Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis

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CRD summary
The authors' conclusion that the evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, for osteoporotic fractures and bone mineral density in adults over 50 appears to follow from the results presented. The authors' conclusions are likely to be reliable.

Authors' objectives
To determine the efficacy of calcium supplementation, with or without vitamin D, for the prevention of osteoporotic fractures and bone loss in adults aged 50 years or older.

Searching
MEDLINE, EMBASE, Current Content, CINAHL, DARE, the Cochrane CENTRAL Register and the Cochrane Database of Systematic Reviews were searched from inception to January 2007. The National Research Register, Current Controlled Trials and Trials Central were also searched for unpublished trials. The search terms were reported. In addition, websites, including the International Osteoporosis Foundation, National Guideline Clearinghouse, American College of Physicians and Computer Retrieval of Information on Scientific Projects were searched. References from relevant articles were also checked. Only published trials were eligible for inclusion in the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Studies that compared calcium, or calcium and vitamin D, with placebo were eligible for inclusion. Studies that used dietary calcium as an intervention, calcium as part of a complex nutritional supplemental regimen, calcium in combination with another treatment, or supplementation with vitamin D alone were excluded from the review. Calcium and vitamin D were used in 13 included studies and calcium alone in the remaining studies.

Participants included in the review
Studies of older adults (50 years plus) with osteoporosis were eligible for inclusion. Studies of participants with secondary osteoporosis were excluded from the review. The majority of the participants in the trials were women (92%); 21 trials included only women. The mean age ranged from 52 to 85 years. The median baseline risk for fracture was 16%.

Outcomes assessed in the review
The primary outcome was fracture of any site, including hip, vertebra and wrist. The secondary outcome was bone mineral density (percentage of change from baseline).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The quality of the primary studies was evaluated using a four-item checklist; this assessed reporting of randomisation, allocation concealment, blinding of the outcome measurement and completeness of follow-up. The authors did not state how many reviewers performed the quality assessment.
Data extraction
Two reviewers independently extracted the data and any disagreements were resolved by consensus. Authors were contacted for missing data. Risk ratios (RRs) were calculated for the primary outcome and the mean percentage difference between groups for the secondary outcome, along with 95% confidence intervals (CIs) for each study. For the purposes of the analysis more than one fracture suffered by the same patient was considered as one event; the first fracture regarded as the primary outcome.

Methods of synthesis
How were the studies combined?
Pooled RRs and the difference in means, with corresponding 95% CIs, were calculated using a random-effects model. On the basis of the pooled RR and baseline risk, the number-needed-to-treat was also calculated. Publication bias was assessed using a linear regression test.

How were differences between studies investigated?
The I-squared statistic was used to quantify variability across studies due to heterogeneity. Meta-regression was used to examine possible reasons for heterogeneity. Sensitivity analyses were conducted by repeating the meta-analysis, excluding each study in turn. Subgroup analyses, including dosage thresholds, were also performed.

Results of the review
Twenty-nine RCTs (n=63,897) were included in the review.

Fracture outcomes (17 RCTs, n=52,625).

Treatment was associated with a 12% risk reduction in any type of fracture (RR 0.88, 95% CI: 0.83, 0.95); there was no evidence of significant heterogeneity.

The fracture risk reduction was significantly greater (24%) in trials where compliance was high, in trials of calcium dosages of at least 1,200 mg compared with dosages of less than 1,200 mg (0.80 versus 0.94, p=0.006), and with vitamin D doses of at least 800 IU compared with dosages of less than 800 IU (0.84 versus 0.87, p=0.03). Those with low vitamin D serum concentration had a greater risk reduction than those whose vitamin D serum concentration was normal, although this was not statistically significant. The treatment effect was greater in people who were institutionalised than in those living in the community (RR 0.76 versus 0.94, p=0.003) and in participants whose daily calcium intake was low (<700 mg/day) (RR 0.80 versus 0.95, p=0.008). The risk reduction was significantly lower in participants aged 50 to 70 years than in those aged 70 to 79 years or older than 80 years (0.97 versus 0.89 versus 0.76, p=0.003). The treatment effect was similar across fracture sites (hips or vertebral) and gender (RR 12 to 13%), and the addition of vitamin D to calcium and previous history did not change treatment effect.

Bone mineral density (24 RCTs, n=41,419).

Treatment was associated with a reduced rate of bone loss at the hip of 0.54% (95% CI: 0.35, 0.73) and at the spine 1.19% (95% CI: 0.76, 1.61); evidence of heterogeneity was found (I-squared 73% and I-squared 49%, respectively).

Results from Egger's regression indicated that publication bias was likely.

Authors' conclusions
Calcium supplementation, alone or in combination with vitamin D, is effective in the preventive treatment of osteoporotic fracture in adults aged 50 years or older.

CRD commentary
The review addressed a clear question and undertook a comprehensive search for published trials. The authors did not restrict the inclusion criteria by language, but only published studies were eligible for inclusion and so publication bias is likely. Steps were taken to minimise reviewer bias and error in the data extraction, but the authors did not state
whether similar procedures were undertaken at the study selection stage. Quality was assessed and appears to have been considered in the sensitivity analyses. Standard statistical methods were used to pool the data and potential sources of heterogeneity were explored. The authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**

Practice: The authors indicated that many formulations of calcium or combined calcium with vitamin D tablets do not contain sufficient quantities of the active ingredient.

Research: The authors suggested that the cost-effectiveness of selecting specific age groups (e.g. 70 years plus) needs to be addressed.

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**Other publications of related interest**

These additional published commentaries may also be of interest.


Forbes DA. Review: calcium supplementation, with or without vitamin D, prevents osteoporotic fractures in people >= 50 years of age. Evid Based Nurs 2008;11:59.


**Indexing Status**

Subject indexing assigned by NLM

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.