
Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials

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CRD summary

The authors concluded that calcium intake was associated with a reduced hip fracture risk in neither men nor women. This was a generally well-conducted review, but in light of the uncertain quality of included studies the reliability of the conclusions was unclear.

Authors' objectives

To assess the relationship between calcium intake and the risk of hip fracture.

Searching

MEDLINE (January 1960 to December 2006) and EMBASE (January 1991 to December 2006) were searched for articles in any language. Search terms were reported. The reference lists and abstracts of the meetings of the American Society for Bone and Mineral Research were searched from 1995 to 2006. Experts were contacted.

Study selection

Separate reviews were conducted for prospective cohort studies and randomised controlled trials (RCTs). Prospective cohort studies of calcium intake in middle-aged or older (undefined) men or women with first incident hip fracture were eligible for inclusion. Only studies where calcium intake was measured prior to the fracture event were included. Studies that did not provide separate data for men and women or hip fractures were excluded. Included studies were of dietary calcium intake only or dietary calcium intake in combination with calcium supplementation. Calcium intake ranged from 558 mg to 787 mg assessed either by 24-hour recall or food-frequency questionnaires. Both mixed sex and single sex studies were included. Where stated, the median age of participants in the cohort studies ranged from 41 to 72 years at baseline. The mean age of participants in the RCTs ranged from 58 to 77 years at baseline. Follow up ranged from 6.6 years to 18 years.

Double-blind RCTs comparing calcium supplementation to placebo with a minimum follow-up of one year and with at least 100 participants were eligible for inclusion. Studies combining calcium supplements with other agents were excluded. Outcomes eligible for inclusion were all non-vertebral fractures. Inclusion criteria for participants were not stated. Included studies were either mixed sex or of post-menopausal women only receiving calcium carbonate, calcium gluconate, calcium citrate or osseino-mineral complex in varying doses for a period ranging from 1.5 years to five years. In one study, participants were also administered a 300,000 IU dose of vitamin D at entry to the study. Outcomes reported in included studies were non-vertebral fractures; separate data on hip fractures was reported in some studies. Follow up ranged from 1.5 years to 10.8 years.

The authors stated neither how the studies were selected for the review nor how many reviewers performed the study selection.

Assessment of study quality

The authors did not state that they assessed validity

Data extraction

For each study, the number of hip fractures and total daily calcium intake were extracted and used to calculate the relative risk of hip fracture per 300 mg increment in total daily calcium intake. Data were independently extracted by two reviewers.

Methods of synthesis

For the cohort studies, a pooled relative risk of hip fracture for a 300 mg increment of daily calcium intake was calculated separately for men and women using a random-effects model. Subgroup analyses were carried out of calcium

intake from diet alone, calcium intake measured using 24-hour recall, calcium intake measured using food-frequency questionnaires and latitude of study location. For RCTs, a pooled relative risk was calculated on an intention-to-treat basis using a random-effects model. Sensitivity analyses conducted included two RCTs with sample size less than 100 and including only adherent participants. For RCTs analyses were conducted on both sexes combined and separately for each sex on an intention-to-treat basis. Heterogeneity was assessed using the Q statistic. Begg and Egger tests and Begg's funnel plots were used to assess publication bias.

Results of the review

Fifteen studies were included for review (n=246,516): eight prospective cohort studies (n=239,597) and seven RCTs (n=6,919).

RCTs: There was no statistically significant advantage of calcium supplementation over placebo in reducing the risk of non-vertebral fracture (five studies n=6,740; pooled relative risk was 0.92, 95% CI: 0.81 to 1.05). Sensitivity analyses including two small trials and including only adherent participants continued to show no statistically significant association between calcium supplementation and risk of non-vertebral fractures. Five trials provided additional data on hip fractures and four were pooled in the primary analysis. The primary analysis found that calcium supplementation increased the risk of hip fracture by 64% (four RCTs, n=6,504; pooled relative risk was 1.64, 95% CI: 1.02 to 2.64). Sensitivity analysis including two small trials, including only adherent subjects and analysing on intention-to treat principles separately for men and women yielded similar pooled relative risks for the risk of hip fracture with calcium supplementation, however, the 95% CI went below 1.0 for all of these analyses. There was no evidence of significant statistical heterogeneity.

Prospective Cohort Studies: Four studies included total calcium intake from dietary sources and supplementation. Four studies assessed total calcium intake from diet alone. There was no statistically significant association between total calcium intake and risk of hip fracture for either men (pooled relative risk was 0.92 per additional 300 mg Ca/day intake, 95% CI: 0.82 to 1.03) or women (pooled relative risk was 1.01 per additional 300 mg Ca/day intake, 95% CI: 0.97 to 1.05). Subgroup analyses also found no statistically significant association between total calcium intake and risk of hip fracture when dietary calcium only was assessed, when calcium intake was measured using 24-hour recall and when calcium intake was measured using food-frequency questionnaires. Women living in more southerly latitudes did not show any significantly stronger protective factor of calcium intake in relation to fractures. There was no evidence of significant heterogeneity.

There was no evidence of publication bias.

Authors' conclusions

Pooled results from prospective cohort studies suggested that calcium intake was associated with hip fracture risk in neither men nor women. Pooled results from RCTs indicated no reduced risk of hip fracture with calcium supplementation and an increased risk was possible. There was no association between calcium intake and risk of non-vertebral fractures.

CRD commentary

The review addressed a clear question and inclusion criteria were defined for intervention, outcomes and study design. Inclusion criteria for participants were unclear for the review of prospective cohort studies and not stated for the review of RCTs. Two relevant databases were searched and appropriate steps were taken to minimise language bias. Some attempts were made to locate unpublished data. Publication bias was assessed and no evidence of bias was found for either the RCTs or prospective cohort studies. Data extraction was carried out independently and in duplicate, however, it was unclear whether similar steps were taken in the study selection process. Therefore, the possibility of reviewer error and bias could not be ruled out. A formal validity assessment did not appear to have been carried out, so it was not possible to determine the quality of the included studies. The decision to combine the studies in a meta-analysis was appropriate. The authors assessed statistical heterogeneity and conducted appropriate sensitivity analyses. However, the majority of included participants were women, which may limit the ability to generalise these findings to men. This was a generally well-conducted review, but in light of the uncertain quality of included studies the reliability of the conclusions is unclear.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research was needed that examined the effects of calcium in combination with vitamin D and using calcium phosphate supplements to correct phosphate deficiency in women. Further studies were needed in men.

Funding

Medical Foundation (Charles H Farnsworth Trust; US Trust Company; Trustee and the Charles A King Trust; Fleet National Bank).

International Foundation for the Promotion of Nutrition Research and Nutrition Education (ISFE).

Swiss Foundation for Nutrition Research (SFEFS).

Swiss National Foundation (SNF Professorship grant).

Bibliographic details

Bischoff-Ferrari H A, Dawson-Hughes B, Baron J A, Burckhardt P, Li R, Spiegelman D, Specker B, Orav J E, Wong J B, Staehelin H B, O'Reilly E, Kiel D P, Willett W C. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *American Journal of Clinical Nutrition* 2007; 86(6): 1780-1790

PubMedID

18065599

Original Paper URL

<http://www.ajcn.org/cgi/content/full/86/6/1780>

Other publications of related interest

Shea B, Wells G, Cranney A, et al. Meta-analyses of therapies for post-menopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of post-menopausal osteoporosis *Endocr Rev* 2002;23(4):552-9.

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Indexing Status

Subject indexing assigned by NLM

MeSH

Adult; Aged; Calcium, Dietary /administration & dosage; Cohort Studies; Female; Hip Fractures /prevention & control; Humans; Male; Middle Aged; Odds Ratio; Prospective Studies; Randomized Controlled Trials as Topic; Vitamin D /administration & dosage

AccessionNumber

12008000153

Date bibliographic record published

03/11/2008

Date abstract record published

12/08/2009

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.