

Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials¹⁻³

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ABSTRACT

Background: The role of total calcium intake in the prevention of hip fracture risk has not been well established.

Objective: The objective of the study was to assess the relation of calcium intake to the risk of hip fracture on the basis of meta-analyses of cohort studies and clinical trials.

Results: In women (7 prospective cohort studies, 170 991 women, 2954 hip fractures), there was no association between total calcium intake and hip fracture risk [pooled risk ratio (RR) per 300 mg total Ca/d = 1.01; 95% CI: 0.97, 1.05]. In men (5 prospective cohort studies, 68 606 men, 214 hip fractures), the pooled RR per 300 mg total Ca/d was 0.92 (95% CI: 0.82, 1.03). On the basis of 5 clinical trials ($n = 5666$ women, primarily postmenopausal, plus 1074 men) with 814 nonvertebral fractures, the pooled RR for nonvertebral fractures between calcium supplementation (800–1600 mg/d) and placebo was 0.92 (95% CI: 0.81, 1.05). On the basis of 4 clinical trials with separate results for hip fracture (6504 subjects with 139 hip fractures), the pooled RR between calcium and placebo was 1.64 (95% CI: 1.02, 2.64). Sensitivity analyses including 2 additional small trials with <100 participants or per-protocol results did not substantially alter results.

Conclusions: Pooled results from prospective cohort studies suggest that calcium intake is not significantly associated with hip fracture risk in women or men. Pooled results from randomized controlled trials show no reduction in hip fracture risk with calcium supplementation, and an increased risk is possible. For any nonvertebral fractures, there was a neutral effect in the randomized trials. *Am J Clin Nutr* 2007;86:1780–90.

KEY WORDS Meta-analysis, hip fracture, nonvertebral fracture, calcium intake, calcium supplementation, cohort studies, randomized controlled trials

KEY WORDS

INTRODUCTION

Calcium supplementation or the consumption of calcium-rich foods such as milk is commonly recommended for the prevention of osteoporosis and fractures. These recommendations are primarily based on evidence from randomized controlled trials (RCTs) with bone density as the outcome. However, in a 2004 meta-analysis of RCTs, supplementation with 500–2000 mg Ca/d in postmenopausal women provided only a modest benefit

for bone density: 2.05% difference in total-body bone density, 1.66% difference in lumbar spine bone density, and 1.64% difference in hip bone density (1, 2). The implications of such differences with respect to fracture risk prevention are unclear. In the same meta-analysis, limited evidence from RCTs (222 subjects in 2 trials) suggested only a modest and nonsignificant benefit of calcium supplementation for the risk of nonvertebral fractures [pooled risk ratio (RR) = 0.86; 95% CI: 0.43, 1.72]. Furthermore, an earlier meta-analysis published in 1997 that summarized observational studies in postmenopausal women found no clear benefit of a 300-mg increment in daily calcium intake for hip fracture risk [pooled RR among 28 511 women from 5 cohorts was 0.96 (95% CI: 0.91, 1.02)] (3). Consequently, considerable uncertainty exists regarding optimal intakes of calcium, and this uncertainty is reflected in markedly different recommended daily intakes among countries. For example, for adults >50 y old, the recommended daily intake is 700 mg Ca/d in the United Kingdom and 1200 mg Ca/d in the United States (4).

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Several RCTs tested the combined effect of calcium plus vitamin D, and this evidence was summarized in 2 recent meta-analyses that suggested, irrespective of trial quality, a small but significant reduction in hip fracture risk [pooled RR = 0.81; 95% CI: 0.68, 0.96 (5); pooled RR = 0.82; 95% CI: 0.71, 0.94 (6)]. However, the benefit of calcium supplementation alone was not addressed in these analyses. Because increased calcium intake alone is still commonly recommended as a fracture-prevention strategy (6, 7), the assessment of calcium intake and its effect on hip fracture risk reduction is of clinical importance.

Thus, we conducted a systematic review and meta-analysis of prospective cohort studies to address these relations with respect to hip fracture prevention. Hip fractures are the most severe and the most frequent fractures in older persons (8, 9). We focused on prospective cohort studies because they are less susceptible to selection and recall biases than are case-control studies. Because several RCTs of calcium supplementation without vitamin D have been conducted since the mid-1990s, and all have had samples sizes that were somewhat small for the assessment of hip fractures (10–14), we also summarized findings regarding the effect of calcium supplementation on all nonvertebral fractures from randomized trials.

METHODS

Search strategy and data extraction

For both prospective cohort studies and RCTs, we conducted a systematic search for relevant English and non-English publications by using MEDLINE (Ovid and PubMed) for the period from January 1960 to December 2006 and by using EMBASE for January 1991 to December 2006. We also contacted experts in the field and searched reference lists and abstracts presented at the meetings of the American Society for Bone and Mineral Research from 1995 through 2006.

For prospective cohort studies, we used numerous medical subject headings (MeSH terms)—“cohort studies” or “prospective studies,” or “retrospective studies,” and “fracture,” or “hip fracture,” and “calcium,” or “calcium analogs or derivatives,” or “calcium carbonate,” or “calcium citrate,” or “calcium gluconate,” or “calcium phosphate,” or “milk,” or “dairy products.” To update the most recent meta-analysis of RCTs on calcium and fracture risk, we also searched for RCTs and fracture risk by using the MeSH terms above plus “randomized-controlled trial” or “controlled-clinical trial” or “random allocation” or “double-blind method” or “uncontrolled trial.” In addition, we searched for fracture data in trials that had bone density as the primary outcome. We received unpublished data from one large published trial for calcium supplementation, the Randomised Evaluation of Calcium Or vitamin D (RECORD) trial (12)].

Eligibility and exclusion criteria were specified in advance. Data extraction was conducted independently by 2 investigators (HAB-F and EO).

Eligible studies

For prospective cohort studies, we included only studies in which calcium intake had been assessed before the fracture events. Our primary outcome was the first incident hip fracture in middle-aged or older men and women. For trials that addressed fracture incidence, we included only double-blind RCTs that studied any dose of calcium supplementation compared with

placebo. Because of limited data on hip fractures, in separate analyses, we also included all nonvertebral fractures. We included only double-blind RCTs that studied calcium supplementation with a minimum follow-up of 1 y and that required >100 study participants. Trials with <100 participants were added in a sensitivity analysis.

Ineligible studies

We excluded uncontrolled trials, cross-sectional and case-control studies, and animal investigations. Of prospective cohort studies, we excluded studies that did not provide separate data for men and women (15) or for hip fracture (16). Of RCTs, we excluded studies in which calcium was combined with other agents, such as vitamin D (17–19), because the effects of the two agents could not be separated. The combination of calcium plus vitamin D has been addressed in 2 recent meta-analyses of RCTs (5, 6).

Studies identified

Prospective cohort studies

A total of 8 separate studies were identified—7 that included women (3, 20–25) and 5 that included men (20–23, 26) (Table 1 and Figure 1A). Total calcium intake included dietary and supplement sources in 4 studies (3, 21, 25, 26) and only dietary calcium intake in 4 studies (20, 22–24). This omission may not have been important in the older studies (20, 23), because calcium intake from supplements became widespread only in the late 1980s (21).

Randomized controlled trials

We identified 5 RCTs that met our criteria for the primary analysis (10, 12–14, 27) and 2 additional smaller trials that were included in the sensitivity analysis (11, 28). RCTs primarily included postmenopausal women (Table 2). Five of these 7 RCTs provided separate data on hip fractures (10–14). Our analyses followed the intention-to-treat principle. Only 3 trials provided a per-protocol analysis (10, 12, 13). Despite limited data for men, results by sex were pooled for the primary intention-to-treat analysis examining both hip and any nonvertebral fractures.

Statistical methods

Sex-specific cohort study analyses were conducted because men and women differ in fracture risk (29) and calcium intake (30). The primary outcome of the pooled analysis was the RR of hip fracture for a 300-mg increment in daily calcium intake, the amount of calcium in an 8-ounce (237-mL) glass of milk or one slice (50 g) of hard cheese.

For the highest and the lowest open-ended calcium intake categories, we chose a previously defined value for a corresponding median—30% lower than the lowest cutoff and 30% higher than the upper cutoff. RRs adjusted for multiple covariates were used whenever available. The study of Holbrook et al (20) provided, for each sex, the RR, the overall sample size, and the overall number of hip fractures. From these numbers, we calculated the number of hip fracture cases in each exposure group and re-ran the analyses of the 2 × 2 tables to retrieve the corresponding 95% CIs for the RRs.

To compare studies on the same scale in the pooled analysis, we calculated the RR for a 300-mg increment in total daily



TABLE 1
Prospective cohort studies that assessed total calcium intake or milk intake and hip fracture risk¹

Reference	Mean duration of follow-up ²	Population	Sex	Age ³	Calcium intake (Fx/no Fx) ²	Total cases	Calcium assessment (calcium supplement included)	Covariates adjusted for
	y			y	mg	n		
Holbrook et al, 1988 (20) ³	14	White community, California		50–79 ⁴			24-h recall (no)	None
Men			426		634/787	15		
Women			531		583/620	18		
Paganini-Hill et al, 1991 (21) ³	6.8	California retirement community		73 ⁵			FFQ (yes)	Age
Men			2966			50		
Women			5752			216		
Looker et al, 1993 (22) ³	16	NHANES I follow-up study		50–74			24-h recall (no)	Alcohol, smoking, physical activity, BMI, HRT use
Men			2116		719/763	44		
Women			2226		558/558	122		
Owusu et al, 1997 (26) ^{3,6}	8	Health Professionals Follow-up Study		54 (40–75) ⁷			FFQ (yes)	Age, BMI, smoking, physical activity, total energy, alcohol, vitamin D intake
Men			43 063			56		
Cumming et al, 1997 (3) ^{3,6}	6.6	Study of Osteoporotic Fractures		71			FFQ (yes)	Age, clinic, weight, history of fracture since age 50 y, fall in past 12 mo, protein intake, caffeine intake, recreational physical activity, walking for exercise, use of vitamin D supplements and Tums antacids
Women			9704			306		
Meyer et al, 1997 (23) ⁶	13.8	National Health Screening Norway		47.1 (40–53)			FFQ (no)	Age, height, BMI, physical activity, DM, disability pension, marital status, smoking
Men			20 035			49		
Women			19 752			154		
Michaelsson et al, 2003 (24) ³	13	Swedish Mammography Screening Study		53.6 (40–74)			FFQ (no)	Age, BMI, energy intake, protein intake, retinol intake, meat consumption, marital status, nulliparity, education level
Women			60 689		560 ⁸	1535		
Feskanich et al, 2003 (25) ^{3,6}	18	Nurses' Health Study		34–59			FFQ (yes)	Protein intake, retinol intake, total vitamin D intake, age, BMI, postmenopausal hormone use, physical activity, smoking, calcium supplement use, multivitamin use, vitamin K, vitamin A intake, total energy intake, alcohol use, caffeine intake
Women			72 337			603		

¹ Fx, fracture; NHANES, National Health and Nutrition Examination Survey; HRT, hormone replacement therapy; FFQ, food-frequency questionnaire; DM, diabetes mellitus.

² If total mean calcium was given per 1000 kcal, the value was multiplied by 2 in women and by 2.5 in men.

³ Subjects with prior hip fracture were excluded.

⁴ Range (all such values).

⁵ Median.

⁶ Subjects with high-trauma fractures were excluded.

⁷ \bar{x} ; range in parentheses (all such values).

⁸ Mean across quintiles.

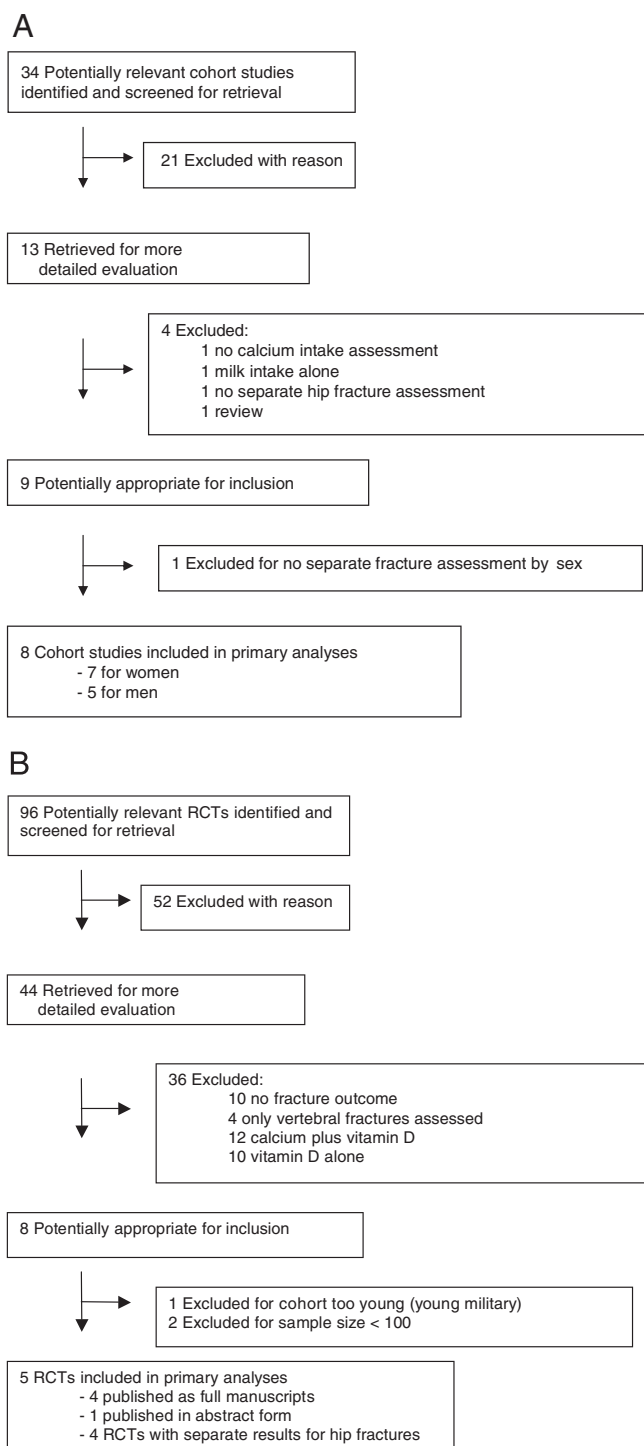


FIGURE 1. A: A Quality of Reporting of Meta-analyses (QUOROM) flow diagram for the prospective cohort studies. B: A QUOROM flow diagram for the randomized controlled trials (RCTs).

calcium intake, which assumes a log-linear association of intake with risk. Because the relative risks within each cohort study depend on a common reference group, they are correlated. Thus, we used a method developed by Greenland et al (31), which yields an efficient point estimator and a consistent variance estimate under these circumstances, to calculate for each study the RR of hip fracture per 300-mg increase in total daily calcium

intake. Results from all studies were then pooled by using random-effects models (32).

RCT outcomes were pooled on an intention-to-treat basis with random-effects models, which control for both within-trial and between trial variance. Heterogeneity among RCTs and among cohort studies was evaluated by using the Q statistic, which is considered significant for $P < 0.10$ (33, 34). To address the effect of poor adherence in some larger trials, a sensitivity analysis was performed on the basis of the per-protocol results of those trials.

To assess potential publication bias, we used the Begg and Egger tests and Begg's funnel plot (35, 36); no evidence of bias was seen in the prospective cohort studies or the RCTs. Statistical analysis was performed by using STATA software (version 7.0; Stata Corp, College Station, TX).

RESULTS

Prospective cohort studies

Characteristics of the 8 prospective cohort studies that met our inclusion criteria are shown in Table 1. Of these 8 studies, 7 included 170 991 women who sustained 2954 hip fractures, and 5 included 68 606 men who sustained 214 hip fractures. The median age at baseline ranged from 41 to 72 y. Mean follow-up varied between 3 and 18 y. Six studies were from the United States (3, 20–22, 25, 26), one was from Norway (23), and one was from Sweden (24).

Primary analysis

The Forest plots for the RR of hip fracture for a 300-mg increase in daily calcium intake are shown in **Figure 2**. In women, there was no association between total calcium intake and hip fracture risk (pooled RR for additional 300 mg Ca/d intake = 1.01; 95% CI: 0.97, 1.05). In men, the pooled RR was 0.92 (95% CI: 0.82, 1.03).

Subgroup analyses for hip fracture risk and total calcium intake

In the 4 studies of women that reported calcium intake from dietary sources alone, ie, ignoring supplemental calcium (20, 22–24), we found no association between dietary calcium intake and risk of hip fracture (pooled RR per additional 300 mg Ca/d intake from dietary calcium = 1.01; 95% CI: 0.96, 1.06). In the 2 studies that measured dietary calcium intakes by using 24-h recall (20, 22), the association between calcium intake and hip fracture risk (pooled RR per additional 300 mg Ca/d intake = 0.90; 95% CI: 0.76, 1.07) was somewhat stronger than that in the 5 studies that used food-frequency questionnaires (pooled RR per additional 300 mg dietary Ca/d calcium = 1.01; 95% CI: 0.98, 1.05).

Because the efficacy of calcium may be enhanced by additional vitamin D, as found in RCTs involving both institutionalized (17) and ambulatory (19) women, we sorted studies by latitude (south to north), taking the mean of the state capitals of the multistate US studies (Figure 2A). This analysis showed no stronger protective effect of calcium intake on hip fracture risk in women living in southern latitudes, who possibly had higher vitamin D status due to increased sunshine exposure, than in women living in northern latitudes. The limited data for men did not allow useful subgroup analyses.

TABLE 2
Randomized controlled trials of calcium supplementation and fracture (fx) risk¹

Author	Total subjects, fx ascertainment	Age, y	Intervention	Duration, y	Baseline calcium intake, mg/d	Fx outcome and hip fx	Baseline 25(OH)D, nmol/L	Loss to follow-up and compliance
Chevalley et al, 1994 (28) ²	n 93 (82 ambulatory women, 11 ambulatory men) Fx ascertainment for nonvertebral fx is not described in the manuscript	72.1 ± 0.61 ³	800 mg Ca from calcium carbonate or osseino-mineral complex versus placebo (300 000 IU vitamin D ₃ orally in a single dose at study entry)	1.5	619 ± 33	Vertebral fx in subjects with no hip fx No new hip fx (according to information from the TC)	62.5 ± 15	14%
Reid et al, 1995 (11) ²	86 postmenopausal women (86 of 122 women agreed to the 2-y extension of the original 2-y study) Fx ascertainment for nonvertebral fx is not described in the manuscript	58 ± 4	Calcium gluconate: 1000 mg/d or placebo	4	745 ± 298	Symptomatic nonvertebral fx	92.5 ± 5	10.3%
Riggs et al, 1998 (27)	236 postmenopausal women Fx ascertainment for nonvertebral fx is not described	66.3 ± 2.6	1600 mg Calcium citrate/d	4	714 ± 286	Nonvertebral fx No information on hip fx	76 ± 25.8	25%
Prince et al, 2006 (13)	1460 postmenopausal women Fxs were reported in a diary and confirmed by radiographic reports	75.1 ± 2.7	1200 mg Calcium carbonate/d	5	897 (704–1146) ⁴	Nonvertebral fx	67.5 ± 35 (winter) 87.5 ± 30 (summer)	Hazard ratio of withdrawal or death: 0.86 (calcium group) and 0.76 (placebo group) Average compliance: 57%
Reid et al, 2006 (10)	1471 postmenopausal women Fxs were assessed at every 6-mo visit and confirmed by a radiograph or a report	74 ± 4	1000 mg Calcium citrate/d	5	861 ± 390 (calcium group) 853 ± 381 (placebo group)	Nonvertebral fx	51.5 ± 19 (calcium group) 52 ± 19.5 (placebo group)	Average compliance: 55–58%
Grant et al, 2006 (12) ⁵	2643 (2241 women and 402 men)	77 ± 6	1000 mg Calcium carbonate/d	2–5	829 ± 353	Nonvertebral fx	38 ± 16.5 (subgroup of 60 subjects)	At 24 mo, 30% were not returning questionnaires (lost to follow-up) Compliance: 42% at 24 mo (among those in the calcium group returning the questionnaire) 10.5% during 4 y of treatment Average compliance: 75–77%
Bischoff-Ferrari et al, 2006 (14) (abstract)	930 (258 women and 672 men) Fxs were assessed by yearly questionnaires throughout the trial phase and follow-up. Fxs were confirmed by a radiology report or a physician report of a fracture	61 ± 9	1200 mg Calcium carbonate/d	4 y of treatment (mean follow-up of 10.8 y)	865 ± 423 (placebo group) 889 ± 451 (calcium group)	Nonvertebral fx	73.0 in the calcium group, 72.8 in the placebo group	

¹ 25(OH)D, 25-hydroxyvitamin D.

² Small trials including <100 subjects.

³ $\bar{x} \pm SD$ (all such values).

⁴ \bar{x} ; interquartile range in parentheses.

⁵ This report was from the Randomized Evaluation of Calcium or Vitamin D (RECORD) trial.

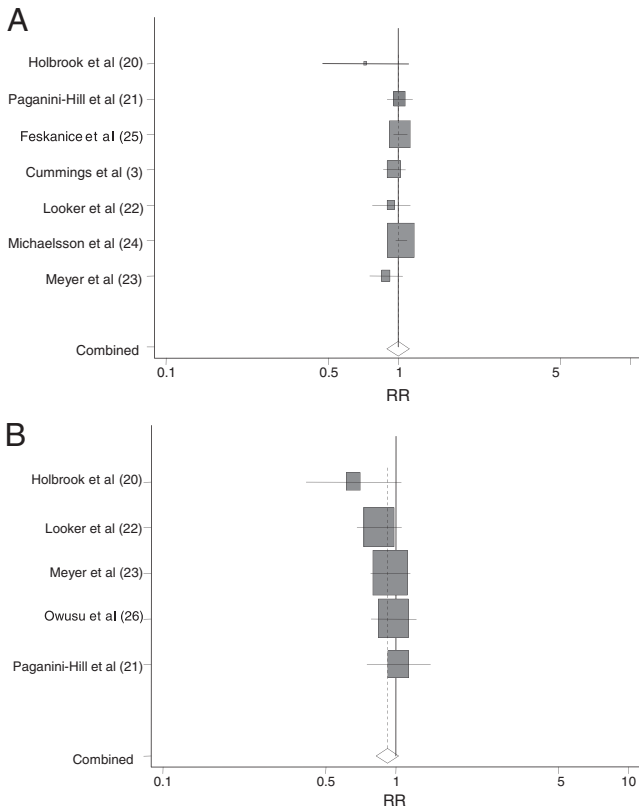


FIGURE 2. Relative risk (RR) of hip fracture for a 300-mg increase in total calcium intake per day from the prospective cohort studies. The size of the squares is proportional to the inverse of the variance. Error bars represent the 95% CIs. The confidence limits for the pooled RR are indicated by the diamond-shaped figure. There was no significant heterogeneity among studies in men or women ($P = 0.34$ and 0.55 for women and men, respectively; Q test). A: In the women, the pooled RR per 300 mg total Ca/d was 1.01 (95% CI: 0.97, 1.05). B: In the men, the pooled RR per 300 mg total Ca/d was 0.92 (95% CI: 0.82, 1.03).

To examine the relation between calcium intake and hip fracture risk in more detail, we pooled RRs for categories of total calcium intake and hip fracture risk among women from each cohort study (Figure 3), using the lowest category as a reference and corresponding RRs for higher intake categories. Figure 3 confirms the findings suggested by the analysis in Figure 2A—ie,

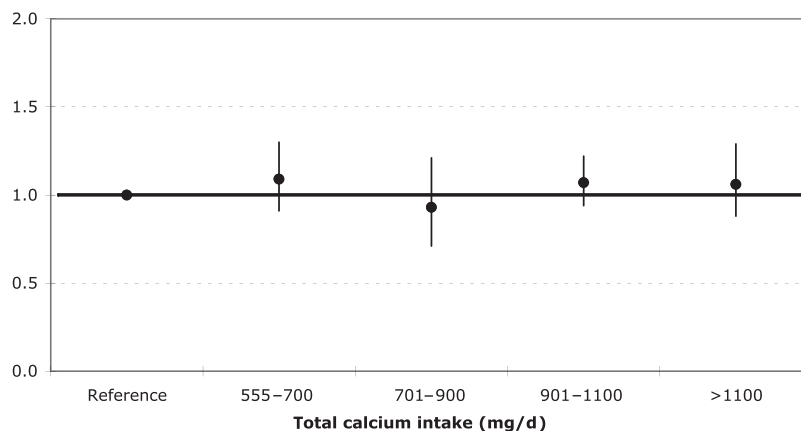


FIGURE 3. Pooled analysis for categories of calcium intake and hip fracture risk in the women from the prospective cohort studies. The reference intake categories in the various studies ranged from 280 to 554 mg total Ca/d.

there is no apparent association between calcium intake and hip fracture risk over a wide range of calcium intakes in women. The limited data for men did not allow useful categorical dose-response analyses.

Randomized controlled trials

Characteristics of the 5 RCTs that met our criteria for the primary analysis(10,12–14, 27) and 2 smaller trials that were included in the sensitivity analysis (11, 28) are shown in Table 2. The mean age ranged from 58 to 77 y. The mean duration of follow-up varied between 1.5 and 10.8 y. One study was from Switzerland (28), 1 study was from the United Kingdom (12), 2 studies were from New Zealand (10, 11), 2 were from the United States (14, 27), and 1 was from Australia (13).

The primary analysis for nonvertebral fracture risk included 5 RCTs (Table 3; Figure 4) in which calcium supplementation between 800 and 1600 mg/d was compared with placebo. Among 6740 subjects (5666 women, primarily postmenopausal, plus 1074 men) who had a total of 814 nonvertebral fractures, the pooled RR was 0.92 (95% CI: 0.81, 1.05). This result did not change substantially in the sensitivity analyses: including the 2 additional small trials, the pooled RR was 0.91 (95% CI: 0.80, 1.03), and including only adherent subjects, the pooled RR was 0.83 (95% CI: 0.64, 1.09).

Intention-to-treat results comparing calcium with placebo in women alone (pooled RR = 0.92; 95% CI: 0.81, 1.06) were similar to the results including men. The pooled RR for men from 2 trials was 0.94 (95% CI: 0.64, 1.37) (12, 14).

The primary analysis for hip fracture risk included 4 RCTs (Table 4; Figure 5) in which calcium supplementation between 800 and 1200 mg/d was compared with placebo. Among 6504 subjects (5430 women, primarily postmenopausal, plus 1074 men) who had a total of 139 hip fractures, the pooled RR was 1.64 (95% CI: 1.02, 2.64). This result did not change significantly in sensitivity analyses: including the 2 additional small trials, the pooled RR was 1.57 (95% CI: 0.96, 2.55), and including only adherent subjects, the pooled RR was 1.42 (95% CI: 0.81, 2.49). Intention-to-treat results comparing calcium with placebo in women alone (pooled RR = 1.66; 95% CI: 0.97, 2.86) were similar to the results including men. The pooled RR for men from 2 trials was 1.55 (95% CI: 0.62, 3.96) (12, 14).



TABLE 3

Evidence table for randomized controlled trials comparing calcium supplementation with placebo for risk of all nonvertebral fractures (fxs)¹

	Outcome	Year	Treated subjects	Control subjects	RR (95% CI)	Total
			<i>n</i>	<i>n</i>		
Chevalley et al (28) ²	Nonvertebral fx	1994	2/54 ³	2/25 ³	0.46 (0.07, 3.02)	79
Reid et al (11) ²	Nonvertebral fx	1995	2/42	7/44	0.30 (0.07, 1.22)	86
Riggs et al (27)	Nonvertebral fx	1998	11/119	12/117	0.91 (0.41, 1.96)	236
Prince et al (13)	Nonvertebral fx	2006	83/730	94/730	0.88 (0.67, 1.16)	1460
Reid et al (10)	Nonvertebral fx	2006	92/732	94/739	0.99 (0.76, 1.29)	1471
Grant et al (12) ⁴	Nonvertebral fx	2006	156/1311	172/1332	0.92 (0.75, 1.13)	2643
Bischoff-Ferrari et al (14)	Nonvertebral fx	2006	46/464	54/466	0.87 (0.60, 1.27)	930
Pooled results						
Primary analysis (intention-to-treat) ⁵			388/3356	426/3384	0.92 (0.81, 1.05)	6740
Sensitivity analysis (intention-to-treat) ⁶			392/3452	435/3453	0.91 (0.80, 1.03)	6905
Per-protocol analysis ⁷			152/1314	202/1464	0.83 (0.64, 1.09)	2778

¹ RR, risk ratio. Intention-to-treat results for women alone based on the primary analysis comparing calcium with placebo (pooled RR = 0.92; 95% CI: 0.81, 1.06; $Q = 0.50$; $P = 0.97$, Q test) were similar to the results including men. The few data available for men alone from the trials of Grant et al (RR = 0.97) and Bischoff-Ferrari et al (RR = 0.92) (pooled RR = 0.94; 95% CI: 0.64, 1.37; $P = 0.90$, Q test) were similar to the pooled risk among women.

² Trial was excluded for the primary analysis. According to the intention-to-treat results, Table 3 shows the pooled results for the RR of having any nonvertebral fx with calcium supplementation compared to placebo.

³ *n* with fracture/total *n* of the group (all such values).

⁴ This report was from the Randomized Evaluation of Calcium or Vitamin D (RECORD) trial.

⁵ In the primary pooled analysis, there was an 8% (NS) lower risk with calcium than with placebo (95% CI: 0.81, 1.05; homogeneity: $Q = 3.3$; $P = 0.77$, Q test).

⁶ In the sensitivity analysis, including 2 additional small trials, nonvertebral fx risk was 9% lower with the 95% CI including 1 (95% CI: 0.80, 1.03; homogeneity: $Q = 0.48$; $P = 0.98$, Q test).

⁷ Per-protocol results were available for references 11–13, which included a total of 2778 subjects (all women). The pooled RR excluding subjects with <80% compliance in the trials of Prince et al and Grant et al and excluding subjects with at least one 6-mo episode with <60% compliance in the trial of Reid et al was 0.83 (95% CI: 0.64, 1.09; $Q = 3.64$; $P = 0.16$, Q test).

DISCUSSION

In our meta-analysis of prospective cohort studies, calcium intake was not significantly associated with hip fracture risk in men or women. Similarly, our meta-analysis of RCTs, which included data largely from postmenopausal women, yielded a neutral effect of

calcium supplementation as compared with placebo for any nonvertebral fracture and suggested a significantly (64%) greater risk of hip fractures with calcium supplementation.

There are several possible explanations for the lack of overall association between total calcium intake and hip fracture risk in

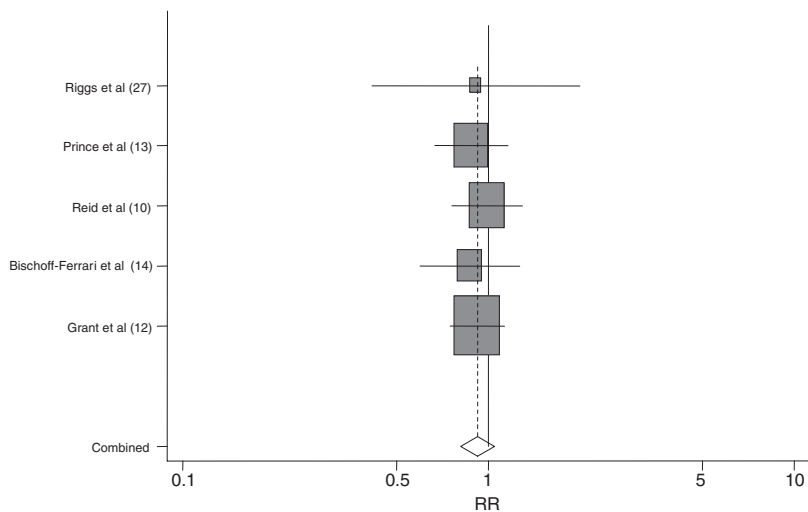


FIGURE 4. Forest plot comparing intention-to-treat data from 5 randomized controlled trials for the risk of nonvertebral fractures between calcium-treated and placebo groups. The squares represent the relative risk (RR) of fracture between subjects who took calcium in any dose and those who took placebo. In a total of 6740 subjects, the pooled RR was 0.92 (95% CI: 0.81, 1.05). There was no heterogeneity between studies ($P = 0.77$, Q test).

TABLE 4

Evidence table for randomized controlled trials comparing calcium supplementation with placebo for risk of hip fractures (fxs)¹

	Outcome	Year	Treated subjects	Control subjects	RR (95% CI)	Total
			<i>n</i>	<i>n</i>		<i>n</i>
Reid et al (11) ²	Hip fracture	1995	0/42 ³	2/44 ³	0.33 (0.03, 4.23)	86
Prince et al (13)	Hip fracture	2006	11/730	6/730	1.83 (0.69, 4.86)	1460
Reid et al (10)	Hip fracture	2006	17/732	5/739	3.43 (1.35, 8.70)	1471
Grant et al (12) ⁴	Hip fracture	2006	49/1311	41/1332	1.21 (0.81, 1.82)	2643
Bischoff-Ferrari et al (14)	Hip fracture	2006	6/464	4/466	1.51 (0.43, 5.26)	930
Pooled results						
Primary analysis (intention-to-treat) ⁵			83/3237	56/3267	1.64 (1.02, 2.64)	6504
Sensitivity analysis (intention-to-treat) ⁶			83/3279	58/3311	1.57 (0.96, 2.55)	6590
Per-protocol analysis ⁷			27/1314	22/1464	1.42 (0.81, 2.49)	2778

¹ RR, risk ratio. Intention-to-treat results for women alone based on the primary analysis comparing calcium with placebo (pooled RR = 1.66; 95% CI: 0.97, 2.86; $Q = 4.41$; $P = 0.22$, Q test) were similar to the results including men. The few data available for men alone from the trials of Grant et al (RR = 1.55) and Bischoff-Ferrari et al (RR = 1.58) (pooled RR = 1.56; 95% CI: 0.62, 3.96; $P = 0.98$, Q test) were similar to the pooled risk among women.

² Trial excluded for the primary analysis. Based on the intention-to-treat results, Table 4 shows the pooled results for the RR of having a hip fracture with calcium supplementation compared with placebo, including data from men and women.

³ *n* with fracture/total *n* of the group (all such values).

⁴ This report was from the Randomized Evaluation of Calcium or Vitamin D (RECORD) trial.

⁵ In the primary pooled analysis, there was a significant 1.64-fold risk with calcium than with placebo (95% CI: 1.02, 2.64; $P = 0.04$; homogeneity: $Q = 4.3$; $P = 0.24$, Q test).

⁶ In the sensitivity analysis, including one additional small trial, hip fracture risk was still 1.57-fold, although the 95% CI included 1 (95% CI: 0.96, 2.55; homogeneity: $Q = 5.64$; $P = 0.23$, Q test).

⁷ Per-protocol results were available for the trials of Prince et al, Reid et al, and Grant et al including a total of 2778 subjects (all women). The pooled RR excluding subjects with <80% compliance in the trials of Prince et al and Grant et al and excluding subjects with at least one 6-mo episode with <60% compliance in the trial of Reid et al was 1.42 (95% CI: 0.81, 2.49; $Q = 1.65$; $P = 0.44$, Q test).

prospective cohort studies. Calcium intake is imperfectly measured in observational studies, and this measurement error—if nondifferential—would lead to an underestimation of a true calcium effect. However, in several of the studies, the validity of the calcium intake estimates was assessed by comparison with more detailed methods (37, 38), and the correlations between food-frequency questionnaires and 1-wk diet records were high, ≈ 0.75 (37, 39). This modest degree of

measurement error would tend to cause a conservative bias, but, with the large number of cases in women than in men, an important association should not have been missed. Moreover, in some of the same studies that reported fracture data, dietary calcium intake has been inversely associated with the risk of kidney stones (38, 40, 41) and colon cancer (42), which showed that the calcium intake measures used were at least accurate enough to detect those relations.

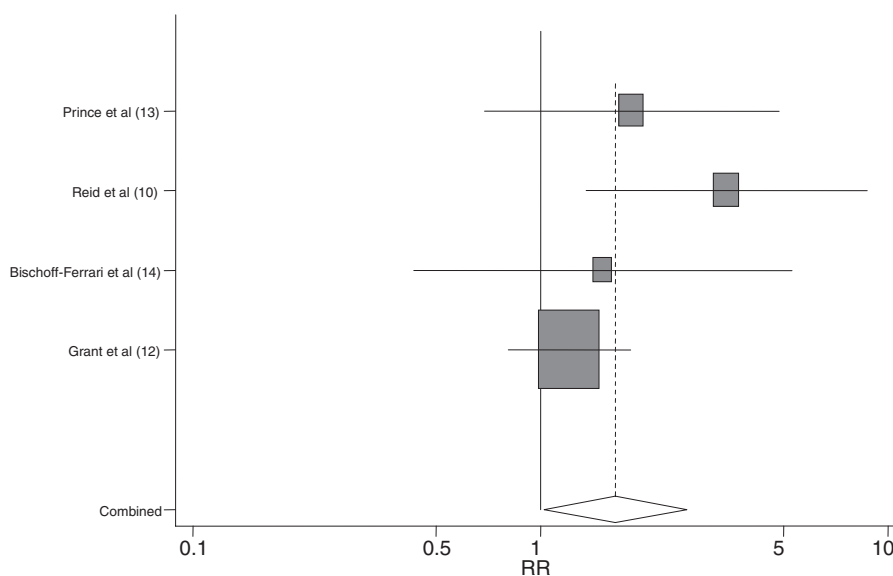


FIGURE 5. Forest plot comparing intention-to-treat data from 4 randomized controlled trials for the risk of hip fracture between calcium-treated and placebo groups. The squares represent the relative risk (RR) of fracture between subjects who took calcium in any dose and those who took placebo. In a total of 6504 subjects, the pooled RR was 1.64 (95% CI: 1.02, 2.64). There was no heterogeneity between studies ($P = 0.24$, Q test).

Another possible explanation for the lack of association is that patients with recognized osteoporosis are generally advised to increase calcium intake, which could mask an inverse association between calcium intake and fracture risk (29). However, in the Nurses' Health Study, the exclusion of women with a history of diagnosed osteoporosis did not appreciably affect its negative findings (25).

Alternatively, calcium alone may not prevent hip fractures in women. In fact, our meta-analysis of RCTs suggests an increased risk with calcium supplementation among men and women. It is possible that, among the frail subjects at risk of hip fracture, other deficiencies, such as vitamin D deficiency and phosphate deficiency due to low protein intake, should be corrected along with ensuring adequate calcium intake (17). Calcium carbonate or calcium citrate supplements can reduce phosphate absorption (43), which may be detrimental, because a balanced ratio of calcium to phosphate is needed for bone mineralization (44). Phosphate deficiency [defined as an intake <70% of adult recommended dietary allowance (700 mg/d)] is found in 10% of US women >60 y old and in 15% of US women >80 y old (45). Each increase in calcium intake by 500 mg/d decreases phosphorus absorption by 166 mg (43), so a calcium supplement of 1000 mg may shift an elderly person with a relatively low phosphorus intake into phosphate deficiency (43, 46). This change could augment bone resorption (43, 47, 48) and thus increase fracture risk. Conversely, in the trial by Chapuy et al (17), the beneficial effect of vitamin D plus calcium on hip fracture risk in frail elderly women may have been enhanced by the use of tricalcium phosphate, which may have avoided a calcium-related phosphate deficiency. Furthermore, vitamin D stimulates phosphate absorption (49), which may enhance phosphate uptake from nutritional sources in calcium supplement users. Such a benefit is supported by a recent meta-analysis showing that hip fracture risk is significantly reduced in trials that combined any calcium supplement with vitamin D (5, 6). Similarly, the main dietary sources of calcium also contain phosphorus, which could explain the lack of a positive association between calcium intake and fracture risk in the cohort studies.

An alternative explanation for the pooled RCT data on hip fractures is poor statistical power. The 4 studies that were pooled for the hip fracture outcome were limited by a relatively small number of cases (139 fractures), and one trial had poor adherence and a focus on secondary fracture prevention (12). Thus the apparent elevation in risk may be due to chance. However, if we considered only adherent subjects from the 3 largest trials, the elevated risk was maintained. Furthermore, each of the 4 trials included in the primary analysis indicated an elevated risk of hip fracture with RRs between 1.21 and 3.43, although only 1 of these trials reached significance (10). Thus the consistency of the evidence argues against a chance finding. Moreover, as discussed above, commonly used calcium supplements with a carbonate or citrate component have been shown to shift older persons into phosphate deficiency (43, 46) and to induce bone loss (43, 47, 48). To build calcium into bone, a calcium-phosphate product is needed, which may be disturbed by the described calcium supplement-induced phosphate malabsorption. This may be especially critical in frail older persons individuals at risk of both hip fracture and phosphate deficiency because of low protein intake. Thus, our findings are mechanistically plausible.

It is most important, however, that, with a CI excluding 1 for the primary analysis, an important reduction in hip fracture risk

with calcium supplementation seems unlikely. Furthermore, despite the limited data on men, a differential effect of calcium on hip fracture risk by sex appears unlikely: the pooled RRs were 1.66 among women and 1.56 among men. Still, more data on fracture risk in men are needed.

The strengths of our meta-analysis of prospective cohort studies are the large number of cases, the long duration of follow-up, and the inclusion of both men and women. Prospective cohort studies have less potential for bias than do other observationally designed studies, because the data on calcium intake are assessed before occurrence of fractures. In the presence of limited data from RCTs, as confirmed in our meta-analysis, summarization of these studies is likely to be the most informative approach.

However, our analysis has limitations. Prospective cohort studies may still be susceptible to bias, including loss to follow-up and residual confounding. Another limitation of our study is that the calcium intake from supplements was not assessed in all of the studies. Nonetheless, we did not detect heterogeneity between studies that assessed calcium intake from both dietary and supplement sources and those that studied only dietary intake. Our study was also limited by the lack of information on baseline 25-hydroxyvitamin D concentrations, phosphate intake, and physical activity. These factors could potentially modify the associations between calcium intake and fracture risk (17, 19, 50). In the RCTs included in our meta-analysis, participants' mean baseline calcium intakes exceeded the estimated mean intake of persons aged ≥ 50 y in the general US population—ie, 763 mg/d in men and 558 mg/d in women (22). Thus, we cannot exclude the possibility that persons with very low baseline calcium intakes may benefit more from calcium supplementation than those with higher calcium intakes; another reason for the negative findings could be that the subjects in the RCTs pooled for this meta-analysis already had "enough" calcium.

In summary, our results do not support an overall beneficial effect of greater calcium intake on hip fracture risk. Among women, the cohort data suggest a neutral effect of calcium intake on hip fractures, but data from RCT's of calcium supplementation suggest an adverse effect, even among adherent women. In addition, RCT data for any nonvertebral fractures indicate a neutral effect of calcium with respect to fracture reduction. Thus, future studies of the prevention of hip fracture or any nonvertebral fracture in women should not consider calcium supplementation alone but, rather, should focus on the optimal combination of calcium plus vitamin D and possibly on the correction of phosphate deficiency by using calcium-phosphate supplements. RCT and prospective cohort study findings for men did not support a beneficial effect of calcium intake on hip fracture risk in men, but further studies in men are needed as data are limited.

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from Wyeth, and, with Dartmouth College, holds a use patent for calcium as a cancer chemopreventive agent. No other authors had any personal or financial conflict of interest.

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