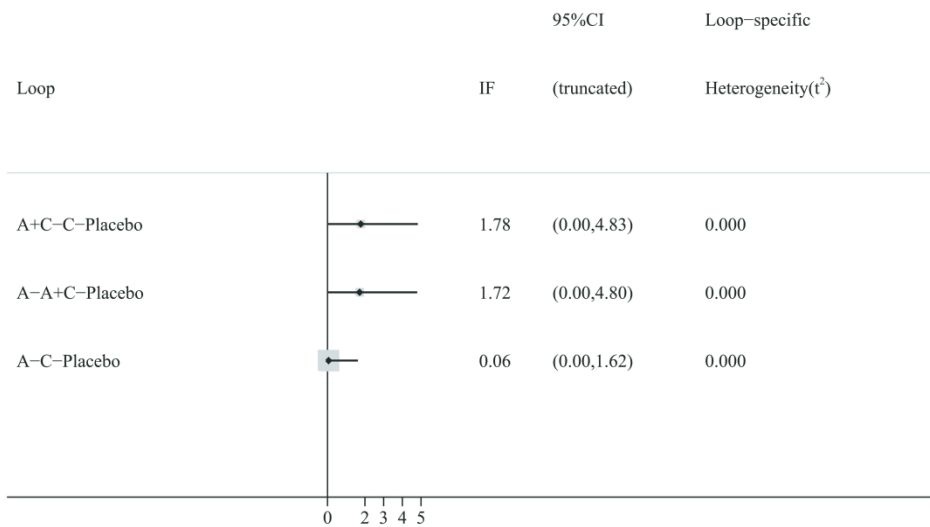
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Graphs by Treatment

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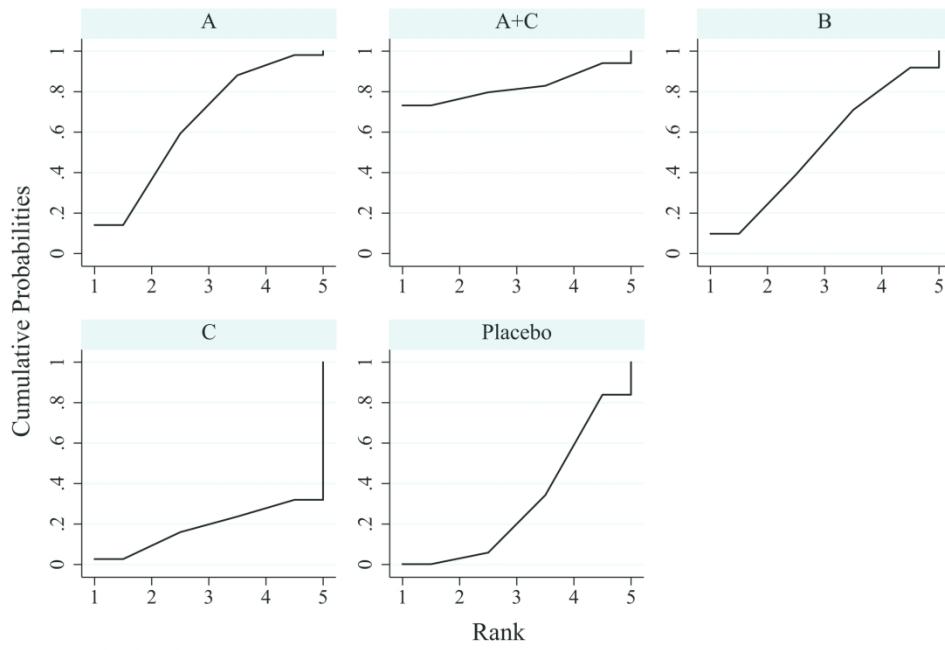
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*** Loop(s) [A-A+C-C] are formed only by multi-arm trial(s) – Consistent by definition

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Graphs by Treatment

101x73mm (600 x 600 DPI)

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

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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

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)	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)[2]	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)[3]	Calcium (0.5g/d) + D ₃ (700IU/d) (n = 187)	213 (54)	71.1	NA	729	29.6 ^e	3 y
	Placebo (n = 202)						
Glendenning et al, 2012 (Australia)[4]	D ₃ (150000 IU every 3 mo) (n = 353)	686 (100)	76.7	NA	864	26.3 ^e	9 mo
	Placebo (n = 333)						
Grant et al, 2005 (United Kingdom)[5]	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)[6]	Calcium (1g/d) (n = 25)	50 (100)	65.9	Yes	NA	NA	3 y
	Placebo (n = 25)						
Harwood et al, 2004 (United Kingdom)[7]	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)						

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3	Hin et al, 2017	D ₃ (4000 IU/d)(n = 102)	150 (49)	71.7	Partial ^c	710	20.1	1 y
4	(United Kingdom)[8]	D ₃ (2000 IU/d)(n = 102)						
5		Placebo (n = 101)						
6								
7	Inkovaara et al, 1983	Calcium (1.2 g/d) (n = 42)	69 (82)	80.1	NA	NA	NA	9 mo
8	(Finland)[9]	Placebo (n = 42)						
9								
10		D ₃ (1000 IU/d) (n = 45)	71 (82)	79.6	NA	NA	NA	9 mo
11		Placebo (n = 42)						
12								
13		Calcium (1.2g/d) + D ₃ (1000	69 (78)	79.0	NA	NA	NA	9 mo
14		IU/d) (n = 46)						
15		Placebo (n = 42)						
16								
17								
18	Jackson et al, 2006	Calcium (1g/d) + D ₃ (400	7972 (100)	62.4	Partial ^c	1151	18.9 ^e	7 y
19	(United States)[10]	IU/d) (n = 4015)						
20		Placebo (n = 3957)						
21								
22	Lips et al, 1996	400 IU/d (n = 1291)	1916 (74)	80.0	No hip fracture	868	10.6 ^e	3-4 y
23	(The Netherlands)[11]	Placebo (n = 1287)						
24								
25	Liu et al, 2015	Calcium (1.5g/d) + D ₃ (600	98 (100)	62.1	No	1500	NA	1 y
26	(China)[12]	IU/d) (n = 50)						
27		Placebo (n = 48)						
28								
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30	Massart et al, 2014	D ₃ (25000 IU every week)	21 (38)	64.1	NA	881	17.8	3 mo
31	(Belgium)[13]	(n = 26)						
32		Placebo (n = 29)						
33								
34	Mitri et al, 2011	D ₃ (2000 IU/d)(n = 23)	25 (53)	58.0	NA	926	25.3	4 mo
35	(United States)[14]	Placebo (n = 24)						
36								
37	Peacock et al, 2000	Calcium (0.75g/d) (n = 126)	187 (72)	73.8	Partial ^c	597	25.0	4 y
38	(United States)[15]	Placebo (n = 135)						
39								
40	Porthouse et al, 2005	Calcium (1g/d) + D ₃ (800	3314 (100)	76.8	Partial ^c	1080	NA	1.5-3.5 y
41	(United Kingdom)[16]	IU/d) (n = 1321)						
42		No treatment (n = 1993)						
43								
44	Prince et al, 2006	Calcium (0.48g/d) (n = 730)	1460 (100)	75.2	Partial ^c	915	31.0 ^e	5 y
45	(Australia)[17]	Placebo (n = 730)						
46								
47	Punthakee et al, 2012	D ₃ (1000 IU/d) (n = 607)	499 (41)	66.6	Partial ^c	NA	NA	4 mo
48	(Canada)[18]	Placebo (n = 614)						
49								
50								
51	Recker et al, 1996	Calcium (1.2 g/d) (n = 95)	197 (100)	73.5	Partial ^c	434	25.5 ^e	4 y
52	(United States)[19]	Placebo (n = 102)						
53								
54	Reid et al, 1993	Calcium (1 g/d) (n = 68)	135 (100)	58	No vertebral	750	37.5	4 y
55	(New Zealand)[20]	Placebo (n = 67)			fracture			
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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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Source	Treatment		No. of Participants		
	Duration	Intervention	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)	6	1	
		Calcium (1g/d) + D ₃ (800IU/d) (n = 39)			
		No treatment (n = 37)	5	1	
Hin et al, 2017 (United Kingdom)[8]	1 y	D ₃ (4000 IU/d)(n = 102)	6		
		D ₃ (2000 IU/d)(n = 102)			
		Placebo (n = 101)	1		

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	

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

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Manuscripts

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4 1 **Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their**
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6 2 **combination: a network meta-analysis of randomized controlled trials**
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9 3 Zhi-Chao Hu^{1,2,3}, Qian Tang^{1,2,3}, Chang-Min Sang⁴, Li Tang^{1,2,3}, Xiao-Bin Li^{1,2,3}, Gang Zheng^{1,2,3},
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58 22 Zhi-Chao Hu and Qian Tang contributed equally to this work.
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4 23 **Abstract**

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6 24 **Objective** Inconsistent findings in regard to association between different concentrations of vitamin D,
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9 25 calcium or their combination and the risk of fracture have been reported during the past decade in
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11 26 community-dwelling older people. This study was designed to compare the fracture risk using different
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14 27 concentrations of vitamin D, calcium or their combination.

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17 28 **Design** A systematic review and network meta-analysis.

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19 29 **Data sources** Randomized controlled trials in PubMed, Cochrane library, and EMBASE databases
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22 30 were systematically searched from the inception dates to December 31, 2017.

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25 31 **Outcomes** Total fracture was defined as the primary outcome. Secondary outcomes were hip fracture
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27 32 and vertebral fracture. Due to the consistency of the original studies, a consistency model was adopted.

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30 33 **Results** A total of 25 randomized controlled trials involving 43510 participants fulfilled the inclusion
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32 34 criteria. There was no evidence that the risk of total fracture was reduced by using different
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35 35 concentrations of vitamin D, calcium or their combination compared with placebo or no treatment. No
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37 36 significant associations were found between calcium, vitamin D, or combined calcium and vitamin D
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40 37 supplements and the incidence of hip, or vertebral fractures.

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43 38 **Conclusions** The use of supplements that included calcium, vitamin D, or both was not found to be
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45 39 better than placebo or no treatment in terms of risk of fractures among community-dwelling older
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48 40 adults. It means the routine use of these supplements in community-dwelling older people should be
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51 41 treated more carefully.

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53 42 **Prospero registration number** CRD42017079624

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56 43 **Keywords:** Calcium; Vitamin D; Fractures; network meta-analysis

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58 44 **Strengths and limitations of this study**
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4 45 • This systematic review and meta-analysis combined the evidence from randomized controlled trials.
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6 46 • Our findings may not support the routine use of these supplements in community-dwelling older
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9 47 people.
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11 48 • This work does not necessarily preclude any benefit of vitamin D and calcium supplementation in
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14 49 older, frail individuals.
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17 50 • Potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence.
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19 51 **Introduction**

22 52 Clinical fractures of the elderly represent a worldwide public health problem that leads to illness and
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24 53 social burden. The patients with osteoporosis in the European Union were estimated to be 27.5 million
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27 54 in 2010, and 3.5 million new fragility fractures were sustained¹. In Asia, the average cost of
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30 55 osteoporotic fractures accounted for 18.95% of the countries' 2014 gross domestic product
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32 56 (GDP)/capita and increased annually²⁻⁴. The overall prevalence of osteoporosis or low bone mass in
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35 57 non-institutional population over the age of 50 in the USA was estimated at 10.3% and 43.9%,
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38 58 respectively, which means that 10.2 million elderly people had osteoporosis and 43.4 million people
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40 59 had low bone mass in 2010⁵. With the demographic trend of ageing and the predicted increase in life
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43 60 expectancy, the cost of fracture treatment is expected to rise.

45 61 Dietary allowances for calcium range from 700 to 1200 mg/d and vitamin D of 600-800 IU/d have
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48 62 long been recommended for the prevention of osteoporotic fractures in the elderly^{6 7}. The supplements
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51 63 of calcium and vitamin D are commonly taken to maintain bone health.

53 64 However, the previous randomized controlled trials (RCT) and meta-analyses concerning vitamin D,
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56 65 calcium, or their combination for fractures yielded different efficacy outcomes. For instance, two
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59 66 meta-analyses demonstrated calcium or vitamin D supplementation alone has a small benefit on bone
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4 67 mineral density (BMD), but no clinically important to prevent fractures^{8 9}, while an updated
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6 68 meta-analysis and a pooled analysis found calcium plus vitamin D supplementation can significantly
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9 69 reduce hip fractures by 30% and total fractures by 15%^{10 11}. Two RCTs reported that low dose of
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11 70 vitamin D supplementation (less than 800 IU/d) can reduce the incidence of falls¹² and may prevent
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14 71 fractures without adverse effects¹³, but other RCTs showed no significant reduction in the incidence of
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17 72 hip or other peripheral fractures^{14 15} and its possible effects were seen only in patients with initial
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20 73 calcium insufficiency. Based on the evidence from meta-analysis, Bischoff-Ferrari et al ¹⁶ illustrated
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22 74 that high-dose vitamin D supplementation (800 IU/d or higher) not only reduced the risk of falls and
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25 75 hip fractures, but also prevented non-vertebral fractures. In contrast, a study reported annual high-dose
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27 76 oral vitamin D resulted in an increased risk of falls and fractures ¹⁷. On the other hand, low-dose
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30 77 calcium supplementation (less than 800mg/d) effectively led to a sustained reduction in the rate of bone
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33 78 loss ¹⁸ and turnover. Although it was also reported that the high dose of calcium (800 mg/d or higher)
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36 79 was associated with a lower risk of clinical fractures ¹⁹. The high-dose calcium with high-dose vitamin
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38 80 D can't prevent fractures according to the evidence from reported RCT ²⁰, but a meta-analysis
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41 81 supported their combination can prevent bone loss and significantly reduce the risk of hip fractures and
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44 82 all osteoporotic fractures ²¹. Thus, it's challenging to conclude a dose-response relation between the
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47 83 intakes of vitamin D, calcium, or their combination and the main outcomes in these heterogeneous
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50 84 literatures.

51 85 Therefore, this study was designed to compare the fracture risk using different concentrations of
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54 86 vitamin D, calcium or their combination, and comprehensively evaluate the optimal concentration to
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57 87 guide clinical practice and public prevention in community-dwelling older people.

58 88 **Methods**

89 Search strategy and selection criteria

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

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

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

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

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4 111 in **supplementary eTable 1**). Related articles and reference lists were searched to avoid original
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7 112 miss. The reference studies of previous systematic reviews, meta-analysis, and included studies were
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10 113 manually searched to avoid initial miss. After 2 authors assessed the potentially eligible studies
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12 114 independently, any disagreement was discussed and resolved with the third independent author (QT).

13 14 115 **Data collection and assessment of risk of bias**

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17 116 Two reviewers (ZHS and XBL) independently extracted data, and the third reviewer (LT) checked
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20 117 the consistency between them. A standard data extracted form was used at this stage, including the
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22 118 authors, publishing date, country, participant characteristics; doses of calcium, vitamin D, or their
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25 119 combination; dietary calcium intake; baseline serum 25-hydroxyvitamin D concentration; and trial
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27 120 duration. For continuous outcomes, the mean, SD (standard deviation) and participant number will be
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30 121 extracted. For dichotomous outcomes, we extracted the total numbers and the numbers of events of
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32 122 both groups. The data in other forms was recalculated when possible to enable pooled analysis.

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35 123 We used the Cochrane risk of bias tool to assess risk bias of included studies. The tool has seven
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38 124 domains including random sequence generation, allocation concealment, blinding of participants and
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41 125 personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other
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43 126 bias. The classification of the judgment for each domain was low risk of bias, high risk of bias, or
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46 127 unclear risk of bias and two authors (ZHF and GZ) independently evaluated the risk of studies.

47 48 128 **Data synthesis and statistical analysis**

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51 129 The data was extracted and input into the STATA software (version 12.0; StataCorp, College
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54 130 Station, TX, USA) for network meta-analysis. And we generated network plots for each outcome to
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57 131 illustrate which interventions had been compared directly in the included studies. Network
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59 132 meta-analysis is an extension of standard meta-analysis to compare multiple treatments based on
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4 133 randomized controlled trial evidence, which forms a connected network of comparisons. Treatment
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6 134 effect estimates from network meta-analysis exploit both the direct comparisons within trials and the
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9 135 indirect comparisons across trials. The heterogeneity was further assessed with the I^2 statistic and a
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11 136 value of more than 50% was considered as statistically significant heterogeneity. Random effects
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14 137 model was applied when significant heterogeneity existed ($P < 0.05$ or I^2 test exhibited $> 50\%$),
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17 138 otherwise, fixed-effects model was utilized²³. Relative risk (RR) with 95% confidence intervals (CIs)
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20 139 was calculated for dichotomous outcomes while weighted mean difference (WMD) with 95% CIs for
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22 140 the continuous. Inconsistency refers to differences between direct and various indirect effect estimates
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25 141 for the same comparison. To assess inconsistency, we estimated the inconsistency factors in closed
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27 142 loop based on the method described by Chaimani et al²⁴. The heterogeneity in each closed loop was
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30 143 estimated by utilizing inconsistency factor (IF). If the 95% confidence intervals (95% CI) of IF values
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33 144 are not truncated at zero, it suggests that the inconsistency among studies has statistical significance.
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35 145 We used the surface under the cumulative ranking probabilities (SUCRA) to indicate which treatment
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38 146 was the best one. The funnel plot was used to identify possible publication bias if the number of studies
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41 147 was larger than 10.

42 43 148 **Patient and public involvement**

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45 149 No patients were involved in setting the research question or the outcome measures, and no patients
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47
48 150 were involved in developing plans for design or implementation of the study. Furthermore, no patients
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51 151 were asked to advice on interpretation or writing up of results. Since this meta-analysis used
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53 152 aggregated data from previous trials, it is unable to disseminate the results of the research to study
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56 153 participants directly.

57 58 154 **Result**

155 **Data Retrieval**

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

159 **Study and Patient Characteristics**

160 The characteristics of all 25 included studies were summarized and shown in **supplementary Table**
161 **2**. And the detailed data of outcomes was collected in **supplementary Table 3**. The papers had similar
162 distributions of sex, age, country, intervention and all of them were community-dwelling older people.
163 Hansson et al²⁹ did not report the residential status of participants, although a previous meta-analysis
164 classified this status as community. The trial by Hansson et al was included, but a sensitivity analysis
165 was performed that excluded that trial (**supplementary Figure 1**).

166 **Supplementary Figure 2** showed the assessment of the risk of bias. All studies were randomized;
167 17 were double-blind, placebo-controlled trials; 13 trials described an adequate random sequence
168 generation process; and 11 trials described the methods used for allocation concealment. No obvious
169 publication bias was reported according to the **supplementary Figure 3, supplementary Figure 4** and
170 **supplementary Figure 5**.

171 **Inconsistence and heterogeneity check**

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

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4 177 **supplementary Figure 10, supplementary Figure 11).**

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7 178 **Primary outcome: total fracture**

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9 179 For estimating the vitamin D, calcium or their combination efficacy against total fractures, we
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11 180 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
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14 181 estimates included 15 studies with one treatment, 1 study with two treatments, and 2 studies with three
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17 182 treatments.

18
19 183 The network plot of comparisons on total fractures was shown in **Figure 2A**. The forest plot for the
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22 184 network meta-analysis was shown in **Figure 3**. The RR values and 95% CIs are summarized in **Figure**
23
24
25 185 **3**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their
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27
28 186 combination that remained in the main network. Neither do the statistical differences between
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31 187 interventions and placebo ($P<0.05$). So we didn't continue to make ranking graph of distribution of
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34 188 probabilities on total fractures.

35 189 **Secondary outcomes: hip fracture and vertebral fracture**

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38 190 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
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41 191 the drug efficacy against hip fractures. Pooled estimates included 13 studies with one treatment, 1 study
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44 192 with two treatments, and two studies with three treatments.

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46 193 The network plot of comparisons on hip fractures was shown in **Figure 2B**. The forest plot for the
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49 194 network meta-analysis was shown in **Figure 4**. The RR values and 95% CIs are summarized in **Figure**
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52 195 **4**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their
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55 196 combination that remained in the main network. Neither do the statistical differences between drug
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58 197 experimental groups and placebo ($P<0.05$). So we didn't continue to make ranking graph of
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60 198 distribution of probabilities on total fractures.

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4 199 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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6 200 fractures. Pooled estimates included 10 studies with one treatment, and two studies with three
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9 201 treatments.

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11 202 The network plot of comparisons on vertebral fractures was shown in **Figure 2C**. The forest plot for
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14 203 the network meta-analysis was shown in **Figure 5**. The RR values and 95% CIs are summarized in
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16
17 204 **Figure 5**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium
18
19 205 or their combination that remained in the main network. Neither do the statistical differences between
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21
22 206 drug experimental groups and placebo ($P < 0.05$). So we didn't continue to make ranking graph of
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25 207 distribution of probabilities on total fractures. In a separate sensitivity analysis, we excluded Hansson's
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27 208 study²⁹ (**supplementary Figure 1**). However, there was still no significant association of vitamin D,
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30 209 calcium or their combination with total fracture.

31 32 210 **Discussion**

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35 211 Vitamin D supplementation and calcium are suggested as interventions to treat and prevent fracture.
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38 212 We found the previous meta-analyses and RCTs are critically inconsistent in efficacy of different doses
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41 213 of vitamin D with calcium on fractures.

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43 214 Results of this meta-analysis showed that calcium, calcium plus vitamin D, and vitamin D
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46 215 supplementation alone were not significantly associated with a lower incidence of hip, vertebral, or
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48
49 216 total fractures in community-dwelling older adults. Sensitivity analyses that excluded low-quality trials
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52 217 and studies that exclusively enrolled patients with particular medical conditions did not alter these
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55 218 results.

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57 219 A meta-analysis conducted by Jia-Guo Zhao et al⁴⁶ showed that no significant difference was found
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59 220 in the incidence of hip or other fractures, which was similar to our result. However, the object of
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4 221 Zhao's study was to investigate whether calcium, vitamin D, or combined calcium and vitamin D
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6 222 supplement are associated with a lower fracture incidence while our study was designed to evaluate the
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9 223 optimal concentration of them. Meanwhile, in Zhao's meta-analysis, the participants of the included
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11 224 study reported by Massart⁴⁷ were adult maintenance hemodialysis patients, which may result in the
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14 225 imbalance of calcium in the body. Patients on hemodialysis may also be receiving
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17 226 1,25-dihydroxyvitamin D, which may affect their response to vitamin D supplementation. So we did
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20 227 not include that trial in our network meta-analysis. What's more, we didn't include studies that lasted
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22 228 less than a year because we thought this time-frame was too short to see anti-fracture efficacy. And we
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25 229 suspected that a network meta-analysis might be a more suitable choice concerning all these different
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28 230 interventions mixed.

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30 231 Bischoff-Ferrari et al⁴⁸ reported that high-dose vitamin D supplementation (800 IU/d or higher)
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32 232 played an important role in the reduction of the risk of falls and hip fractures, as well as prevented
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35 233 non-vertebral fractures in adults 65 years or older. However, their findings may have been influenced
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38 234 by the trial of Chapuy et al⁴⁹, which only enrolled participants living in an institution. What's more,
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41 235 differences in conclusions of previous meta-analyses and the current meta-analysis were due to the
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43 236 recently published trials which reported neutral or harmful associations of vitamin D supplementation
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46 237 and fracture incidence more and more. Study findings here indicated that vitamin D might result in a
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48 238 higher risk for hip fracture, but this conclusion did not reach statistical significance. This finding may
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51 239 be attributable to lack of statistical power in this meta-analysis.

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53 240 Most recently there was a meta-analysis published in the Lancet by Bolland et al⁵⁰, whose findings
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56 241 suggested that vitamin D supplementation does not prevent fractures or falls, or have clinically
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59 242 meaningful effects on bone mineral density. Although it was similar to our study to some extent, they
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243 are really different. First, we only included community-dwelling older people. We found that some
244 meta-analyses equated community-dwelling older people with those in nursing institution. The lack of
245 exercise, dietary intake and exposure to sunlight made people in nursing institution turned more
246 susceptible to the use of supplements including vitamin D, calcium or their combination. Although the
247 studies involving participants living in nursing institution were only a small part, but it could change
248 the whole outcomes and produce false positive results. We found only Avenell's study paid attention to
249 this question when they conducted a subgroup analysis, but they did not discussed separately.
250 Meanwhile, we only enrolled adults older than 50 years and trial duration more than 1 year to reduce
251 the statistical heterogeneity in network meta-analysis. Furthermore, the current analyses included
252 calcium supplementation, where the Bolland's study focused on vitamin D.

253 However, possible limitations of this study protocol include potential missing data and meta-biases,
254 heterogeneity, which may limit the quality of evidence. Some RCTs were of poor quality and, for
255 example, used unclear allocation concealment. So we made a sensitivity analysis by excluding
256 low-quality trials. Although some study characteristics such as baseline serum 25-hydroxyvitamin D
257 concentrations might be to contribute heterogeneity, we could not perform subgroup analysis or
258 meta-regression analysis to evaluate it due to the extreme complexity and the limitation of Stata
259 software for network meta-analysis. What's more, we combined bolus dosing by injection with oral
260 supplements taken daily/monthly/yearly, which might have different effects on vitamin D status in the
261 body. In addition, the report ignored the effect of treatment with vitamin D on plasma
262 25-hydroxy-vitamin D concentrations and sub-types of fracture, such as pathologic fractures; this work
263 does not necessarily preclude any benefit of vitamin D and calcium supplementation in older, frail
264 individuals.

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4 265 **Conclusions**

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6 266 In this meta-analysis of randomized clinical trials, we found that the use of different concentrations of
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9 267 vitamin D, calcium or their combination in community-dwelling older adults was not associated with a
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12 268 lower risk of fractures. Our findings may not support the routine use of these supplements in
13
14
15 269 community-dwelling older people.

16
17 270 **Contributors**

18
19 271 ZCH and AMW conceived the study. The search strategy was developed by LT and XBL. ZHF, GZ
20
21
22 272 and QT will complete electronic search, select publications and assess their eligibility. ZHS and XBL
23
24
25 273 will extract information of the included studies after screening. JWX will check the data entry for
26
27
28 274 accuracy and completeness. ZCH and LT will give advice for data analysis and presentation of study
29
30
31 275 result. LYS and CMS contributed to the text revision. WFN and AMW supervised the overall conduct
32
33 276 of the study. All the authors drafted and critically reviewed and approved the final manuscript.

34
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46
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48
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50
51 283 **Conflicts of interest**

52
53 284 None declared

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56 285 **Patient consent**

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58 286 Not required.
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60287 **Provenance and peer review**

288 Not commissioned; externally peer reviewed.

289 **Data sharing statement**

290 No additional data are available.

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4 453 **Figure 1.** The selection of literature for included studies.
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9 454 **Figure 2.** The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral
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11 fractures (C). A: high calcium (800 mg/d or higher); B: low calcium (less than 800 mg/d); C: high
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13 vitamin D (800 IU/d or higher); D: low vitamin D (less than 800 IU/d)
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19 457 **Figure 3.** The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher); B: low
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21 calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low vitamin D (less than
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23 800 IU/d)
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30 460 **Figure 4.** The forest plot for the risk of hip fractures. A: high calcium (800 mg/d or higher); B: low
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32 calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low vitamin D (less than
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34 800 IU/d)
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40 463 **Figure 5.** The forest plot for the risk of vertebral fractures. A: high calcium (800 mg/d or higher); B:
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42 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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44 than 800 IU/d)
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50 466 **supplementary Figure 1.** A sensitivity analysis excluded the trial of Hansson et al. A: high calcium
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52 (800 mg/d or higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher);
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54 D: low vitamin D (less than 800 IU/d)
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4 469 **supplementary Figure 2.** Risk of Bias Assessment of All Included Studies
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9 470 **supplementary Figure 3.** Publication bias for the total fractures. A: high calcium (800 mg/d or higher);
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11 471 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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19 473 **supplementary Figure 4.** Publication bias for the hip fractures. A: high calcium (800 mg/d or higher);
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21 474 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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29 476 **supplementary Figure 5.** Publication bias for the vertebral fractures. A: high calcium (800 mg/d or
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31 477 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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33 478 vitamin D (less than 800 IU/d)
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39 479 **supplementary Figure 6.** Inconsistency test for the total fractures. A: high calcium (800 mg/d or
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41 480 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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43 481 vitamin D (less than 800 IU/d)
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49 482 **supplementary Figure 7.** Inconsistency test for the hip fractures. A: high calcium (800 mg/d or
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51 483 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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53 484 vitamin D (less than 800 IU/d)
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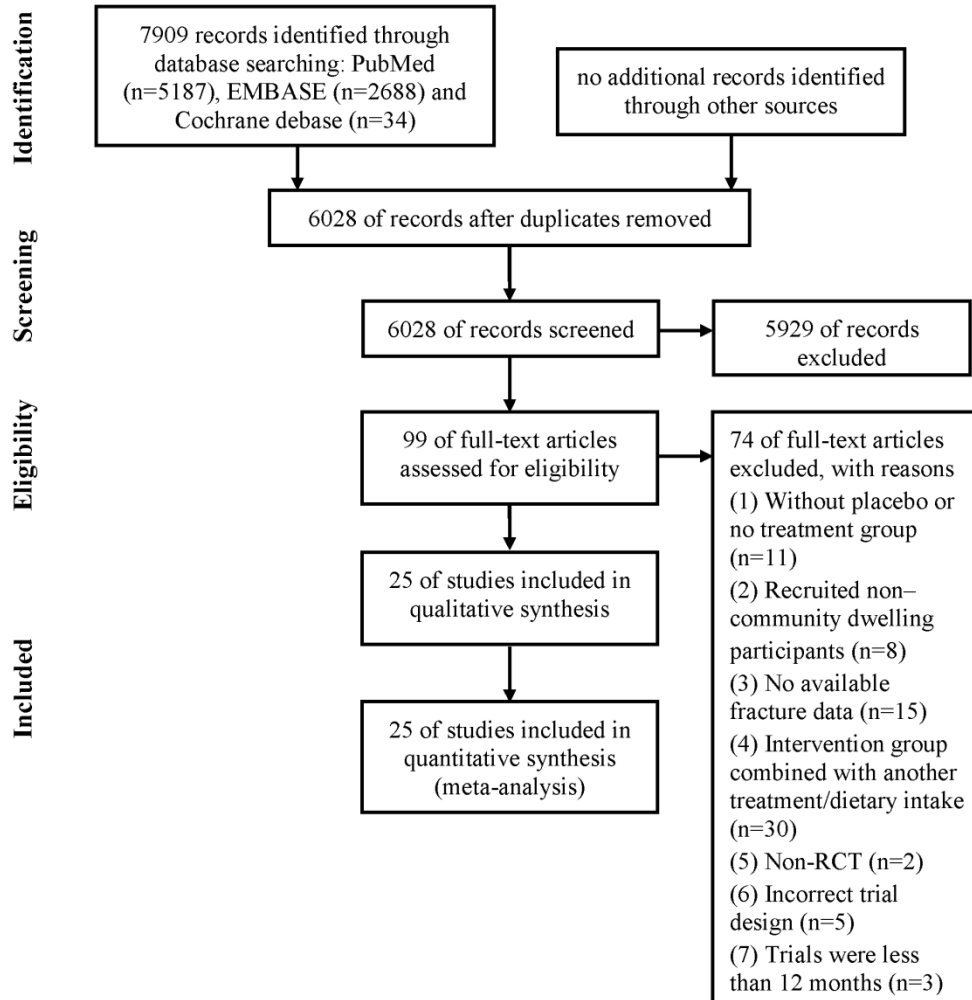
485 **supplementary Figure 8.** Inconsistency test for the vertebral fractures. A: high calcium (800 mg/d or
486 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low vitamin
487 D (less than 800 IU/d)

488 **supplementary Figure 9.** Heterogeneity test for the total fractures.

489 **supplementary Figure 10.** Heterogeneity test for the hip fractures.

490 **supplementary Figure 11.** Heterogeneity test for the vertebral fractures.

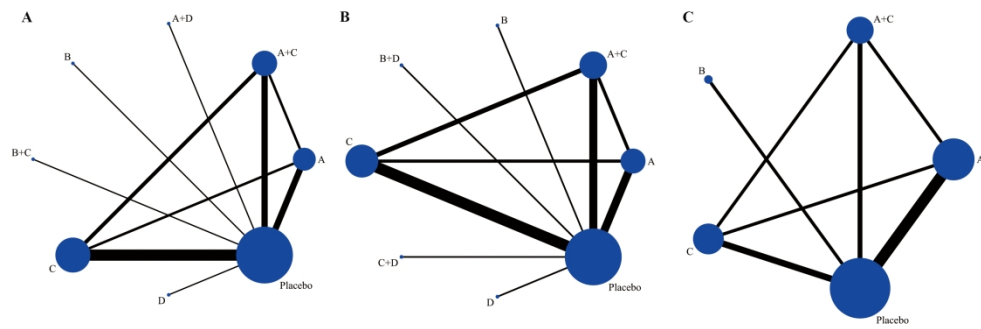
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The selection of literature for included studies.

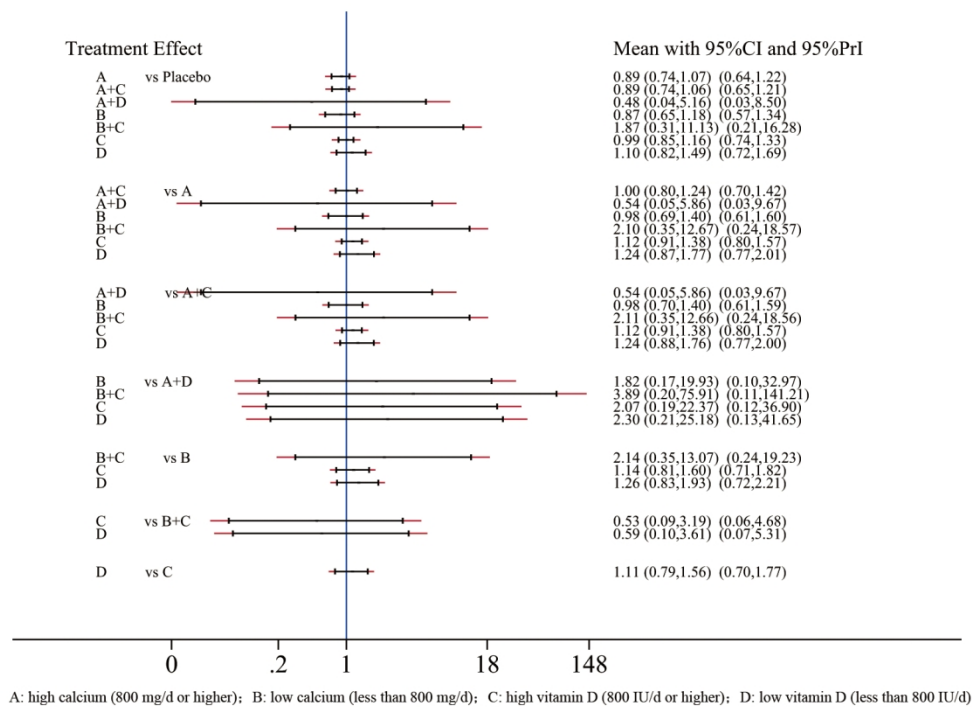
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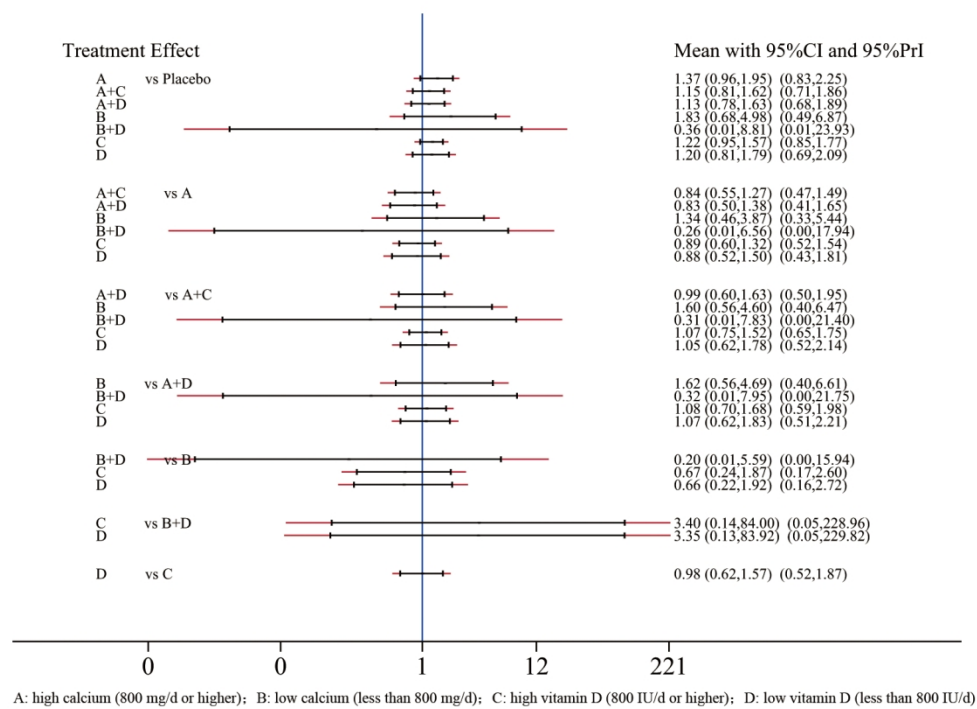


The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral fractures (C). A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)

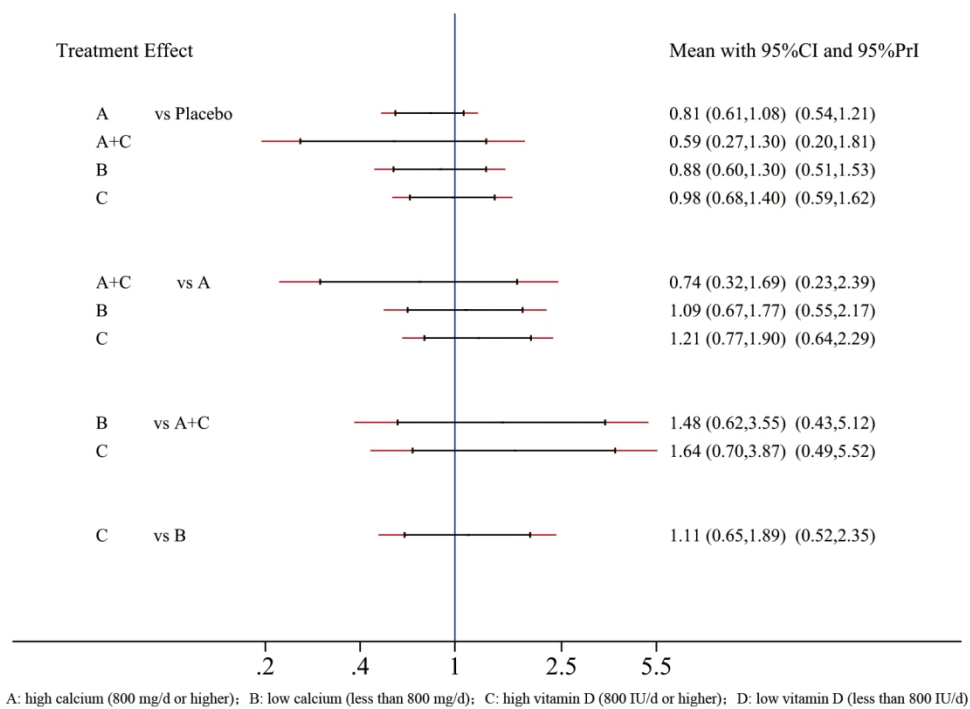
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The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)



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

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

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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

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) 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)	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)	Calcium (0.5g/d) + D ₃ (700IU/d) (n = 187) Placebo (n = 202)	213 (54)	71.1	NA	729	29.6 ^e	3 y
Grant et al, 2005 (United Kingdom)	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)	Calcium (1g/d) (n = 25) Placebo (n = 25)	50 (100)	65.9	Yes	NA	NA	3 y
Harwood et al, 2004 (United Kingdom)	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
Hin et al, 2017 (United Kingdom)	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
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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3		Placebo (n = 3957)					
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5	Lips et al, 1996	400 IU/d (n = 1291)	1916 (74)	80.0	No hip fracture	868	10.6 ^e
6							3-4 y
7	The Netherlands)	Placebo (n = 1287)					
8							
9	Liu et al, 2015	Calcium (1.5g/d) + D ₃ (600	98 (100)	62.1	No	1500	NA
10	China)	IU/d) (n = 50)					1 y
11		Placebo (n = 48)					
12							
13	Mitri et al, 2011	D ₃ (2000 IU/d)(n = 23)	25 (53)	58.0	NA	926	25.3
14							4 mo
15	United States)	Placebo (n = 24)					
16							
17	Peacock et al, 2000	Calcium (0.75g/d) (n = 126)	187 (72)	73.8	Partial ^c	597	25.0
18							4 y
19	United States)	Placebo (n = 135)					
20							
21	Porthouse et al, 2005	Calcium (1g/d) + D ₃ (800	3314 (100)	76.8	Partial ^c	1080	NA
22							1.5-3.5 y
23	United Kingdom)	IU/d) (n = 1321)					
24		No treatment (n = 1993)					
25							
26	Prince et al, 2006	Calcium (0.48g/d) (n = 730)	1460 (100)	75.2	Partial ^c	915	31.0 ^e
27							5 y
28	Australia)	Placebo (n = 730)					
29							
30	Recker et al, 1996	Calcium (1.2 g/d) (n = 95)	197 (100)	73.5	Partial ^c	434	25.5 ^e
31							4 y
32	United States)	Placebo (n = 102)					
33							
34	Reid et al, 1993	Calcium (1 g/d) (n = 68)	135 (100)	58	No vertebral	750	37.5
35							4 y
36	New Zealand)	Placebo (n = 67)			fracture		
37							
38	Reid et al, 2006	Calcium (1 g/d) (n = 732)	1471 (100)	74.3	Partial ^c	857	20.7
39							5 y
40	New Zealand)	Placebo (n = 739)					
41							
42	Higgs et al, 1998	Calcium (1.6 g/d) (n = 119)	236 (100)	66.2	No	714	30.1
43							4 y
44	United States)	Placebo (n = 117)					
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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 ^e	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.

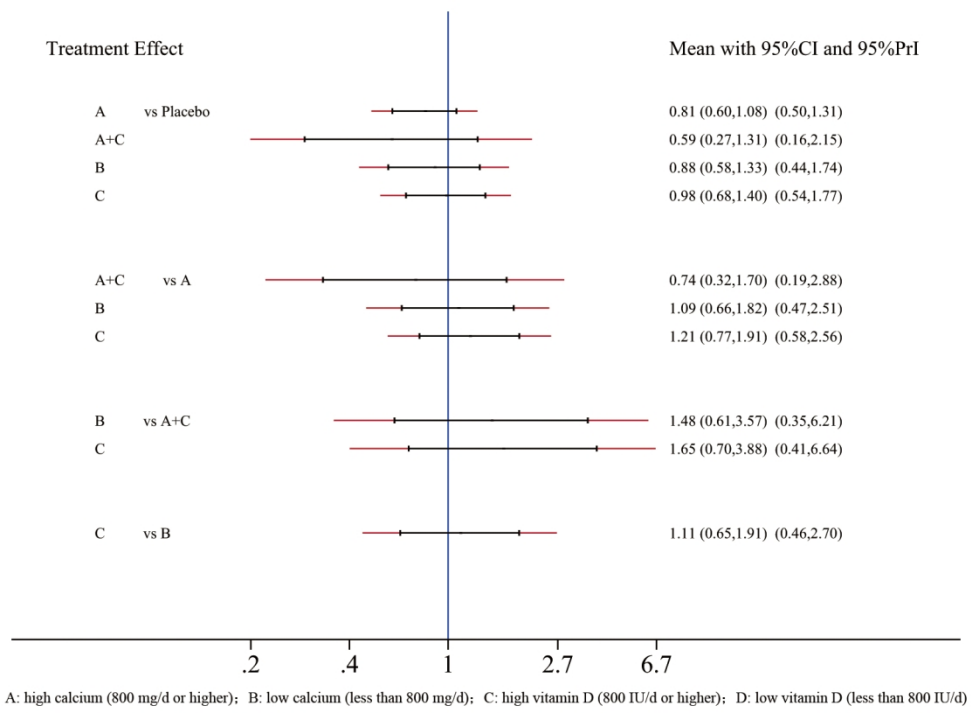
Source	Treatment		No. of Participants		
	Duration	Intervention	Total Fracture	Hip fracture	Vertebral Fracture
Avenell et al, 2004 (United Kingdom)	3.8 y	Calcium(1 g/d) (n = 29)	4	1	0
		D ₃ (800IU/d) (n = 35)	3	0	0
		Calcium (1g/d) + D ₃ (800IU/d) (n = 35)	2	1	0
		No treatment (n = 35)	4	1	1
Baron et 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)	6	1	
		Calcium (1g/d) + D ₃ (800IU/d) (n = 39)			
		No treatment (n = 37)	5	1	
Hin et al, 2017 (United Kingdom)	1 y	D ₃ (4000 IU/d)(n = 102)	6		
		D ₃ (2000 IU/d)(n = 102)			
		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	

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

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

Supplementary Table 3. The detailed data of outcomes

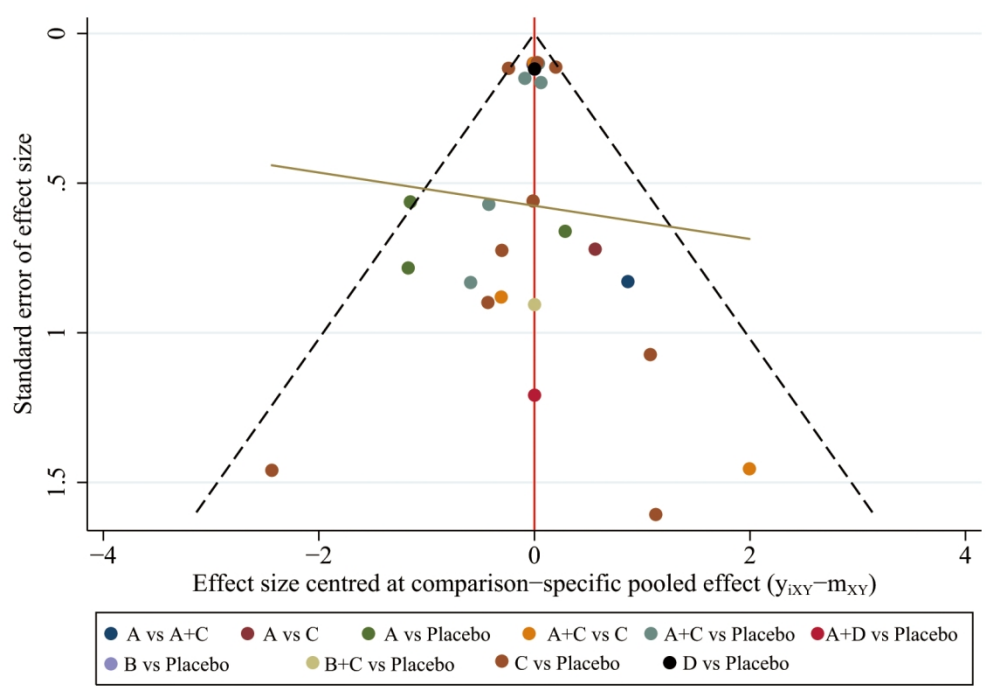
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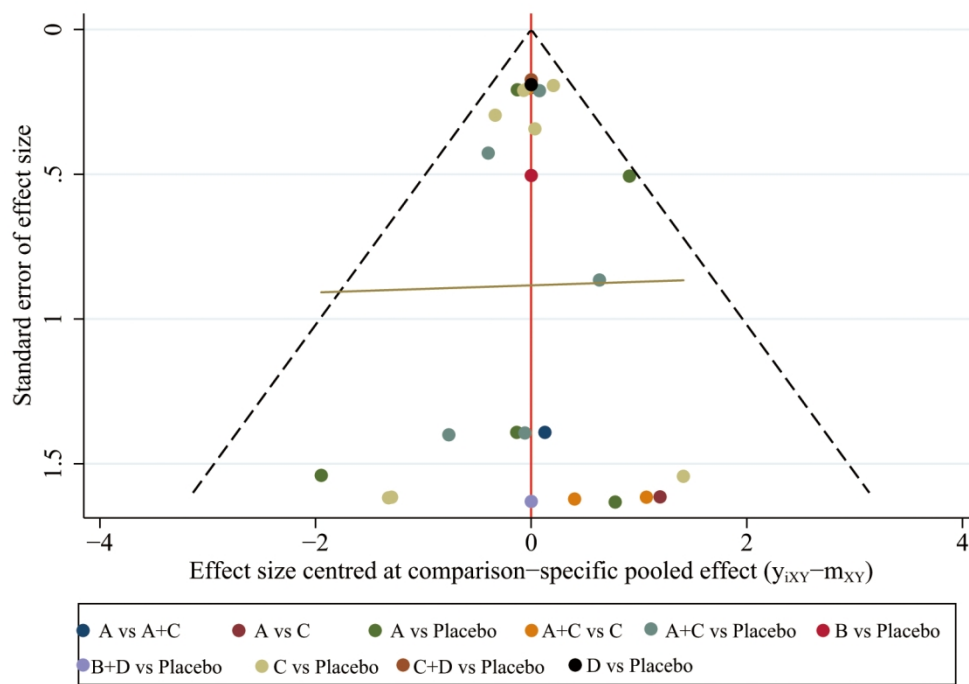


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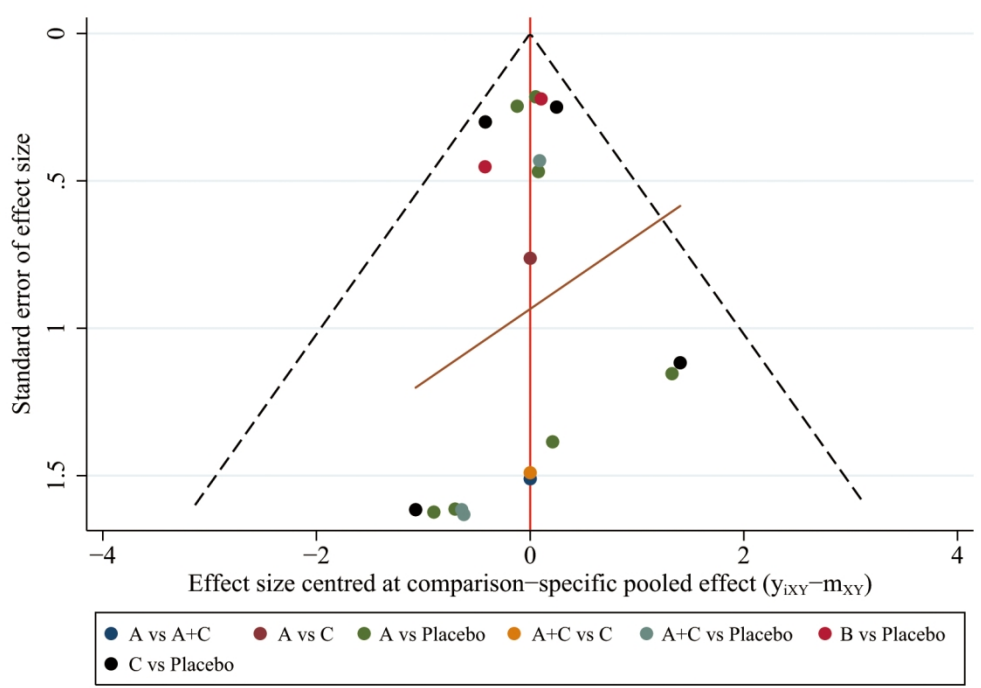
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Avenell et al, 2004	+	+	?	+	+	?	?
Baron et al, 1999	+	?	+	+	+	?	+
Dawson-Hughes et al, 1997	?	?	+	+	?	?	?
Grant et al, 2005	+	+	?	+	?	+	+
Hansson and Roos, 1987	?	?	?	?	?	?	?
Harwood et al, 2004	+	+	+	+	+	?	?
Hin et al, 2017	+	?	+	+	+	+	+
Jackson et 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	+	?	?	?	+	?	?

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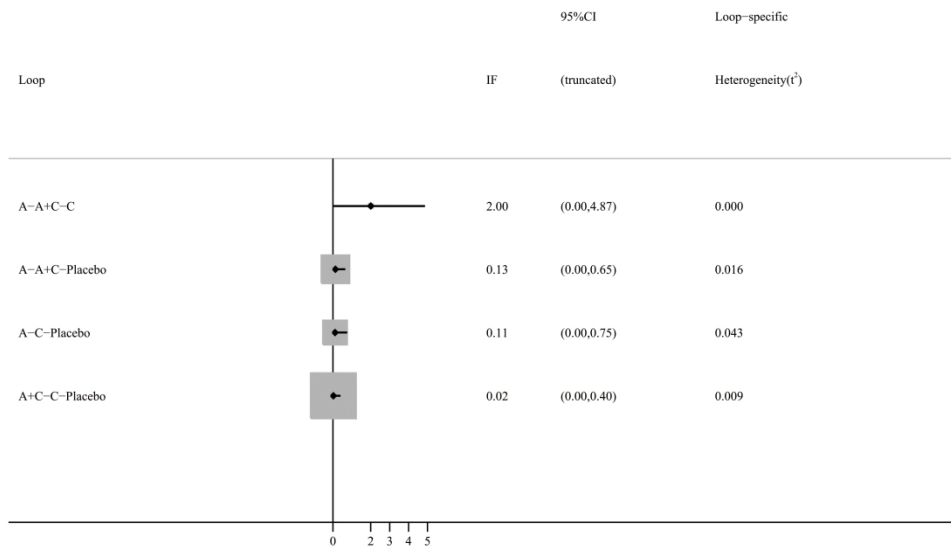




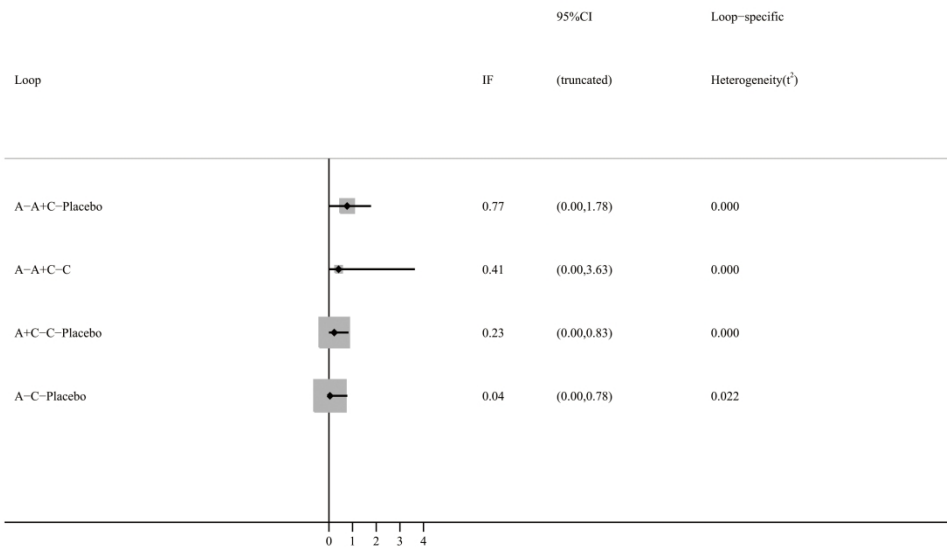
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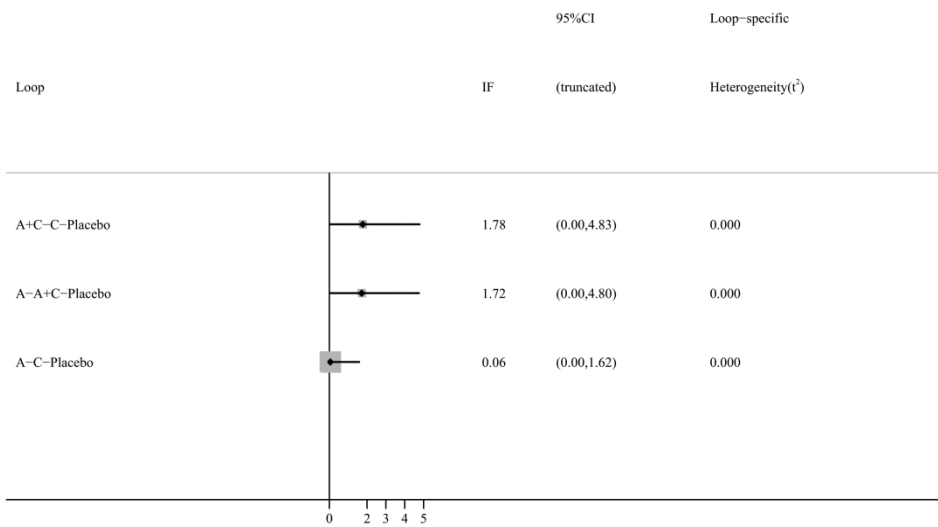
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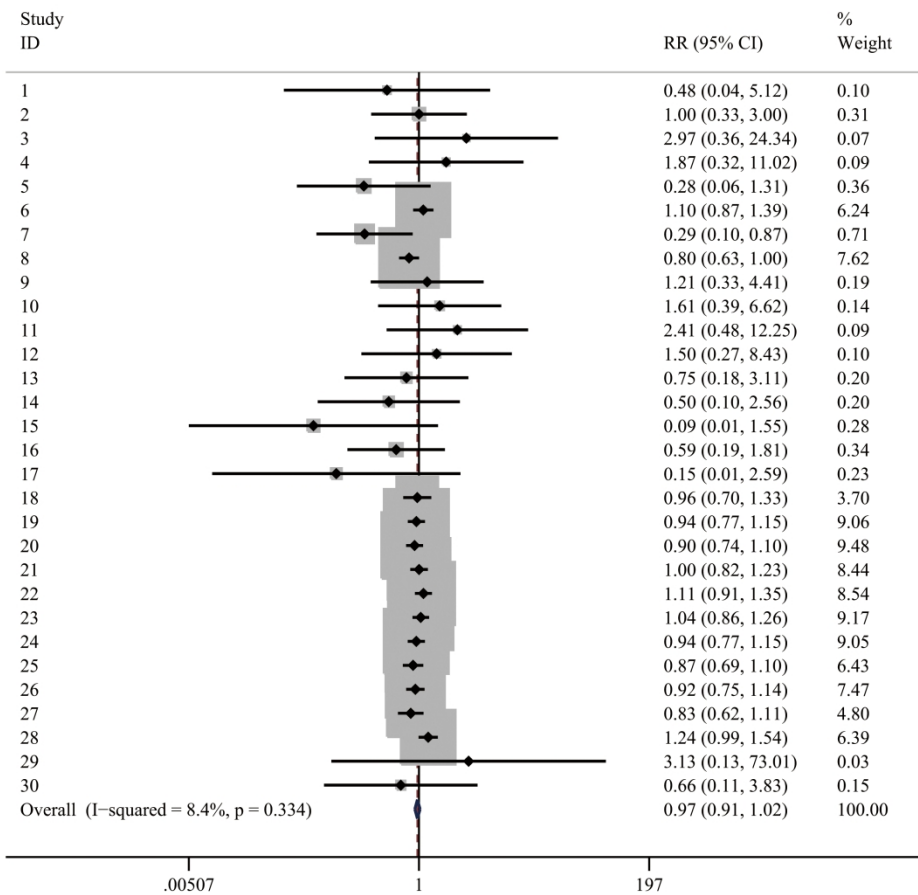


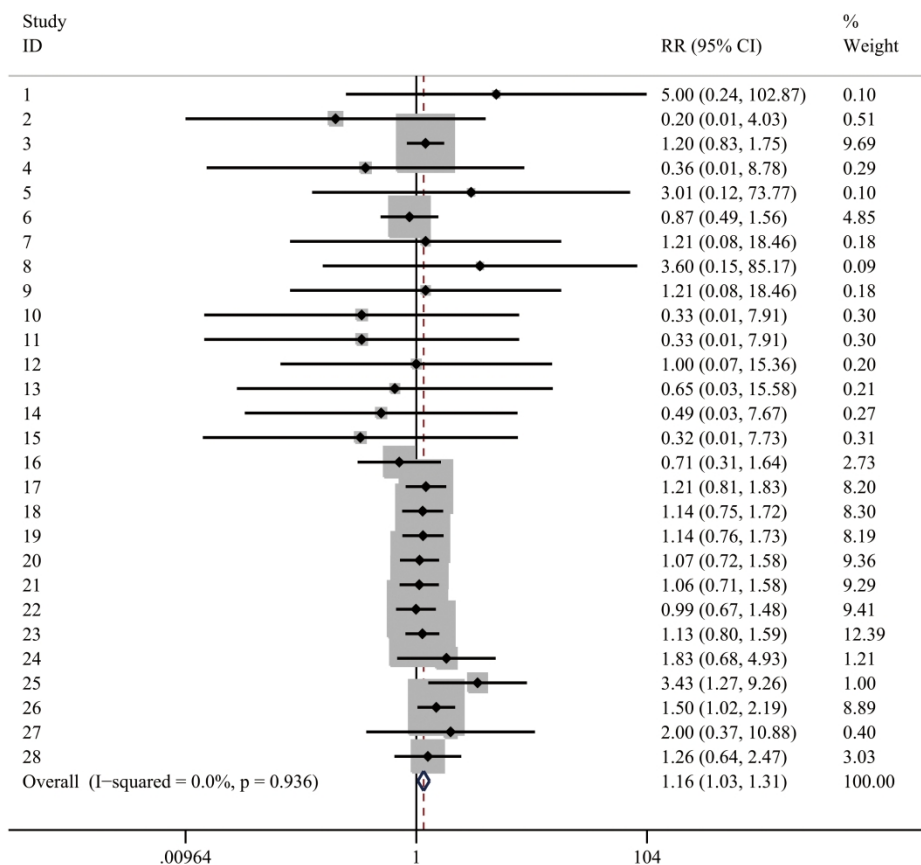
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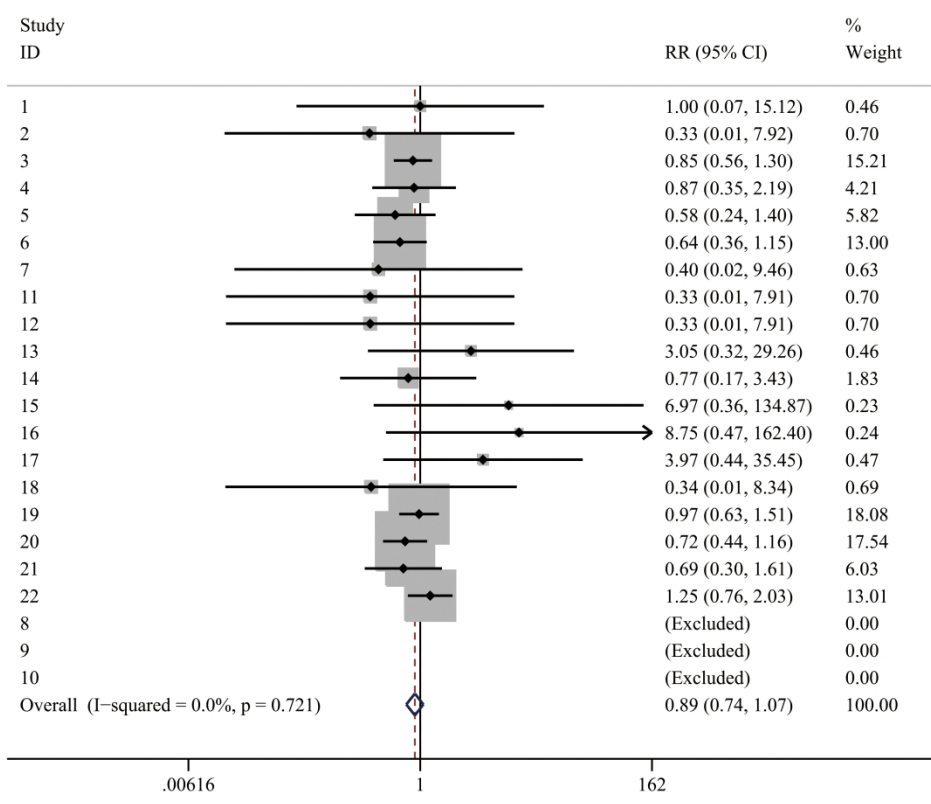
*** Loop(s) [A-A+C-C] are formed only by multi-arm trial(s) – Consistent by definition

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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

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



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4 1 **Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their**
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7 2 **combination: a network meta-analysis of randomized controlled trials**

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56 21 Zhi-Chao Hu and Qian Tang contributed equally to this work.
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4 23 **Abstract**

5
6 24 **Objective** Inconsistent findings in regard to association between different concentrations of vitamin D,
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9 25 calcium or their combination and the risk of fracture have been reported during the past decade in
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11 26 community-dwelling older people. This study was designed to compare the fracture risk using different
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14 27 concentrations of vitamin D, calcium or their combination.

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17 28 **Design** A systematic review and network meta-analysis.

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19 29 **Data sources** Randomized controlled trials in PubMed, Cochrane library, and EMBASE databases
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22 30 were systematically searched from the inception dates to December 31, 2017.

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25 31 **Outcomes** Total fracture was defined as the primary outcome. Secondary outcomes were hip fracture
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27 32 and vertebral fracture. Due to the consistency of the original studies, a consistency model was adopted.

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30 33 **Results** A total of 25 randomized controlled trials involving 43510 participants fulfilled the inclusion
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32 34 criteria. There was no evidence that the risk of total fracture was reduced by using different
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35 35 concentrations of vitamin D, calcium or their combination compared with placebo or no treatment. No
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37 36 significant associations were found between calcium, vitamin D, or combined calcium and vitamin D
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40 37 supplements and the incidence of hip, or vertebral fractures.

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43 38 **Conclusions** The use of supplements that included calcium, vitamin D, or both was not found to be
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45 39 better than placebo or no treatment in terms of risk of fractures among community-dwelling older
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48 40 adults. It means the routine use of these supplements in community-dwelling older people should be
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51 41 treated more carefully.

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53 42 **Prospero registration number** CRD42017079624

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56 43 **Keywords:** Calcium; Vitamin D; Fractures; network meta-analysis

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58 44 **Strengths and limitations of this study**
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4 45 • This systematic review and meta-analysis combined the evidence from randomized controlled trials.
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6 46 • Our findings may not support the routine use of these supplements in community-dwelling older
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9 47 people.
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11 48 • This work does not necessarily preclude any benefit of vitamin D and calcium supplementation in
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14 49 older, frail individuals.
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17 50 • Potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence.
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19 51 **Introduction**

22 52 Clinical fractures of the elderly represent a worldwide public health problem that leads to illness and
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24 53 social burden. The patients with osteoporosis in the European Union were estimated to be 27.5 million
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27 54 in 2010, and 3.5 million new fragility fractures were sustained¹. In Asia, the average cost of
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30 55 osteoporotic fractures accounted for 18.95% of the countries' 2014 gross domestic product
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32 56 (GDP)/capita and increased annually²⁻⁴. The overall prevalence of osteoporosis or low bone mass in
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35 57 non-institutional population over the age of 50 in the USA was estimated at 10.3% and 43.9%,
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38 58 respectively, which means that 10.2 million elderly people had osteoporosis and 43.4 million people
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40 59 had low bone mass in 2010⁵. With the demographic trend of ageing and the predicted increase in life
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43 60 expectancy, the cost of fracture treatment is expected to rise.

45 61 Dietary allowances for calcium range from 700 to 1200 mg/d and vitamin D of 600-800 IU/d have
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48 62 long been recommended for the prevention of osteoporotic fractures in the elderly^{6 7}. The supplements
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51 63 of calcium and vitamin D are commonly taken to maintain bone health.

53 64 However, the previous randomized controlled trials (RCT) and meta-analyses concerning vitamin D,
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56 65 calcium, or their combination for fractures yielded different efficacy outcomes. For instance, two
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59 66 meta-analyses demonstrated calcium or vitamin D supplementation alone has a small benefit on bone
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4 67 mineral density (BMD), but no clinically important to prevent fractures^{8 9}, while an updated
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6 68 meta-analysis and a pooled analysis found calcium plus vitamin D supplementation can significantly
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9 69 reduce hip fractures by 30% and total fractures by 15%^{10 11}. Two RCTs reported that low dose of
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11 70 vitamin D supplementation (less than 800 IU/d) can reduce the incidence of falls¹² and may prevent
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14 71 fractures without adverse effects¹³, but other RCTs showed no significant reduction in the incidence of
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17 72 hip or other peripheral fractures^{14 15} and its possible effects were seen only in patients with initial
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20 73 calcium insufficiency. Based on the evidence from meta-analysis, Bischoff-Ferrari et al ¹⁶ illustrated
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22 74 that high-dose vitamin D supplementation (800 IU/d or higher) not only reduced the risk of falls and
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25 75 hip fractures, but also prevented non-vertebral fractures. In contrast, a study reported annual high-dose
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28 76 oral vitamin D resulted in an increased risk of falls and fractures ¹⁷. On the other hand, low-dose
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31 77 calcium supplementation (less than 800mg/d) effectively led to a sustained reduction in the rate of bone
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34 78 loss ¹⁸ and turnover. Although it was also reported that the high dose of calcium (800 mg/d or higher)
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37 79 was associated with a lower risk of clinical fractures ¹⁹. The high-dose calcium with high-dose vitamin
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40 80 D can't prevent fractures according to the evidence from reported RCT ²⁰, but a meta-analysis
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43 81 supported their combination can prevent bone loss and significantly reduce the risk of hip fractures and
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46 82 all osteoporotic fractures ²¹. Thus, it's challenging to conclude a dose-response relation between the
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49 83 intakes of vitamin D, calcium, or their combination and the main outcomes in these heterogeneous
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52 84 literatures.

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56 85 Therefore, this study was designed to compare the fracture risk using different concentrations of
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59 86 vitamin D, calcium or their combination, and comprehensively evaluate the optimal concentration to
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87 guide clinical practice and public prevention in community-dwelling older people.

88 **Methods**

89 Search strategy and selection criteria

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

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

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

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

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4 111 in **supplementary eTable 1**). Related articles and reference lists were searched to avoid original
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6 112 miss. The reference studies of previous systematic reviews, meta-analysis, and included studies were
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9 113 manually searched to avoid initial miss. After 2 authors assessed the potentially eligible studies
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12 114 independently, any disagreement was discussed and resolved with the third independent author (QT).

13 14 115 **Data collection and assessment of risk of bias**

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17 116 Two reviewers (ZHS and XBL) independently extracted data, and the third reviewer (LT) checked
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20 117 the consistency between them. A standard data extracted form was used at this stage, including the
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22 118 authors, publishing date, country, participant characteristics; doses of calcium, vitamin D, or their
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25 119 combination; dietary calcium intake; baseline serum 25-hydroxyvitamin D concentration; and trial
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27 120 duration. For continuous outcomes, the mean, SD (standard deviation) and participant number will be
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30 121 extracted. For dichotomous outcomes, we extracted the total numbers and the numbers of events of
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33 122 both groups. The data in other forms was recalculated when possible to enable pooled analysis.

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35 123 We used the Cochrane risk of bias tool to assess risk bias of included studies. The tool has seven
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38 124 domains including random sequence generation, allocation concealment, blinding of participants and
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41 125 personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other
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43 126 bias. The classification of the judgment for each domain was low risk of bias, high risk of bias, or
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46 127 unclear risk of bias and two authors (ZHF and GZ) independently evaluated the risk of studies.

47 48 128 **Data synthesis and statistical analysis**

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51 129 The data was extracted and input into the STATA software (version 12.0; StataCorp, College
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53 130 Station, TX, USA) for network meta-analysis. And we generated network plots for each outcome to
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56 131 illustrate which interventions had been compared directly in the included studies. Network
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59 132 meta-analysis is an extension of standard meta-analysis to compare multiple treatments based on
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4 133 randomized controlled trial evidence, which forms a connected network of comparisons. Treatment
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6 134 effect estimates from network meta-analysis exploit both the direct comparisons within trials and the
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9 135 indirect comparisons across trials. To choose the random effects or fixed effects model, we either make
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11 136 a judgement about what is most likely to be appropriate based on the assumptions of the different
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14 137 models or conduct both fixed or random effects and compare which seems to fit the data better²³.
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17 138 Relative risk (RR) with 95% confidence intervals (CIs) was calculated for dichotomous outcomes
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19 139 while weighted mean difference (WMD) with 95% CIs for the continuous. Inconsistency refers to
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22 140 differences between direct and various indirect effect estimates for the same comparison. To assess
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25 141 inconsistency, we estimated the inconsistency factors in closed loop based on the method described by
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27 142 Chaimani et al²⁴. The heterogeneity in each closed loop was estimated by utilizing inconsistency factor
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30 143 (IF). If the 95% confidence intervals (95% CI) of IF values are not truncated at zero, it suggests that the
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33 144 inconsistency among studies has statistical significance. We used the surface under the cumulative
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36 145 ranking probabilities (SUCRA) to indicate which treatment was the best one. The funnel plot was used
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38 146 to identify possible publication bias if the number of studies was larger than 10.

147 **Patient and public involvement**

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

153 **Result**

154 **Data Retrieval**

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4 155 In summary, a total of 7909 potential records were initially identified through PubMed (5187),
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6 156 Embase (2688), Cochrane Data base (34). Based on our review of the title and abstract, 99 full-text
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9 157 papers were reviewed and 25 studies^{13 17 19 20 25-45} met inclusion criteria (**Figure 1**).

11 158 **Study and Patient Characteristics**

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14 159 The characteristics of all 25 included studies were summarized and shown in **supplementary Table**
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17 160 **2**. And the detailed data of outcomes was collected in **supplementary Table 3**. The papers had similar
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19 161 distributions of sex, age, country, intervention and all of them were community-dwelling older people.
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21
22 162 Hansson et al²⁹ did not report the residential status of participants, although a previous meta-analysis
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24 163 classified this status as community. The trial by Hansson et al was included, but a sensitivity analysis
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27 164 was performed that excluded that trial (**supplementary Figure 1**).

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30 165 **Supplementary Figure 2** showed the assessment of the risk of bias. All studies were randomized;
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32 166 17 were double-blind, placebo-controlled trials; 13 trials described an adequate random sequence
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35 167 generation process; and 11 trials described the methods used for allocation concealment. No obvious
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38 168 publication bias was reported according to the **supplementary Figure 3, supplementary Figure 4** and
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40 169 **supplementary Figure 5**.

41 170 **Inconsistence and heterogeneity check**

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45 171 The statistical inconsistency between direct and indirect comparisons was generally low according to
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48 172 inconsistency test because the CI values included zero (**supplementary Figure 6, supplementary**
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50 173 **Figure 7, supplementary Figure 8**). Therefore, we adopted a consistency model in all three groups.
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53 174 Meanwhile, the global heterogeneity parameter I^2 values were 8.4%, 0% and 0% respectively, which
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56 175 indicated no obvious heterogeneity was observed in all these results (**supplementary Figure 9,**
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58 176 **supplementary Figure 10, supplementary Figure 11**).

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4 177 **Primary outcome: total fracture**

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6 178 For estimating the vitamin D, calcium or their combination efficacy against total fractures, we
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9 179 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
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11 180 estimates included 15 studies with one treatment, 1 study with two treatments, and 2 studies with three
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13 181 treatments.

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16 182 The network plot of comparisons on total fractures was shown in **Figure 2A**. The forest plot for the
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18 183 network meta-analysis was shown in **Figure 3**. The RR values and 95% CIs are summarized in **Figure**
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20 184 **3**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their
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22 185 combination that remained in the main network. Neither do the statistical differences between
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24 186 interventions and placebo ($P<0.05$). So we didn't continue to make ranking graph of distribution of
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26 187 probabilities on total fractures.

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32 188 **Secondary outcomes: hip fracture and vertebral fracture**

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35 189 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
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37 190 the drug efficacy against hip fractures. Pooled estimates included 13 studies with one treatment, 1 study
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39 191 with two treatments, and two studies with three treatments.

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42 192 The network plot of comparisons on hip fractures was shown in **Figure 2B**. The forest plot for the
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44 193 network meta-analysis was shown in **Figure 4**. The RR values and 95% CIs are summarized in **Figure**
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46 194 **4**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their
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48 195 combination that remained in the main network. Neither do the statistical differences between drug
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50 196 experimental groups and placebo ($P<0.05$). So we didn't continue to make ranking graph of
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52 197 distribution of probabilities on total fractures.

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58 198 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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4 199 fractures. Pooled estimates included 10 studies with one treatment, and two studies with three
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6 200 treatments.

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9 201 The network plot of comparisons on vertebral fractures was shown in **Figure 2C**. The forest plot for
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11 202 the network meta-analysis was shown in **Figure 5**. The RR values and 95% CIs are summarized in
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14 203 **Figure 5**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium
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17 204 or their combination that remained in the main network. Neither do the statistical differences between
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20 205 drug experimental groups and placebo ($P < 0.05$). So we didn't continue to make ranking graph of
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22 206 distribution of probabilities on total fractures. In a separate sensitivity analysis, we excluded Hansson's
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25 207 study²⁹ (**supplementary Figure 1**). However, there was still no significant association of vitamin D,
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27 208 calcium or their combination with total fracture.

29 209 **Discussion**

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32 210 Vitamin D supplementation and calcium are suggested as interventions to treat and prevent fracture.
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35 211 We found the previous meta-analyses and RCTs are critically inconsistent in efficacy of different doses
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38 212 of vitamin D with calcium on fractures.

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40 213 Results of this meta-analysis showed that calcium, calcium plus vitamin D, and vitamin D
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43 214 supplementation alone were not significantly associated with a lower incidence of hip, vertebral, or
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46 215 total fractures in community-dwelling older adults. Sensitivity analyses that excluded low-quality trials
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49 216 and studies that exclusively enrolled patients with particular medical conditions did not alter these
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51 217 results.

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53 218 A meta-analysis conducted by Jia-Guo Zhao et al⁴⁶ showed that no significant difference was found
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56 219 in the incidence of hip or other fractures, which was similar to our result. However, the object of
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59 220 Zhao's study was to investigate whether calcium, vitamin D, or combined calcium and vitamin D
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4 221 supplement are associated with a lower fracture incidence while our study was designed to evaluate the
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6 222 optimal concentration of them. Meanwhile, in Zhao's meta-analysis, the participants of the included
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9 223 study reported by Massart⁴⁷ were adult maintenance hemodialysis patients, which may result in the
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11 224 imbalance of calcium in the body. Patients on hemodialysis may also be receiving
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14 225 1,25-dihydroxyvitamin D, which may affect their response to vitamin D supplementation. So we did
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17 226 not include that trial in our network meta-analysis. What's more, we didn't include studies that lasted
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19 227 less than a year because we thought this time-frame was too short to see anti-fracture efficacy. And we
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22 228 suspected that a network meta-analysis might be a more suitable choice concerning all these different
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25 229 interventions mixed.

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27 230 Bischoff-Ferrari et al ⁴⁸ reported that high-dose vitamin D supplementation (800 IU/d or higher)
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30 231 played an important role in the reduction of the risk of falls and hip fractures, as well as prevented
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32 232 non-vertebral fractures in adults 65 years or older. However, their findings may have been influenced
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35 233 by the trial of Chapuy et al ⁴⁹, which only enrolled participants living in an institution. What's more,
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38 234 differences in conclusions of previous meta-analyses and the current meta-analysis were due to the
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40 235 recently published trials which reported neutral or harmful associations of vitamin D supplementation
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43 236 and fracture incidence more and more. Study findings here indicated that vitamin D might result in a
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46 237 higher risk for hip fracture, but this conclusion did not reach statistical significance. This finding may
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49 238 be attributable to lack of statistical power in this meta-analysis.

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51 239 Most recently there was a meta-analysis published in the Lancet by Bolland et al⁵⁰, whose findings
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53 240 suggested that vitamin D supplementation does not prevent fractures or falls, or have clinically
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56 241 meaningful effects on bone mineral density. Although it was similar to our study to some extent, they
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59 242 are really different. First, we only included community-dwelling older people. We found that some
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4 243 meta-analyses equated community-dwelling older people with those in nursing institution. The lack of
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7 244 exercise, dietary intake and exposure to sunlight made people in nursing institution turned more
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9 245 susceptible to the use of supplements including vitamin D, calcium or their combination. Although the
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12 246 studies involving participants living in nursing institution were only a small part, but it could change
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15 247 the whole outcomes and produce false positive results. We found only Avenell's study paid attention to
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18 248 this question when they conducted a subgroup analysis, but they did not discussed separately.
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21 249 Meanwhile, we only enrolled adults older than 50 years and trial duration more than 1 year to reduce
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24 250 the statistical heterogeneity in network meta-analysis. Furthermore, the current analyses included
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27 251 calcium supplementation, where the Bolland's study focused on vitamin D.

27 252 However, possible limitations of this study protocol include potential missing data and meta-biases,
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30 253 heterogeneity, which may limit the quality of evidence. Some RCTs were of poor quality and, for
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33 254 example, used unclear allocation concealment. So we made a sensitivity analysis by excluding
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36 255 low-quality trials. Meanwhile, some study characteristics such as baseline serum 25-hydroxyvitamin D
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39 256 concentrations might be to contribute heterogeneity so future analyses are still needed to explore this
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42 257 potential heterogeneity. What's more, we combined bolus dosing by injection with oral supplements
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45 258 taken daily/monthly/yearly, which might have different effects on vitamin D status in the body. In
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48 259 addition, the report ignored the effect of treatment with vitamin D on plasma 25-hydroxy-vitamin D
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51 260 concentrations and sub-types of fracture, such as pathologic fractures; this work does not necessarily
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54 261 preclude any benefit of vitamin D and calcium supplementation in older, frail individuals.

262 **Conclusions**

263 In this meta-analysis of randomized clinical trials, we found that the use of different concentrations of
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266 264 vitamin D, calcium or their combination in community-dwelling older adults was not associated with a

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4 265 lower risk of fractures. Our findings may not support the routine use of these supplements in
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6 266 community-dwelling older people.
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9 267 **Contributors**

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11 268 ZCH and AMW conceived the study. The search strategy was developed by LT and XBL. ZHF, GZ
12
13
14 269 and QT will complete electronic search, select publications and assess their eligibility. ZHS and XBL
15
16
17 270 will extract information of the included studies after screening. JWX will check the data entry for
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19
20 271 accuracy and completeness. ZCH and LT will give advice for data analysis and presentation of study
21
22
23 272 result. LYS and CMS contributed to the text revision. WFN and AMW supervised the overall conduct
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25 273 of the study. All the authors drafted and critically reviewed and approved the final manuscript.
26

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37
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43 280 **Conflicts of interest**

44
45 281 None declared
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48 282 **Patient consent**

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50 283 Not required.
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53 284 **Provenance and peer review**

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56 285 Not commissioned; externally peer reviewed.
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58 286 **Data availability statement**
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287 All data relevant to the study are included in the article or uploaded as supplementary information.

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449 **Legends:**

450 **Figure 1.** The selection of literature for included studies.

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

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

454 **Figure 3.** The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher); B: low
455 calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low vitamin D (less than
456 800 IU/d)

457 **Figure 4.** The forest plot for the risk of hip fractures. A: high calcium (800 mg/d or higher); B: low
458 calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low vitamin D (less than
459 800 IU/d)

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

463 **supplementary Figure 1.** A sensitivity analysis excluded the trial of Hansson et al. A: high calcium
464 (800 mg/d or higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher);
465 D: low vitamin D (less than 800 IU/d)

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

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

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4 468 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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11 470 **supplementary Figure 4.** Publication bias for the hip fractures. A: high calcium (800 mg/d or higher);
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14 471 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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22 473 **supplementary Figure 5.** Publication bias for the vertebral fractures. A: high calcium (800 mg/d or
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25 474 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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27 475 vitamin D (less than 800 IU/d)
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32 476 **supplementary Figure 6.** Inconsistency test for the total fractures. A: high calcium (800 mg/d or
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35 477 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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37 478 vitamin D (less than 800 IU/d)
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43 479 **supplementary Figure 7.** Inconsistency test for the hip fractures. A: high calcium (800 mg/d or
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46 480 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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48 481 vitamin D (less than 800 IU/d)
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53 482 **supplementary Figure 8.** Inconsistency test for the vertebral fractures. A: high calcium (800 mg/d or
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56 483 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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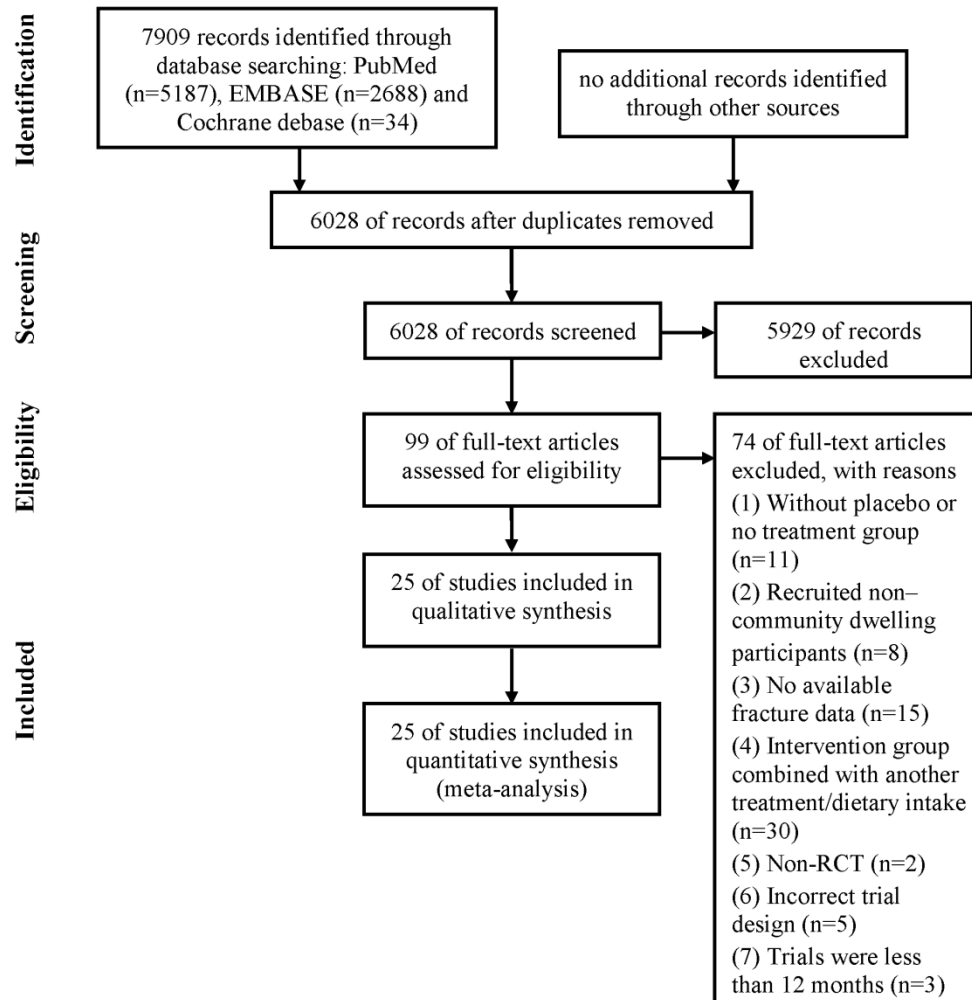
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485 **supplementary Figure 9.** Heterogeneity test for the total fractures.

486 **supplementary Figure 10.** Heterogeneity test for the hip fractures.

487 **supplementary Figure 11.** Heterogeneity test for the vertebral fractures.

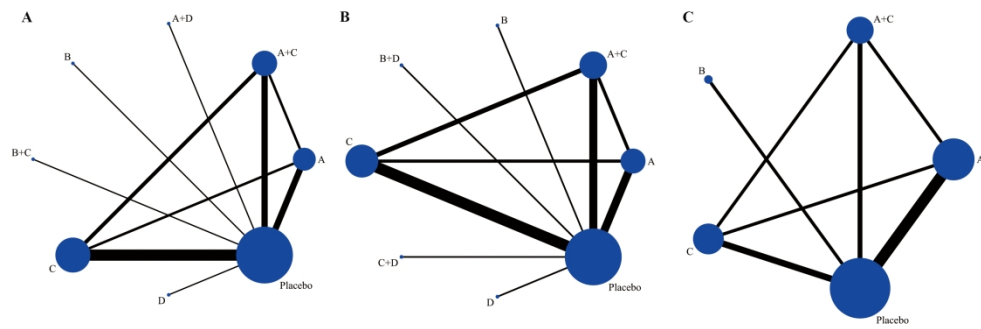
For peer review only



The selection of literature for included studies.

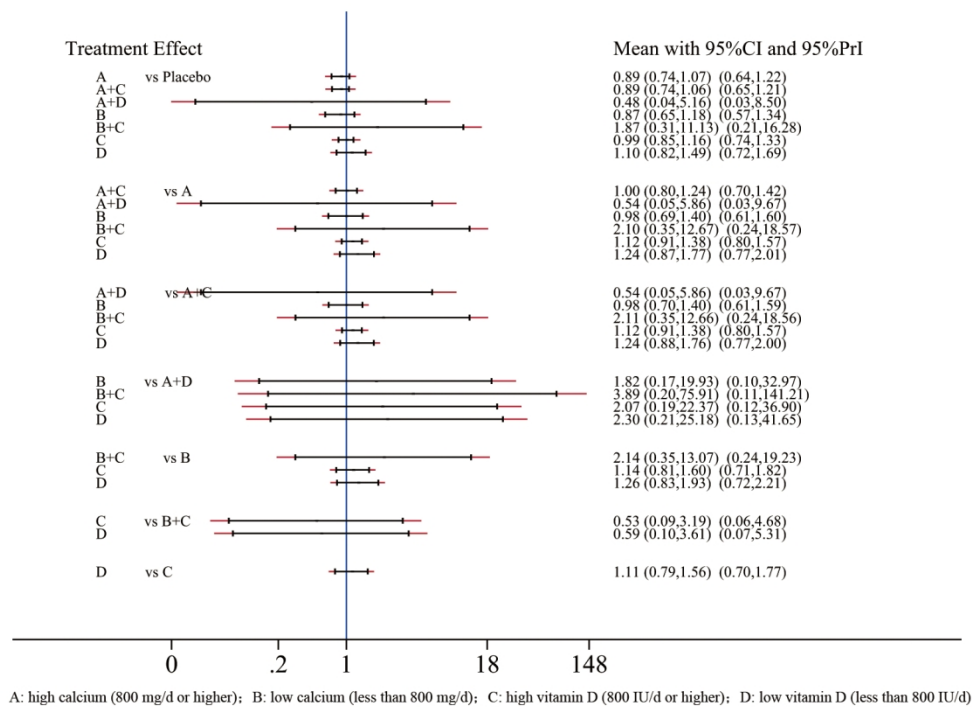
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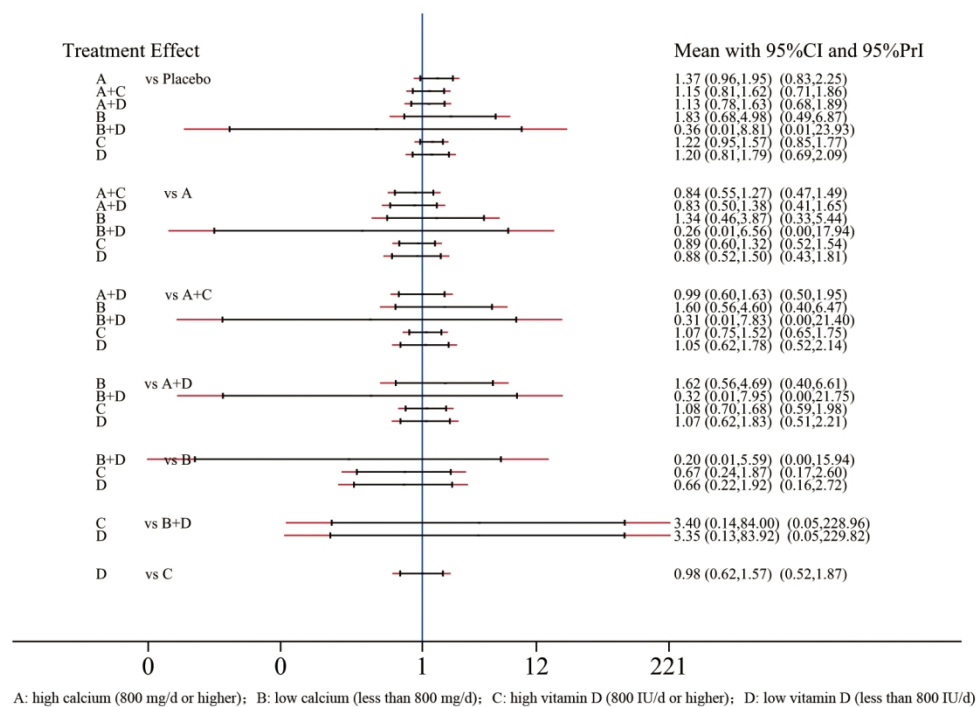


The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral fractures (C). A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)

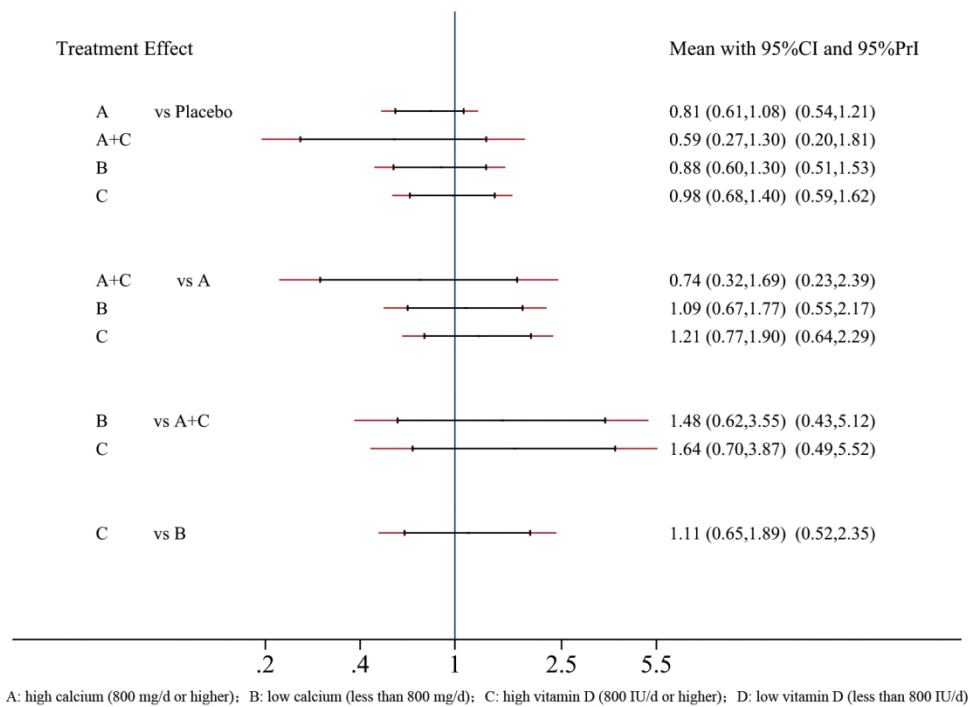
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The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)



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

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

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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

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) 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)	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)	Calcium (0.5g/d) + D ₃ (700IU/d) (n = 187) Placebo (n = 202)	213 (54)	71.1	NA	729	29.6 ^e	3 y
Grant et al, 2005 (United Kingdom)	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)	Calcium (1g/d) (n = 25) Placebo (n = 25)	50 (100)	65.9	Yes	NA	NA	3 y
Harwood et al, 2004 (United Kingdom)	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
Hin et al, 2017 (United Kingdom)	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
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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3		Placebo (n = 3957)					
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5	Lips et al, 1996	400 IU/d (n = 1291)	1916 (74)	80.0	No hip fracture	868	10.6 ^e
6							3-4 y
7	The Netherlands)	Placebo (n = 1287)					
8							
9	Liu et al, 2015	Calcium (1.5g/d) + D ₃ (600	98 (100)	62.1	No	1500	NA
10	China)	IU/d) (n = 50)					1 y
11		Placebo (n = 48)					
12							
13	Mitri et al, 2011	D ₃ (2000 IU/d)(n = 23)	25 (53)	58.0	NA	926	25.3
14							4 mo
15	United States)	Placebo (n = 24)					
16							
17	Peacock et al, 2000	Calcium (0.75g/d) (n = 126)	187 (72)	73.8	Partial ^c	597	25.0
18							4 y
19	United States)	Placebo (n = 135)					
20							
21	Porthouse et al, 2005	Calcium (1g/d) + D ₃ (800	3314 (100)	76.8	Partial ^c	1080	NA
22							1.5-3.5 y
23	United Kingdom)	IU/d) (n = 1321)					
24		No treatment (n = 1993)					
25							
26	Pince et al, 2006	Calcium (0.48g/d) (n = 730)	1460 (100)	75.2	Partial ^c	915	31.0 ^e
27							5 y
28	Australia)	Placebo (n = 730)					
29							
30	Recker et al, 1996	Calcium (1.2 g/d) (n = 95)	197 (100)	73.5	Partial ^c	434	25.5 ^e
31							4 y
32	United States)	Placebo (n = 102)					
33							
34	Reid et al, 1993	Calcium (1 g/d) (n = 68)	135 (100)	58	No vertebral	750	37.5
35							4 y
36	New Zealand)	Placebo (n = 67)			fracture		
37							
38	Reid et al, 2006	Calcium (1 g/d) (n = 732)	1471 (100)	74.3	Partial ^c	857	20.7
39							5 y
40	New Zealand)	Placebo (n = 739)					
41							
42	Higgs et al, 1998	Calcium (1.6 g/d) (n = 119)	236 (100)	66.2	No	714	30.1
43							4 y
44	United States)	Placebo (n = 117)					
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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 ^e	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 2. The characteristics of the included studies.

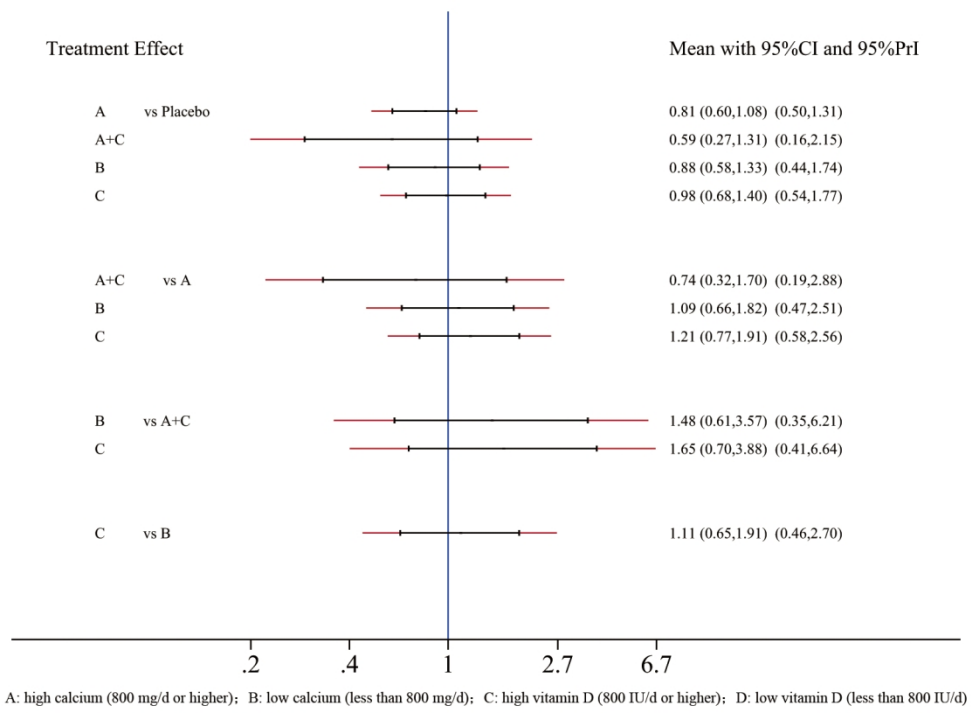
Source	Treatment		No. of Participants		
	Duration	Intervention	Total Fracture	Hip fracture	Vertebral Fracture
Avenell et al, 2004 (United Kingdom)	3.8 y	Calcium(1 g/d) (n = 29)	4	1	0
		D ₃ (800IU/d) (n = 35)	3	0	0
		Calcium (1g/d) + D ₃ (800IU/d) (n = 35)	2	1	0
		No treatment (n = 35)	4	1	1
Baron et 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)	6	1	
		Calcium (1g/d) + D ₃ (800IU/d) (n = 39)			
		No treatment (n = 37)	5	1	
Hin et al, 2017 (United Kingdom)	1 y	D ₃ (4000 IU/d)(n = 102)	6		
		D ₃ (2000 IU/d)(n = 102)			
		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	

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

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

Supplementary Table 3. The detailed data of outcomes

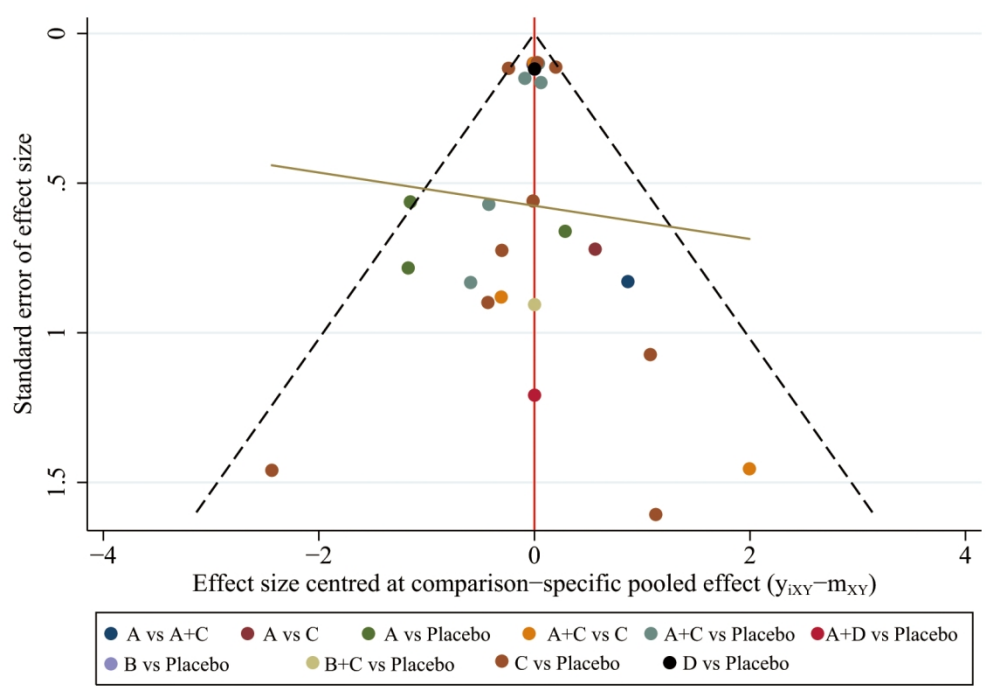
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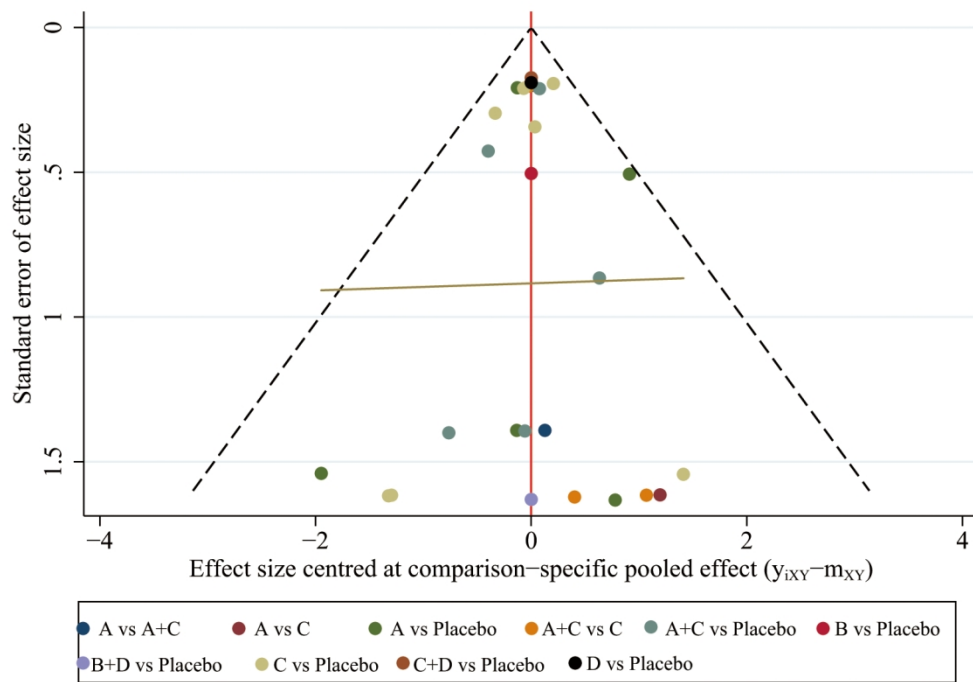


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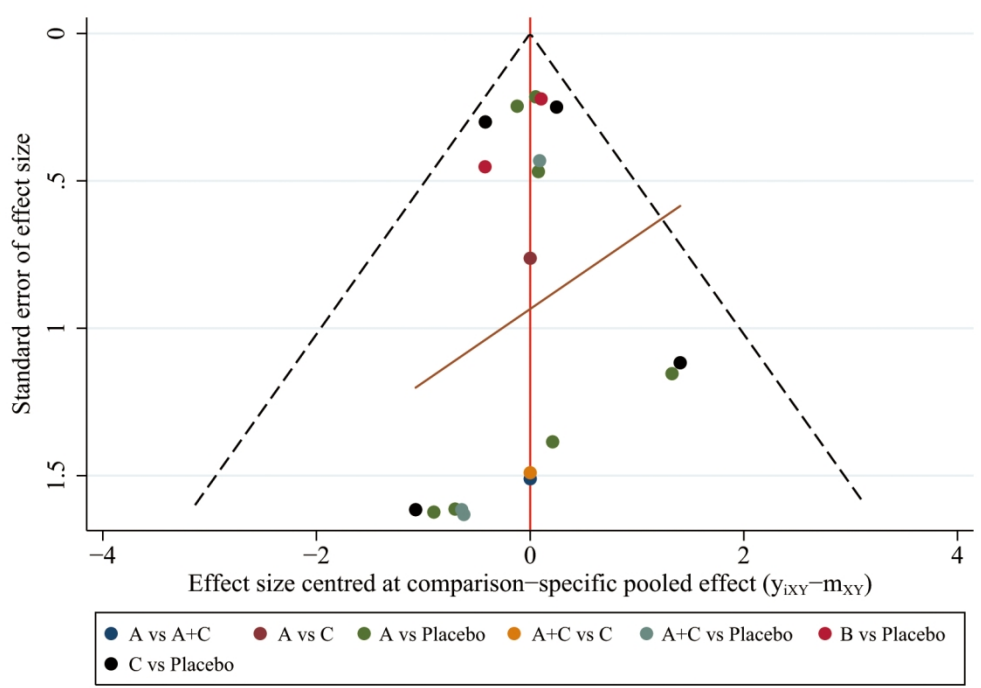
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Avenell et al, 2004	+	+	?	+	+	?	?
Baron et al, 1999	+	?	+	+	+	?	+
Dawson-Hughes et al, 1997	?	?	+	+	?	?	?
Grant et al, 2005	+	+	?	+	?	+	+
Hansson and Roos, 1987	?	?	?	?	?	?	?
Harwood et al, 2004	+	+	+	+	+	?	?
Hin et al, 2017	+	?	+	+	+	+	+
Jackson et 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	+	?	+	?	+	+	+
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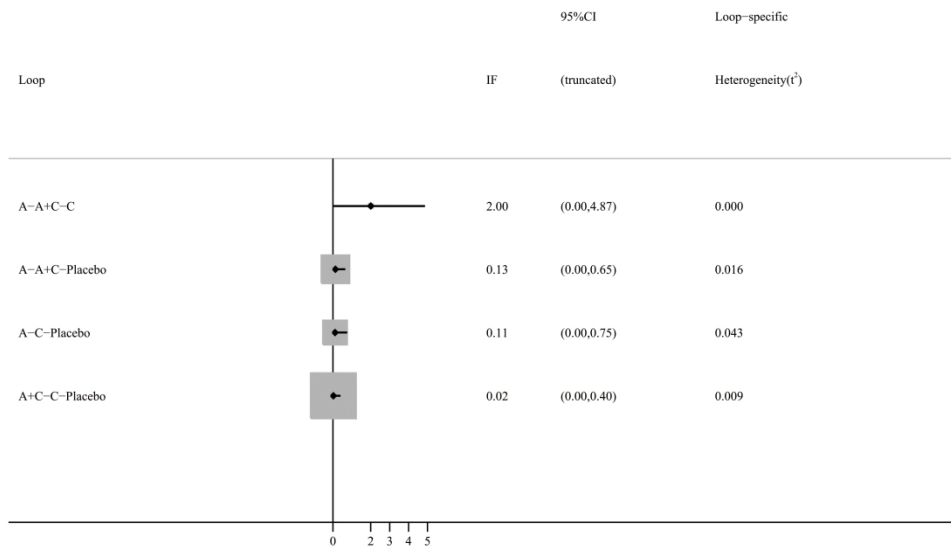




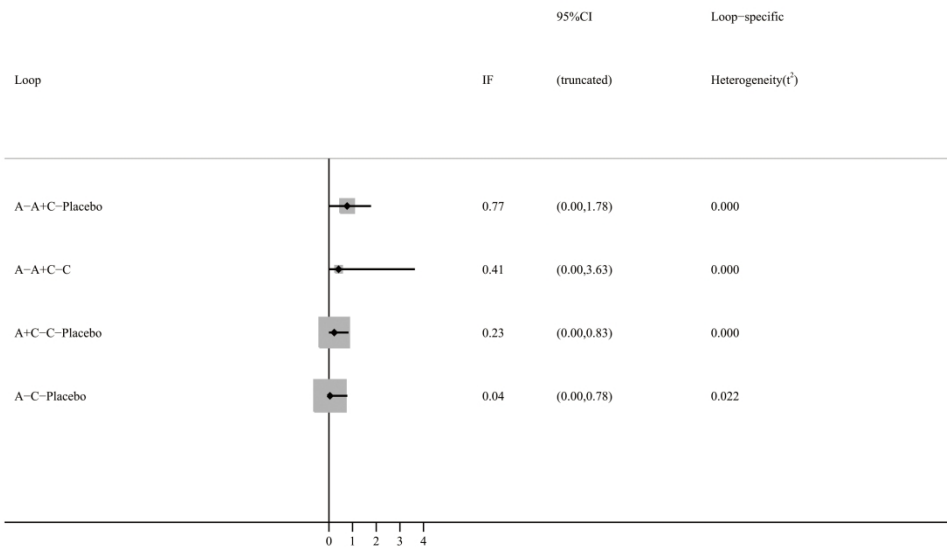
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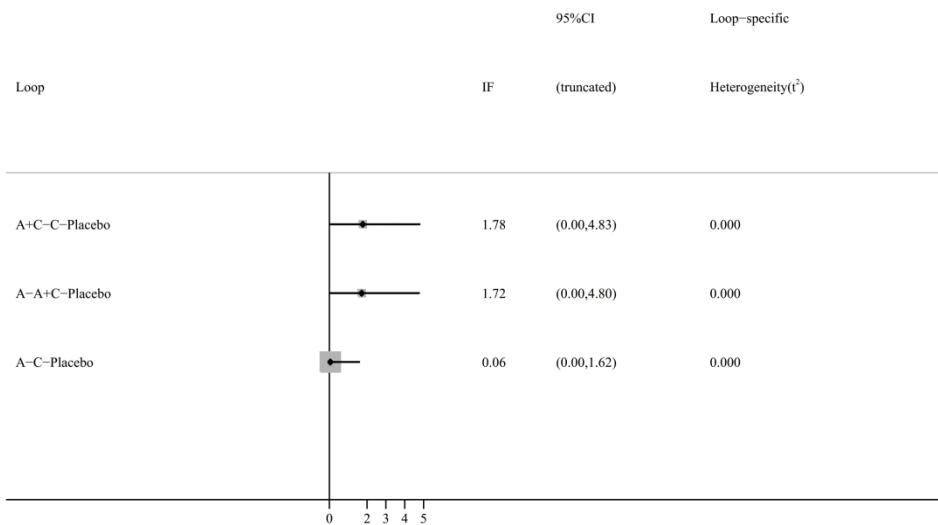
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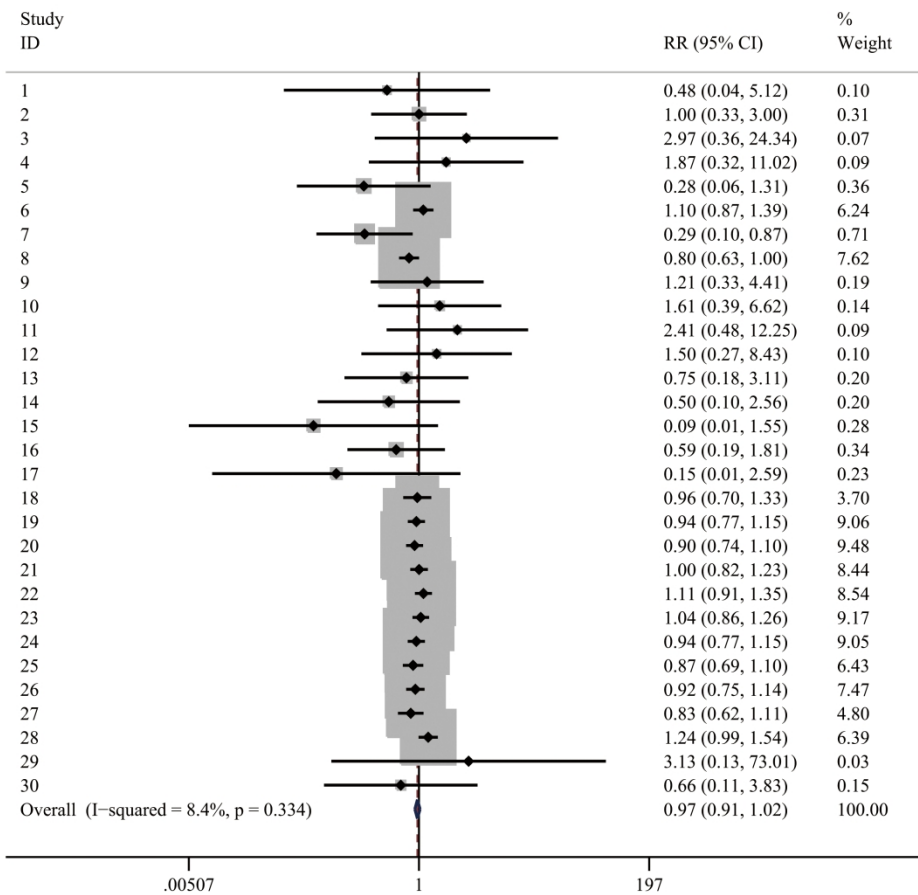


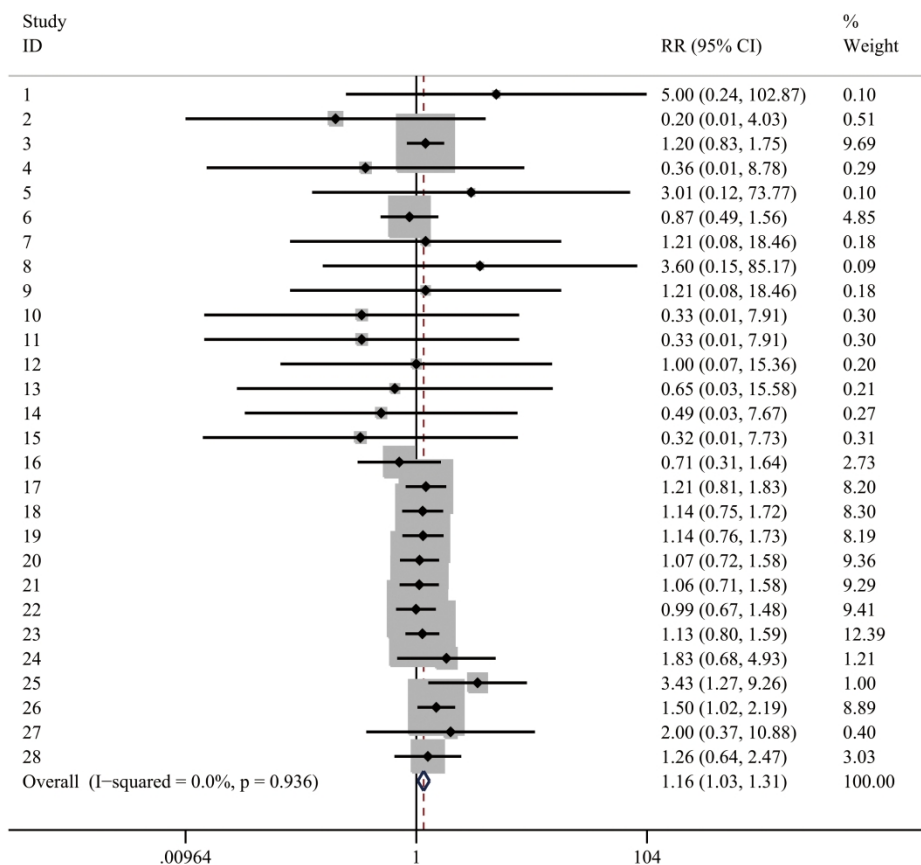
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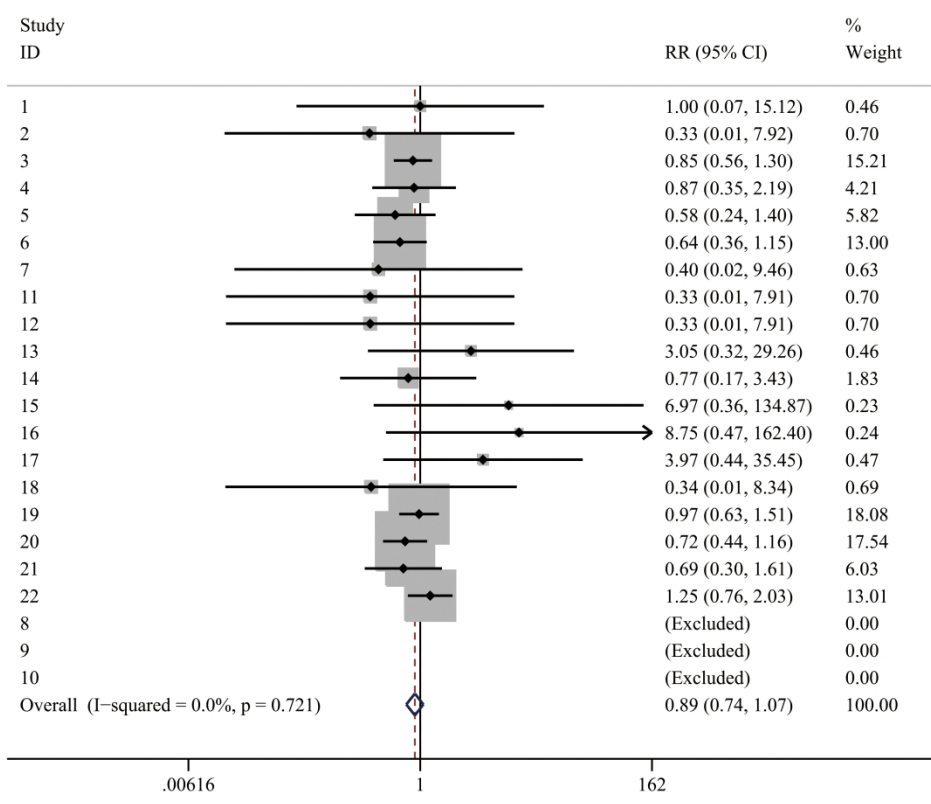
*** Loop(s) [A-A+C-C] are formed only by multi-arm trial(s) – Consistent by definition

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



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4 1 **Comparison of fracture risk using different supplemental doses of vitamin D, calcium or their**
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6 2 **combination: a network meta-analysis of randomized controlled trials**
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56 21 Zhi-Chao Hu and Qian Tang contributed equally to this work.

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4 23 **Abstract**

5
6 24 **Objective** Inconsistent findings in regard to association between different concentrations of vitamin D,
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9 25 calcium or their combination and the risk of fracture have been reported during the past decade in
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11 26 community-dwelling older people. This study was designed to compare the fracture risk using different
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14 27 concentrations of vitamin D, calcium or their combination.

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17 28 **Design** A systematic review and network meta-analysis.

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19 29 **Data sources** Randomized controlled trials in PubMed, Cochrane library, and EMBASE databases
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21
22 30 were systematically searched from the inception dates to December 31, 2017.

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25 31 **Outcomes** Total fracture was defined as the primary outcome. Secondary outcomes were hip fracture
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27 32 and vertebral fracture. Due to the consistency of the original studies, a consistency model was adopted.

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30 33 **Results** A total of 25 randomized controlled trials involving 43510 participants fulfilled the inclusion
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32 34 criteria. There was no evidence that the risk of total fracture was reduced by using different
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35 35 concentrations of vitamin D, calcium or their combination compared with placebo or no treatment. No
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37 36 significant associations were found between calcium, vitamin D, or combined calcium and vitamin D
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40 37 supplements and the incidence of hip, or vertebral fractures.

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43 38 **Conclusions** The use of supplements that included calcium, vitamin D, or both was not found to be
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45 39 better than placebo or no treatment in terms of risk of fractures among community-dwelling older
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48 40 adults. It means the routine use of these supplements in community-dwelling older people should be
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51 41 treated more carefully.

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53 42 **Prospero registration number** CRD42017079624

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56 43 **Keywords:** Calcium; Vitamin D; Fractures; network meta-analysis

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58 44 **Strengths and limitations of this study**
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4 45 • This systematic review and meta-analysis combined the evidence from randomized controlled trials.
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6 46 • Our findings may not support the routine use of these supplements in community-dwelling older
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9 47 people.
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11 48 • This work does not necessarily preclude any benefit of vitamin D and calcium supplementation in
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14 49 older, frail individuals.
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17 50 • Potential missing data and meta-biases, heterogeneity, which may limit the quality of evidence.
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19 51 **Introduction**

22 52 Clinical fractures of the elderly represent a worldwide public health problem that leads to illness and
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25 53 social burden. The patients with osteoporosis in the European Union were estimated to be 27.5 million
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28 54 in 2010, and 3.5 million new fragility fractures were sustained¹. In Asia, the average cost of
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31 55 osteoporotic fractures accounted for 18.95% of the countries' 2014 gross domestic product
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34 56 (GDP)/capita and increased annually²⁻⁴. The overall prevalence of osteoporosis or low bone mass in
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37 57 non-institutional population over the age of 50 in the USA was estimated at 10.3% and 43.9%,
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40 58 respectively, which means that 10.2 million elderly people had osteoporosis and 43.4 million people
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43 59 had low bone mass in 2010⁵. With the demographic trend of ageing and the predicted increase in life
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46 60 expectancy, the cost of fracture treatment is expected to rise.

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48 61 Dietary allowances for calcium range from 700 to 1200 mg/d and vitamin D of 600-800 IU/d have
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51 62 long been recommended for the prevention of osteoporotic fractures in the elderly^{6 7}. The supplements
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54 63 of calcium and vitamin D are commonly taken to maintain bone health.

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56 64 However, the previous randomized controlled trials (RCT) and meta-analyses concerning vitamin D,
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59 65 calcium, or their combination for fractures yielded different efficacy outcomes. For instance, two
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62 66 meta-analyses demonstrated calcium or vitamin D supplementation alone has a small benefit on bone

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4 67 mineral density (BMD), but no clinically important to prevent fractures^{8 9}, while an updated
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6 68 meta-analysis and a pooled analysis found calcium plus vitamin D supplementation can significantly
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9 69 reduce hip fractures by 30% and total fractures by 15%^{10 11}. Two RCTs reported that low dose of
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11 70 vitamin D supplementation (less than 800 IU/d) can reduce the incidence of falls¹² and may prevent
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14 71 fractures without adverse effects¹³, but other RCTs showed no significant reduction in the incidence of
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17 72 hip or other peripheral fractures^{14 15} and its possible effects were seen only in patients with initial
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20 73 calcium insufficiency. Based on the evidence from meta-analysis, Bischoff-Ferrari et al ¹⁶ illustrated
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22 74 that high-dose vitamin D supplementation (800 IU/d or higher) not only reduced the risk of falls and
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25 75 hip fractures, but also prevented non-vertebral fractures. In contrast, a study reported annual high-dose
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28 76 oral vitamin D resulted in an increased risk of falls and fractures ¹⁷. On the other hand, low-dose
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31 77 calcium supplementation (less than 800mg/d) effectively led to a sustained reduction in the rate of bone
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34 78 loss ¹⁸ and turnover. Although it was also reported that the high dose of calcium (800 mg/d or higher)
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37 79 was associated with a lower risk of clinical fractures ¹⁹. The high-dose calcium with high-dose vitamin
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40 80 D can't prevent fractures according to the evidence from reported RCT ²⁰, but a meta-analysis
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43 81 supported their combination can prevent bone loss and significantly reduce the risk of hip fractures and
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46 82 all osteoporotic fractures ²¹. Thus, it's challenging to conclude a dose-response relation between the
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49 83 intakes of vitamin D, calcium, or their combination and the main outcomes in these heterogeneous
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52 84 literatures.

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56 85 Therefore, this study was designed to compare the fracture risk using different concentrations of
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59 86 vitamin D, calcium or their combination, and comprehensively evaluate the optimal concentration to
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87 guide clinical practice and public prevention in community-dwelling older people.

88 **Methods**

89 Search strategy and selection criteria

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

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

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

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

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4 111 **supplementary Table 2**). Related articles and reference lists were searched to avoid original miss. The
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6 112 reference studies of previous systematic reviews, meta-analysis, and included studies were manually
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9 113 searched to avoid initial miss. After 2 authors assessed the potentially eligible studies independently,
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11 114 any disagreement was discussed and resolved with the third independent author (QT).

14 115 **Data collection and assessment of risk of bias**

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17 116 Two reviewers (ZHS and XBL) independently extracted data, and the third reviewer (LT) checked
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19 117 the consistency between them. A standard data extracted form was used at this stage, including the
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21 118 authors, publishing date, country, participant characteristics; doses of calcium, vitamin D, or their
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23 119 combination; dietary calcium intake; baseline serum 25-hydroxyvitamin D concentration; and trial
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25 120 duration. For continuous outcomes, the mean, SD (standard deviation) and participant number will be
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27 121 extracted. For dichotomous outcomes, we extracted the total numbers and the numbers of events of
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29 122 both groups. The data in other forms was recalculated when possible to enable pooled analysis.

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35 123 We used the Cochrane risk of bias tool to assess risk bias of included studies. The tool has seven
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37 124 domains including random sequence generation, allocation concealment, blinding of participants and
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39 125 personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other
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41 126 bias. The classification of the judgment for each domain was low risk of bias, high risk of bias, or
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43 127 unclear risk of bias and two authors (ZHF and GZ) independently evaluated the risk of studies.

48 128 **Data synthesis and statistical analysis**

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50 129 The data was extracted and input into the STATA software (version 12.0; StataCorp, College
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52 130 Station, TX, USA) for network meta-analysis. And we generated network plots for each outcome to
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54 131 illustrate which interventions had been compared directly in the included studies. Network
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56 132 meta-analysis is an extension of standard meta-analysis to compare multiple treatments based on
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4 133 randomized controlled trial evidence, which forms a connected network of comparisons. Treatment
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6 134 effect estimates from network meta-analysis exploit both the direct comparisons within trials and the
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9 135 indirect comparisons across trials. To choose the random effects or fixed effects model, we either make
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11 136 a judgement about what is most likely to be appropriate based on the assumptions of the different
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14 137 models or conduct both fixed or random effects and compare which seems to fit the data better²³.
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17 138 Relative risk (RR) with 95% confidence intervals (CIs) was calculated for dichotomous outcomes
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19 139 while weighted mean difference (WMD) with 95% CIs for the continuous. Inconsistency refers to
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22 140 differences between direct and various indirect effect estimates for the same comparison. To assess
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25 141 inconsistency, we estimated the inconsistency factors in closed loop based on the method described by
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27 142 Chaimani et al²⁴. The heterogeneity in each closed loop was estimated by utilizing inconsistency factor
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30 143 (IF). If the 95% confidence intervals (95% CI) of IF values are not truncated at zero, it suggests that the
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33 144 inconsistency among studies has statistical significance. We used the surface under the cumulative
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36 145 ranking probabilities (SUCRA) to indicate which treatment was the best one. The funnel plot was used
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38 146 to identify possible publication bias if the number of studies was larger than 10.

147 **Patient and public involvement**

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

153 **Result**

154 **Data Retrieval**

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4 155 In summary, a total of 7909 potential records were initially identified through PubMed (5187),
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6 156 Embase (2688), Cochrane Data base (34). Based on our review of the title and abstract, 99 full-text
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9 157 papers were reviewed and 25 studies^{13 17 19 20 25-45} met inclusion criteria (**Figure 1**).

11 158 **Study and Patient Characteristics**

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14 159 The characteristics of all 25 included studies were summarized and shown in **supplementary Table**
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17 160 **3**. And the detailed data of outcomes was collected in **supplementary Table 4**. The papers had similar
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19 161 distributions of sex, age, country, intervention and all of them were community-dwelling older people.
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22 162 Hansson et al²⁹ did not report the residential status of participants, although a previous meta-analysis
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24 163 classified this status as community. The trial by Hansson et al was included, but a sensitivity analysis
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27 164 was performed that excluded that trial (**supplementary Figure 1**).

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30 165 **Supplementary Figure 2** showed the assessment of the risk of bias. All studies were randomized;
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32 166 17 were double-blind, placebo-controlled trials; 13 trials described an adequate random sequence
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35 167 generation process; and 11 trials described the methods used for allocation concealment. No obvious
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38 168 publication bias was reported according to the **supplementary Figure 3, supplementary Figure 4** and
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40 169 **supplementary Figure 5**.

41 170 **Inconsistence and heterogeneity check**

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45 171 The statistical inconsistency between direct and indirect comparisons was generally low according to
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48 172 inconsistency test because the CI values included zero (**supplementary Figure 6, supplementary**
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50 173 **Figure 7, supplementary Figure 8**). Therefore, we adopted a consistency model in all three groups.
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53 174 Meanwhile, we adopted the fixed effects models and the heterogeneity parameter I^2 values were 8.4%,
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56 175 0% and 0% respectively, which indicated no obvious heterogeneity was observed in all these results
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59 176 (**supplementary Figure 9, supplementary Figure 10, supplementary Figure 11**).

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4 177 **Primary outcome: total fracture**

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6 178 For estimating the vitamin D, calcium or their combination efficacy against total fractures, we
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9 179 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
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11 180 estimates included 15 studies with one treatment, 1 study with two treatments, and 2 studies with three
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14 181 treatments.

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17 182 The network plot of comparisons on total fractures was shown in **Figure 2A**. The forest plot for the
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19 183 network meta-analysis was shown in **Figure 3**. The RR values and 95% CIs are summarized in **Figure**
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22 184 **3**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their
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25 185 combination that remained in the main network. Neither do the statistical differences between
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27 186 interventions and placebo ($P<0.05$). So we didn't continue to make ranking graph of distribution of
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30 187 probabilities on total fractures.

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33 188 **Secondary outcomes: hip fracture and vertebral fracture**

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35 189 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
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37 190 the drug efficacy against hip fractures. Pooled estimates included 13 studies with one treatment, 1 study
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40 191 with two treatments, and two studies with three treatments.

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43 192 The network plot of comparisons on hip fractures was shown in **Figure 2B**. The forest plot for the
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45 193 network meta-analysis was shown in **Figure 4**. The RR values and 95% CIs are summarized in **Figure**
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48 194 **4**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium or their
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51 195 combination that remained in the main network. Neither do the statistical differences between drug
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53 196 experimental groups and placebo ($P<0.05$). So we didn't continue to make ranking graph of
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56 197 distribution of probabilities on total fractures.

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58 198 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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4 199 fractures. Pooled estimates included 10 studies with one treatment, and two studies with three
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6 200 treatments.

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9 201 The network plot of comparisons on vertebral fractures was shown in **Figure 2C**. The forest plot for
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11 202 the network meta-analysis was shown in **Figure 5**. The RR values and 95% CIs are summarized in
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14 203 **Figure 5**. The direct and indirect comparisons indicated no differences among the vitamin D, calcium
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17 204 or their combination that remained in the main network. Neither do the statistical differences between
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20 205 drug experimental groups and placebo ($P < 0.05$). So we didn't continue to make ranking graph of
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22 206 distribution of probabilities on total fractures. In a separate sensitivity analysis, we excluded Hansson's
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25 207 study²⁹ (**supplementary Figure 1**). However, there was still no significant association of vitamin D,
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27 208 calcium or their combination with total fracture.

29 209 **Discussion**

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32 210 Vitamin D supplementation and calcium are suggested as interventions to treat and prevent fracture.
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35 211 We found the previous meta-analyses and RCTs are critically inconsistent in efficacy of different doses
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38 212 of vitamin D with calcium on fractures.

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40 213 Results of this meta-analysis showed that calcium, calcium plus vitamin D, and vitamin D
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43 214 supplementation alone were not significantly associated with a lower incidence of hip, vertebral, or
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46 215 total fractures in community-dwelling older adults. Sensitivity analyses that excluded low-quality trials
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49 216 and studies that exclusively enrolled patients with particular medical conditions did not alter these
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51 217 results.

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53 218 A meta-analysis conducted by Jia-Guo Zhao et al⁴⁶ showed that no significant difference was found
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56 219 in the incidence of hip or other fractures, which was similar to our result. However, the object of
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59 220 Zhao's study was to investigate whether calcium, vitamin D, or combined calcium and vitamin D
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4 221 supplement are associated with a lower fracture incidence while our study was designed to evaluate the
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6 222 optimal concentration of them. Meanwhile, in Zhao's meta-analysis, the participants of the included
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9 223 study reported by Massart⁴⁷ were adult maintenance hemodialysis patients, which may result in the
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11 224 imbalance of calcium in the body. Patients on hemodialysis may also be receiving
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14 225 1,25-dihydroxyvitamin D, which may affect their response to vitamin D supplementation. So we did
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17 226 not include that trial in our network meta-analysis. What's more, we didn't include studies that lasted
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19 227 less than a year because we thought this time-frame was too short to see anti-fracture efficacy. And we
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22 228 suspected that a network meta-analysis might be a more suitable choice concerning all these different
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25 229 interventions mixed.

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27 230 Bischoff-Ferrari et al ⁴⁸ reported that high-dose vitamin D supplementation (800 IU/d or higher)
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30 231 played an important role in the reduction of the risk of falls and hip fractures, as well as prevented
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33 232 non-vertebral fractures in adults 65 years or older. However, their findings may have been influenced
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36 233 by the trial of Chapuy et al ⁴⁹, which only enrolled participants living in an institution. What's more,
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38 234 differences in conclusions of previous meta-analyses and the current meta-analysis were due to the
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44 236 and fracture incidence more and more. Study findings here indicated that vitamin D might result in a
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47 237 higher risk for hip fracture, but this conclusion did not reach statistical significance. This finding may
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50 238 be attributable to lack of statistical power in this meta-analysis.

51 239 Most recently there was a meta-analysis published in the Lancet by Bolland et al⁵⁰, whose findings
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54 240 suggested that vitamin D supplementation does not prevent fractures or falls, or have clinically
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57 241 meaningful effects on bone mineral density. Although it was similar to our study to some extent, they
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60 242 are really different. First, we only included community-dwelling older people. We found that some

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4 243 meta-analyses equated community-dwelling older people with those in nursing institution. The lack of
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7 244 exercise, dietary intake and exposure to sunlight made people in nursing institution turned more
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9 245 susceptible to the use of supplements including vitamin D, calcium or their combination. Although the
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12 246 studies involving participants living in nursing institution were only a small part, but it could change
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15 247 the whole outcomes and produce false positive results. We found only Avenell's study paid attention to
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18 248 this question when they conducted a subgroup analysis, but they did not discussed separately.
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21 249 Meanwhile, we only enrolled adults older than 50 years and trial duration more than 1 year to reduce
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24 250 the statistical heterogeneity in network meta-analysis. Furthermore, the current analyses included
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27 251 calcium supplementation, where the Bolland's study focused on vitamin D.

27 252 However, possible limitations of this study protocol include potential missing data and meta-biases,
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30 253 heterogeneity, which may limit the quality of evidence. Some RCTs were of poor quality and, for
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33 254 example, used unclear allocation concealment. So we made a sensitivity analysis by excluding
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36 255 low-quality trials. Meanwhile, some study characteristics such as baseline serum 25-hydroxyvitamin D
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39 256 concentrations might be to contribute heterogeneity so future analyses are still needed to explore this
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42 257 potential heterogeneity. What's more, we combined bolus dosing by injection with oral supplements
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45 258 taken daily/monthly/yearly, which might have different effects on vitamin D status in the body. In
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48 259 addition, the report ignored the effect of treatment with vitamin D on plasma 25-hydroxy-vitamin D
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51 260 concentrations and sub-types of fracture, such as pathologic fractures; this work does not necessarily
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54 261 preclude any benefit of vitamin D and calcium supplementation in older, frail individuals.

262 **Conclusions**

263 In this meta-analysis of randomized clinical trials, we found that the use of different concentrations of
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266 264 vitamin D, calcium or their combination in community-dwelling older adults was not associated with a

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4 265 lower risk of fractures. Our findings may not support the routine use of these supplements in
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6 266 community-dwelling older people.
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9 267 **Contributors**

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11 268 ZCH and AMW conceived the study. The search strategy was developed by LT and XBL. ZHF, GZ
12
13
14 269 and QT will complete electronic search, select publications and assess their eligibility. ZHS and XBL
15
16
17 270 will extract information of the included studies after screening. JWX will check the data entry for
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19
20 271 accuracy and completeness. ZCH and LT will give advice for data analysis and presentation of study
21
22
23 272 result. LYS and CMS contributed to the text revision. WFN and AMW supervised the overall conduct
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25 273 of the study. All the authors drafted and critically reviewed and approved the final manuscript.
26

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43 280 **Conflicts of interest**

44
45 281 None declared
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48 282 **Patient consent**

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50 283 Not required.
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53 284 **Provenance and peer review**

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56 285 Not commissioned; externally peer reviewed.
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58 286 **Data availability statement**
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287 All data relevant to the study are included in the article or uploaded as supplementary information.

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449 **Legends:**

450 **Figure 1.** The selection of literature for included studies.

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

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

454 **Figure 3.** The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher); B: low
455 calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low vitamin D (less than
456 800 IU/d)

457 **Figure 4.** The forest plot for the risk of hip fractures. A: high calcium (800 mg/d or higher); B: low
458 calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low vitamin D (less than
459 800 IU/d)

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

463 **supplementary Figure 1.** A sensitivity analysis excluded the trial of Hansson et al. A: high calcium
464 (800 mg/d or higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher);
465 D: low vitamin D (less than 800 IU/d)

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

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

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4 468 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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11 470 **supplementary Figure 4.** Publication bias for the hip fractures. A: high calcium (800 mg/d or higher);
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14 471 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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22 473 **supplementary Figure 5.** Publication bias for the vertebral fractures. A: high calcium (800 mg/d or
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24 474 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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26 475 vitamin D (less than 800 IU/d)
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32 476 **supplementary Figure 6.** Inconsistency test for the total fractures. A: high calcium (800 mg/d or
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34 477 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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36 478 vitamin D (less than 800 IU/d)
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42 479 **supplementary Figure 7.** Inconsistency test for the hip fractures. A: high calcium (800 mg/d or
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44 480 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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52 482 **supplementary Figure 8.** Inconsistency test for the vertebral fractures. A: high calcium (800 mg/d or
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54 483 higher); B: low calcium (less than 800 mg/d); C: high vitamin D (800 IU/d or higher); D: low
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56 484 vitamin D (less than 800 IU/d)
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485 **supplementary Figure 9.** Heterogeneity test for the total fractures. A: the result of random effects

486 model; B: the result of fixed effects model.

487 **supplementary Figure 10.** Heterogeneity test for the hip fractures. A: the result of random effects

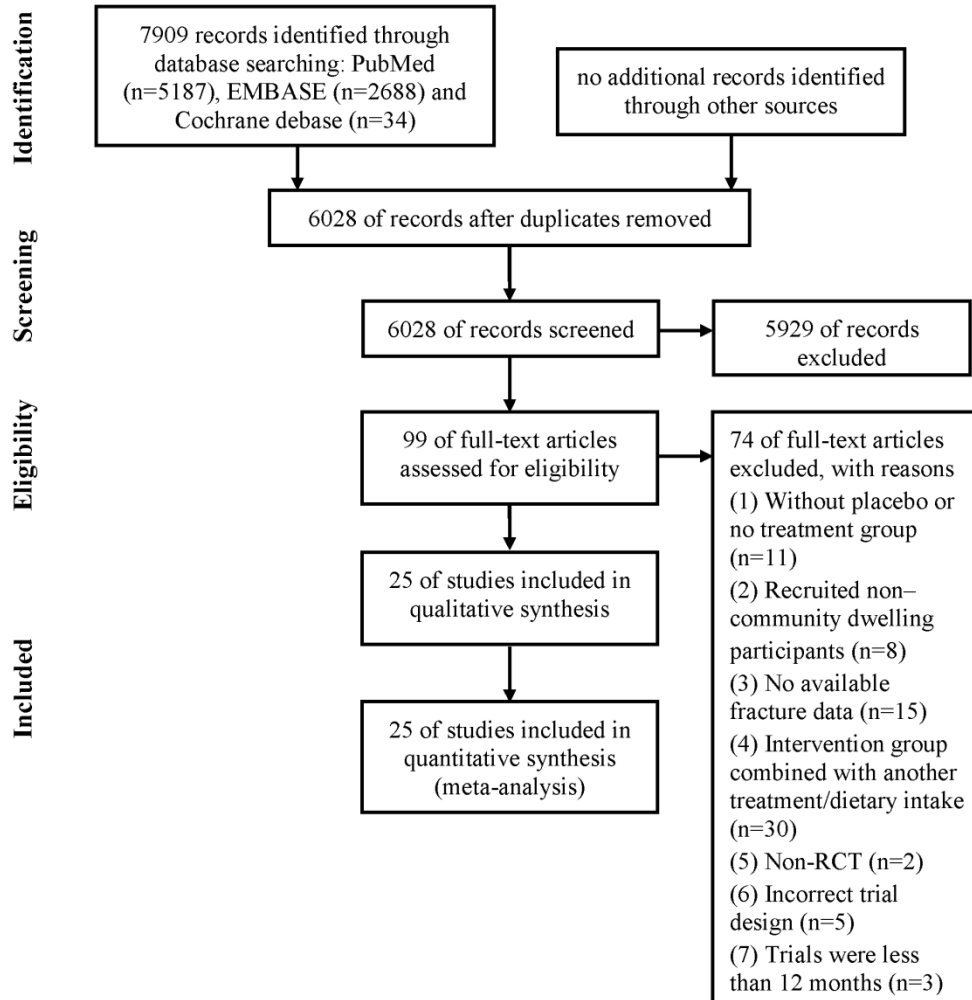
488 model; B: the result of fixed effects model.

489 **supplementary Figure 11.** Heterogeneity test for the vertebral fractures. A: the result of random

490 effects model; B: the result of fixed effects model.

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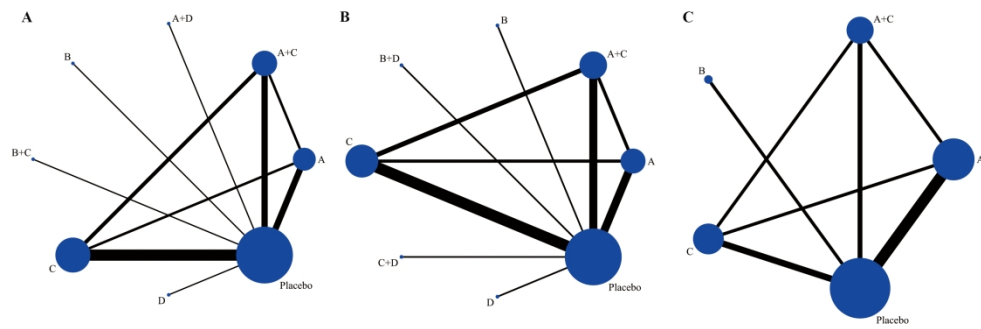
For peer review only



The selection of literature for included studies.

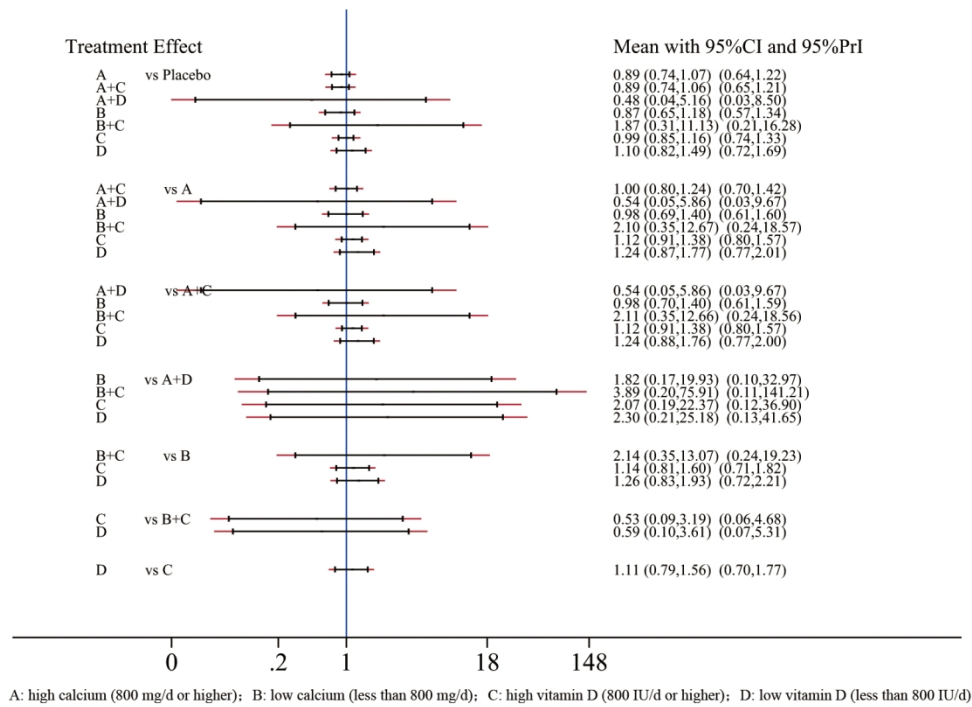
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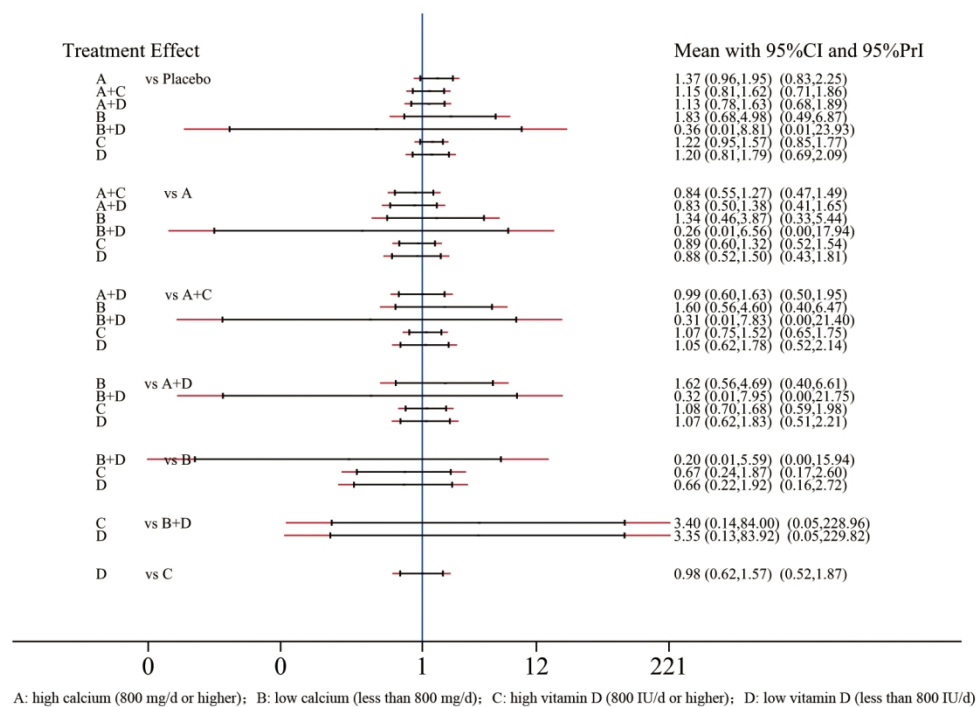


The network plot of comparisons on total fractures (A), hip fractures (B) and vertebral fractures (C). A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)

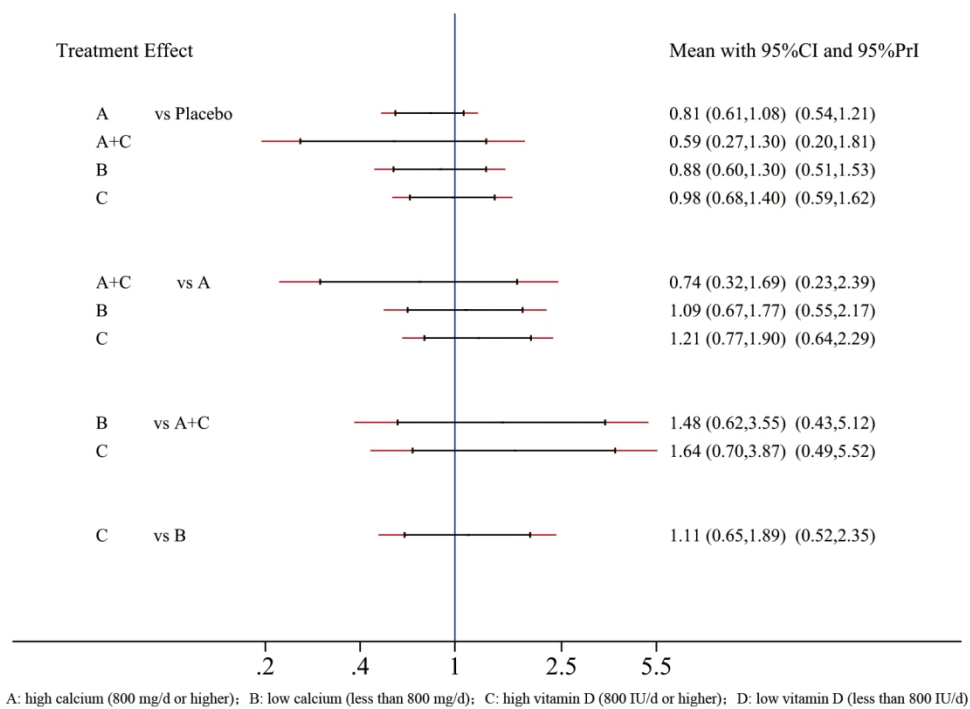
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The forest plot for the risk of total fractures. A: high calcium (800 mg/d or higher) ; B: low calcium (less than 800 mg/d) ; C: high vitamin D (800 IU/d or higher) ; D: low vitamin D (less than 800 IU/d)



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

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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

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

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) 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)	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)	Calcium (0.5g/d) + D ₃ (700IU/d) (n = 187) Placebo (n = 202)	213 (54)	71.1	NA	729	29.6 ^e	3 y
Grant et al, 2005 (United Kingdom)	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)	Calcium (1g/d) (n = 25) Placebo (n = 25)	50 (100)	65.9	Yes	NA	NA	3 y
Harwood et al, 2004 (United Kingdom)	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
Hin et al, 2017 (United Kingdom)	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
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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3		Placebo (n = 3957)					
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5	Lips et al, 1996	400 IU/d (n = 1291)	1916 (74)	80.0	No hip fracture	868	10.6 ^e
6							3-4 y
7	The Netherlands)	Placebo (n = 1287)					
8							
9	Liu et al, 2015	Calcium (1.5g/d) + D ₃ (600	98 (100)	62.1	No	1500	NA
10	China)	IU/d) (n = 50)					1 y
11		Placebo (n = 48)					
12							
13	Mitri et al, 2011	D ₃ (2000 IU/d)(n = 23)	25 (53)	58.0	NA	926	25.3
14							4 mo
15	United States)	Placebo (n = 24)					
16							
17	Peacock et al, 2000	Calcium (0.75g/d) (n = 126)	187 (72)	73.8	Partial ^c	597	25.0
18							4 y
19	United States)	Placebo (n = 135)					
20							
21	Porthouse et al, 2005	Calcium (1g/d) + D ₃ (800	3314 (100)	76.8	Partial ^c	1080	NA
22							1.5-3.5 y
23	United Kingdom)	IU/d) (n = 1321)					
24		No treatment (n = 1993)					
25							
26	Prince et al, 2006	Calcium (0.48g/d) (n = 730)	1460 (100)	75.2	Partial ^c	915	31.0 ^e
27							5 y
28	Australia)	Placebo (n = 730)					
29							
30	Recker et al, 1996	Calcium (1.2 g/d) (n = 95)	197 (100)	73.5	Partial ^c	434	25.5 ^e
31							4 y
32	United States)	Placebo (n = 102)					
33							
34	Reid et al, 1993	Calcium (1 g/d) (n = 68)	135 (100)	58	No vertebral	750	37.5
35							4 y
36	New Zealand)	Placebo (n = 67)			fracture		
37							
38	Reid et al, 2006	Calcium (1 g/d) (n = 732)	1471 (100)	74.3	Partial ^c	857	20.7
39							5 y
40	New Zealand)	Placebo (n = 739)					
41							
42	Higgs et al, 1998	Calcium (1.6 g/d) (n = 119)	236 (100)	66.2	No	714	30.1
43							4 y
44	United States)	Placebo (n = 117)					
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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 3. The characteristics of the included studies.

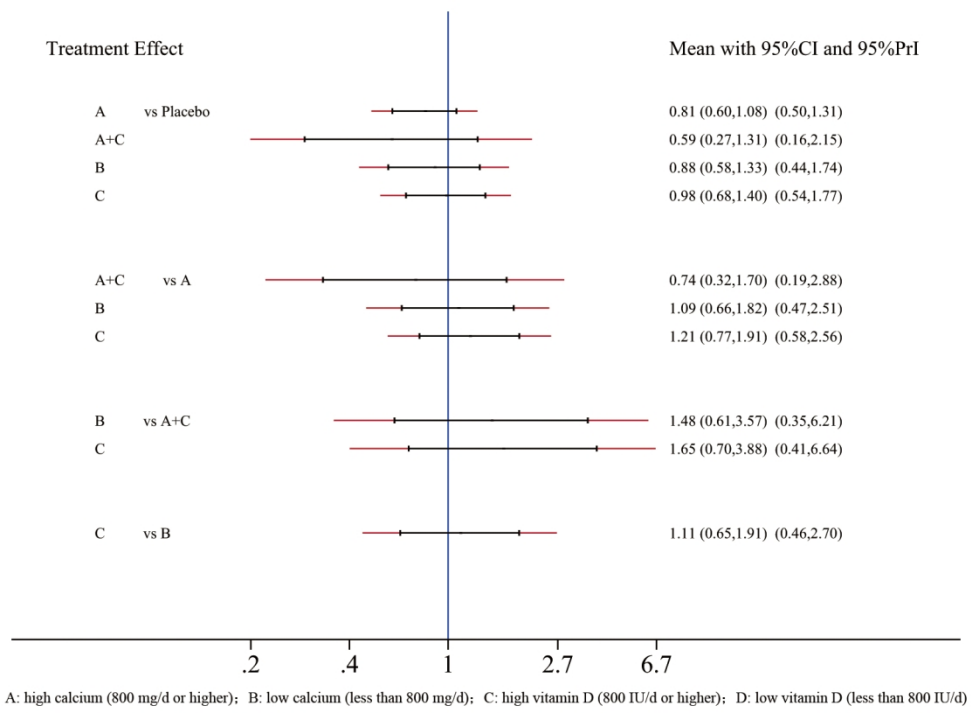
Source	Treatment		No. of Participants		
	Duration	Intervention	Total Fracture	Hip fracture	Vertebral Fracture
Avenell et al, 2004 (United Kingdom)	3.8 y	Calcium(1 g/d) (n = 29)	4	1	0
		D ₃ (800IU/d) (n = 35)	3	0	0
		Calcium (1g/d) + D ₃ (800IU/d) (n = 35)	2	1	0
		No treatment (n = 35)	4	1	1
Baron et 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)	6	1	
		Calcium (1g/d) + D ₃ (800IU/d) (n = 39)			
		No treatment (n = 37)	5	1	
Hin et al, 2017 (United Kingdom)	1 y	D ₃ (4000 IU/d)(n = 102)	6		
		D ₃ (2000 IU/d)(n = 102)			
		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	

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

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

Supplementary Table 4. The detailed data of outcomes

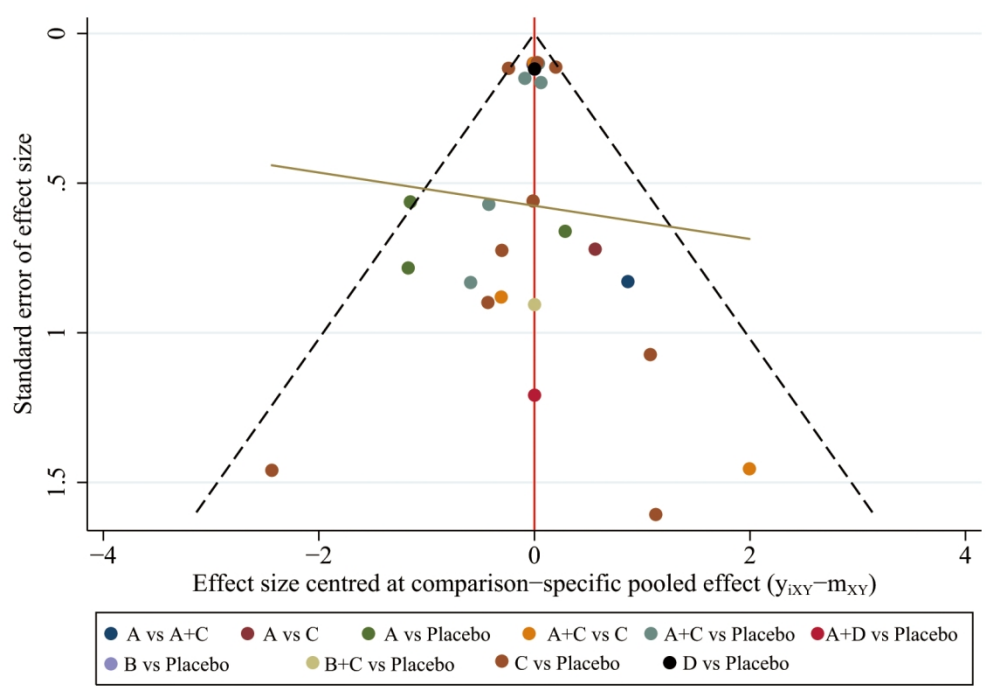
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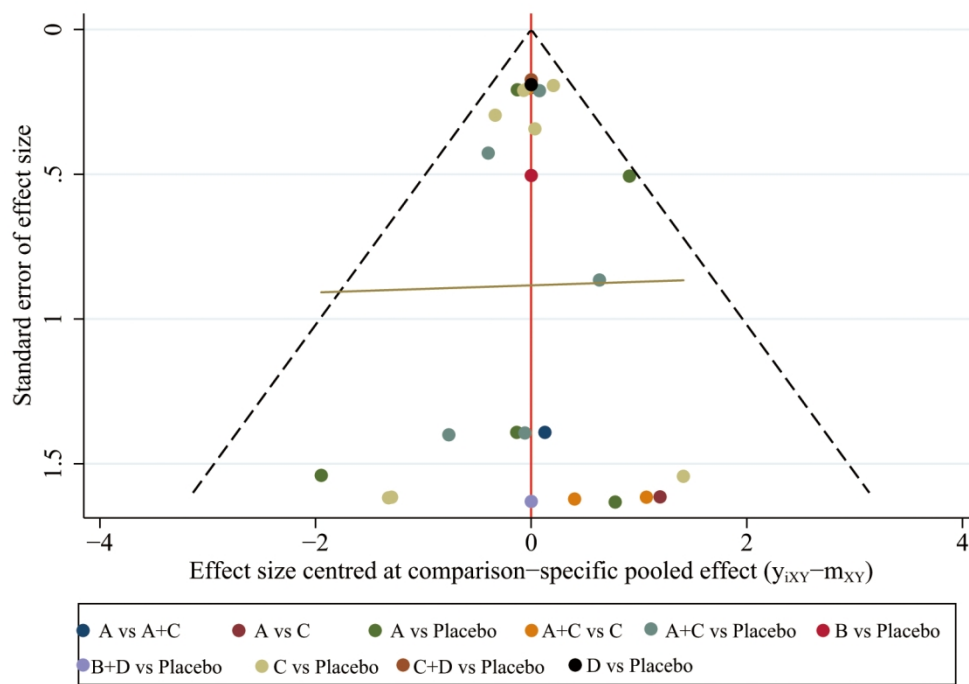


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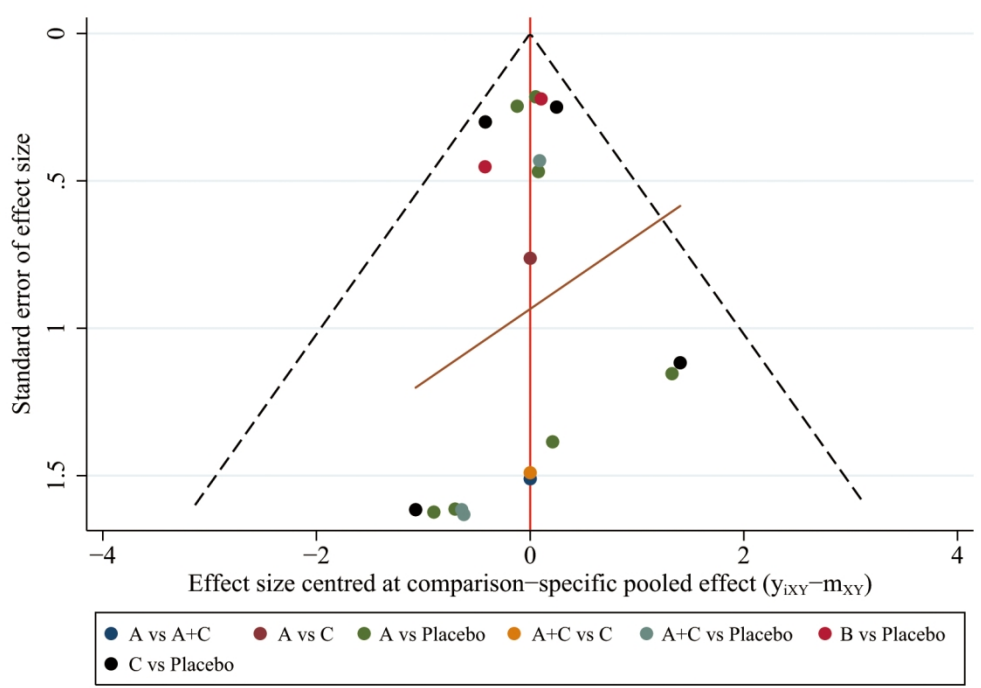
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Avenell et al, 2004	+	+	?	+	-	?	?
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	+	?	?	?	+	?	?

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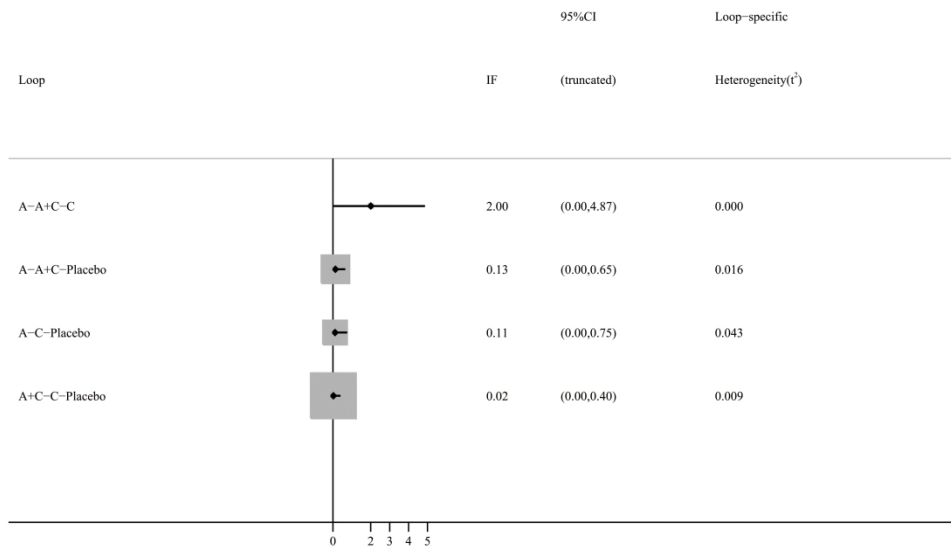




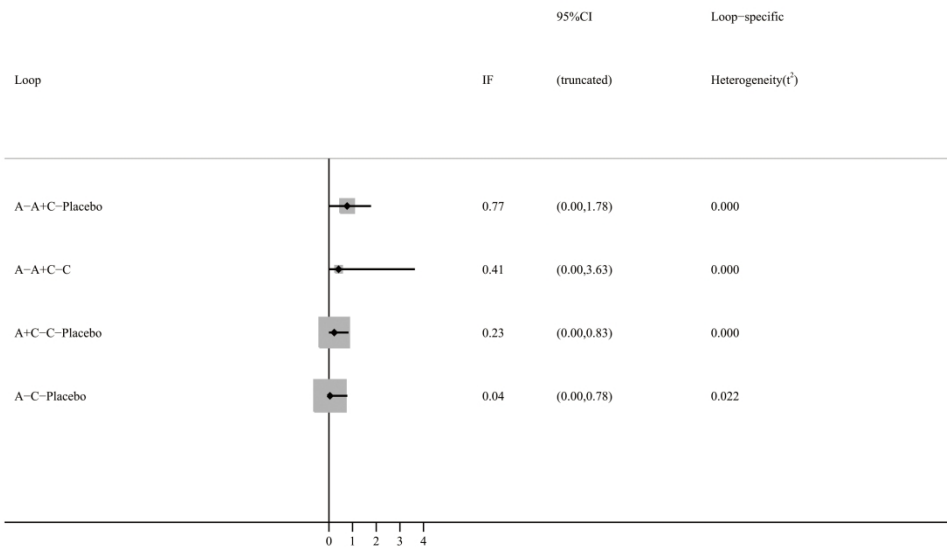
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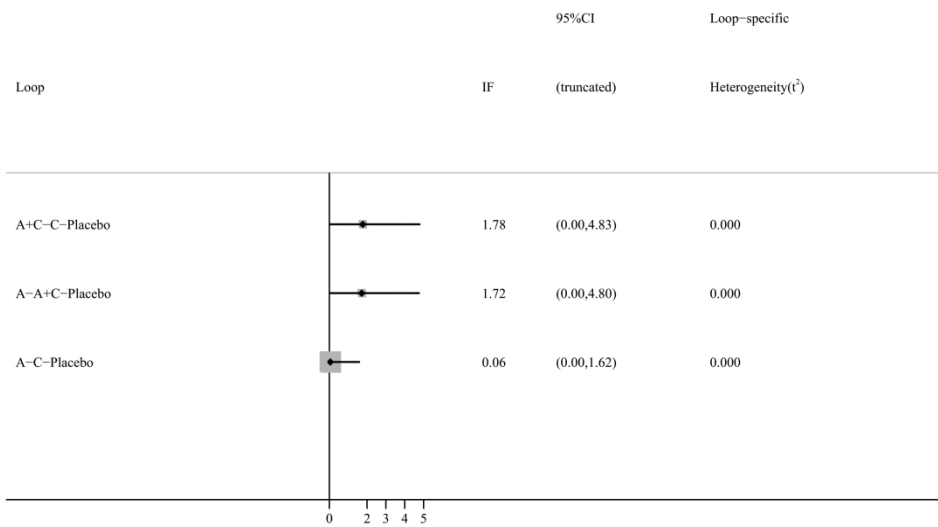
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*** Loop(s) [A-A+C-C] are formed only by multi-arm trial(s) – Consistent by definition

