0163-769X/02/$20.00/0
Printed in U.S.A.

Endocrine Reviews 23(4):552–559

doi: 10.1210/er.2001-7002

VII. Meta-Analysis of Calcium Supplementation for the Prevention of Postmenopausal Osteoporosis

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A. Abstract

Objective: To summarize controlled trials examining the effect of calcium on bone density and fractures in postmenopausal women.

Data Source: We searched MEDLINE and EMBASE up to 1998 and the Cochrane Controlled Register up to 2000, and we examined citations of relevant articles and proceedings of international meetings. We contacted osteoporosis investigators to identify additional studies, and primary authors for unpublished data.

Study Selection: We included 15 trials (1806 patients) that randomized postmenopausal women to calcium supplementation or usual calcium intake in the diet and reported bone mineral density of the total body, vertebral spine, hip, or forearm, or recorded the number of fractures, and followed patients for at least 1 yr.

Data Extraction: For each trial, three independent reviewers assessed the methodological quality and extracted data.

Data Synthesis: We found calcium to be more effective than placebo in reducing rates of bone loss after two or more years of treatment. The pooled difference in percentage change from baseline was 2.05% [95% confidence interval (CI) 0.24–3.86] for total body bone density, 1.66% (95% CI 0.92–2.39) for the lumbar spine, 1.64% (95% CI 0.70–2.57) for the hip, and 1.91% (95% CI 0.33–3.50) for the distal radius. The relative risk (RR) of fractures of the vertebrae was 0.77, with a wide CI (95% CI 0.54–1.09); the RR for nonvertebral fractures was 0.86 (95% CI 0.43–1.72).

Conclusions: Calcium supplementation alone has a small positive effect on bone density. The data show a trend toward reduction in vertebral fractures, but do not meaningfully address the possible effect of calcium on reducing the incidence of nonvertebral fractures.

B. Introduction

OF ALL THE available preventive strategies for osteoporotic fractures, calcium is the simplest and least expensive. An essential nutrient with minimal toxicity, calcium supplementation is nevertheless not without controversy (1, 2). The Food and Drug Administration in the United States has permitted a bone health claim for calcium-rich foods, and the NIH in its Consensus Development Process approved a statement that high calcium intake reduces the risk of osteoporosis.

Cumming *et al.* (3) reviewed both observational and controlled clinical trials relating calcium intake to fracture incidence. Observational studies often provide biased estimates, and the authors did not find conclusive evidence of benefit from the controlled trials alone. Furthermore, they did not examine the effect of calcium supplementation on bone mineral density (3). Mackerras and Lumley (4) conducted a meta-analysis of randomized controlled trials (RCTs) examining the effect of increasing calcium ingestion on bone density in women, but their analysis omitted 4 of the 15 available studies, failed to contact authors to obtain missing data and clarify data report accuracy, and did not address the effect on fractures. We have therefore conducted a systematic review to quantify the effect of calcium supplementation on postmenopausal bone loss and fractures.

This section is the seventh in our series presenting RCT evidence regarding major antiosteoporotic therapy. In *Section I*, we presented the rationale for the series and described in detail the methods common to each systematic review. In this analysis, we will briefly summarize our methods and consider the effect of calcium supplementation alone. We deal with studies that examined the effects of calcium and vitamin D given together in the next section.

C. Methods

1. Inclusion criteria. We developed and published an *a priori* protocol according to the methods recommended by the Cochrane Collaboration (5). Studies satisfied the following inclusion criteria, as indicated in *Section I*, as well as the following: 1) RCTs of calcium supplementation in women older than 45 yr with absence of menses for a minimum of 6 months; 2) treatment with doses of calcium at least 400 mg/d. We also included RCTs in which both active and control groups received a maintenance dose of vitamin D, providing the loading dose was no more than 300,000 IU, and the maintenance dose was no more than 400 IU/d (6, 7).

2. Study search and selection. To identify RCTs of calcium supplementation, we evaluated MEDLINE and EMBASE from January 1966 to April 1998 including Current Contents of the 6 months before April 1998, and the Cochrane Controlled Trials Register up to 2000 (8, 9). We also conducted hand searches of bibliographic reference. We asked content experts to identify published or unpublished relevant RCTs

Abbreviations: CI, Confidence interval; RCT, randomized controlled trial; RR, relative risk.

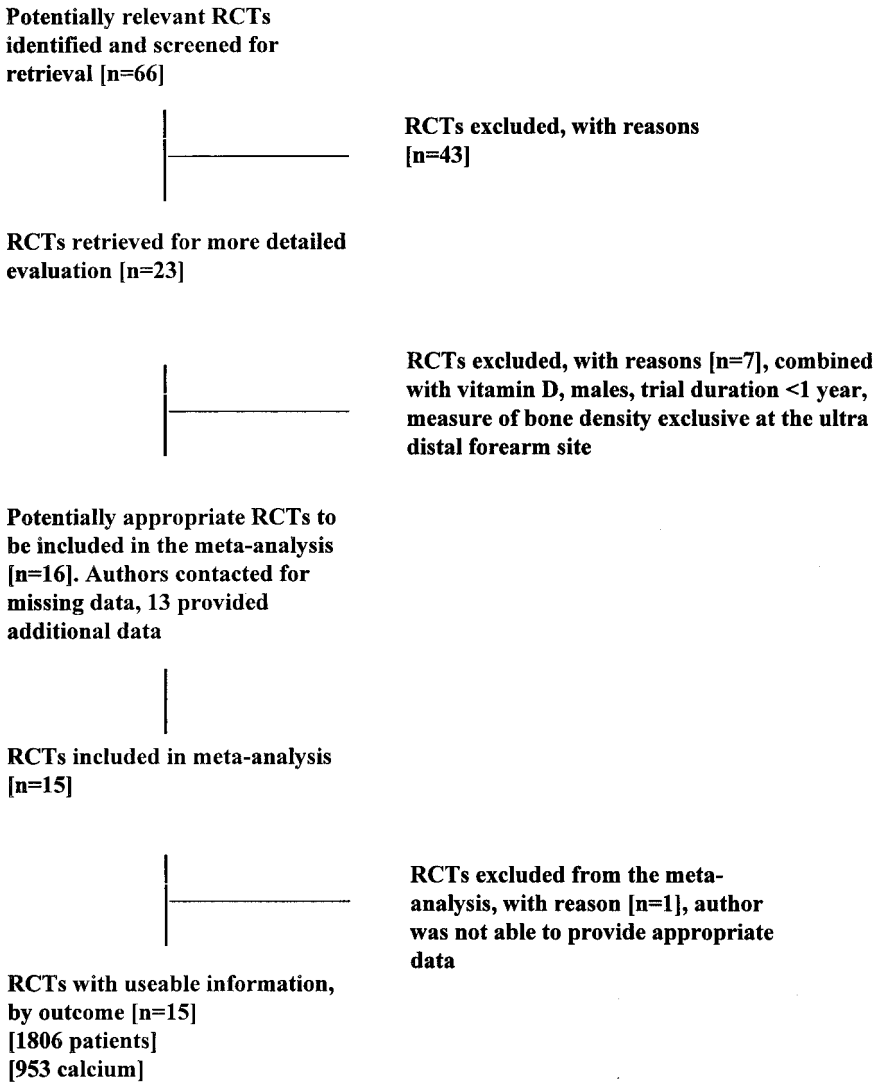

FIG. 1. Results of search for eligible studies.

we had overlooked. Two reviewers (J.P., B.S.) examined each title generated from the search and identified potentially eligible articles for which we obtained the abstracts. For abstracts consistent with study eligibility, we obtained the full article text.

3. Methodological quality. Three reviewers (J.P., N.Z., B.S.) rated the methodological quality of each eligible study with respect to whether patients, caregivers, and those measuring outcome are blind to allocation, and the extent of loss to follow-up.

4. Reliability of judgements. We used more than one reviewer in the selection of studies, the assessment of methodological quality, and the extraction of data. For all aspects of the review in which raters made duplicate judgements, they resolved disagreements by consensus. The interobserver agreement measured for the quality assessment with κ (10) for blind to allocation 0.85, and for follow-up was 0.49.

5. A priori hypotheses regarding heterogeneity. To explore reasons for large differences in results between studies (heterogeneity) we developed *a priori* hypotheses relating to the methodological quality of the study, the study population, and the dose and type of calcium administered. Specifically, we compared results in RCTs grouped in the following ways: 1) different methodological quality (randomization concealed or unconcealed; blinded or unblinded; extent of loss to follow-up); 2) different doses of calcium supplementation (above and below 800 mg/d, a value that approximates the median dose of calcium supplementation in the eligible trials); 3) type of calcium formulation (a manuscript reviewer suggested this hypothesis); 4) early postmenopausal women ($\leq$5 yr) and late postmenopausal women (5 yr); 5) different levels of baseline calcium intake (less than or greater than 750 mg, a value that approximates the median baseline intake in the eligible trials); and 6) for forearm and hip bone density, subregion of measurement.

6. Statistical analysis. For each bone density site (lumbar spine, total body, combined hip, and combined forearm), we calculated the weighted mean difference in bone density between treatment and control groups using the percentage

TABLE 1. Study characteristics from the calcium trials

Study (first author/ year/Ref.) (primary/secondary prevention)[a]	No. of participants (treatment/control)	Study sample Mean age (SD) BMD g/cm^{2b} T-score	Baseline dietary calcium intake (SD)	Intervention (Vitamin D supplementation)	Duration (years)	Outcomes measured	Lost to follow-up (%)
Riggs, 1998 (23) (secondary)	119/117	66.3 (2.6) 0.91 g/cm^2 (0.10) −1.2 0% vertebral fracture prevalence	714 (286) mg/d	Calcium citrate salt 1600 mg *vs.* placebo	4	BMD: Lumbar spine, total body, total hip Fractures: vertebral and nonvertebral	59/236 (25%)
Recker, 1996 (20) (secondary)	93/104 Fractures 52/42 No fractures 41/62	73.5 (7.1) 0.727g (0.14) 47.7% vertebral fracture prevalence	431 (194) mg/d	Calcium carbonate 1200 mg *vs.* placebo	4	BMC: Distal forearm Fractures: vertebral fractures	17/197 (8.6%)
Prince, 1995 (19) (secondary)	42/42	62.5 (4.5) 0.87 g/cm^2 (0.13) −1.6 Independent of fracture prevalence	804 (299) mg/d	Calcium lactate gluconate 1000 mg *vs.* placebo, also calcium and exercise and milk powder group (not included)	2	BMD: Total spine, femoral neck, total hip, intero-trochanteric, trochanter, ultradistal ankle	13/84 (15.5%)
Aloia, 1994 (7) (primary)	38/40	51.8 (1.7) 1.01 g/cm^2 (0.06) 0.0 0% vertebral fracture prevalence	481 (114) mg/d	Calcium carbonate 600 mg *vs.* placebo. (400 IU vitamin D/d)	3	BMD: Lumbar spine, femoral neck, trochanter, total body, 1/3 radius, ward's triangle	8/78 (10.3%)
Chevally, 1994 (6) (secondary)	31/31	72.1 (0.6) 0.98 g/cm^2 (0.02) −0.6 0% recent hip fracture prevalence	619 (318) mg/d	Calcium carbonate 800 mg, *vs.* placebo or Osseino mineral complex (300,000 IU vitamin D at study start)	1.5	BMD: Femoral neck, femoral shaft Fractures: vertebral and nonvertebral	10/62 (16.1%)
Strause, 1994 (14) (secondary)	29/28	65.4 (5.3) 0.92 g/cm^2 (0.15) −1.2 Independent of fracture prevalence	572 (288) mg/d	Calcium citrate malate 1000 mg *vs.* placebo or trace minerals with/out calcium	2	BMD: Lumbar spine	31/57 (57.4%)
Reid, 1993 (16) (primary)	68/67	58.0 (5.0) 0.87 g/cm^2 (0.14) −1.6 0% symptomatic vertebral fractures prevalence	745 (298) mg/d	Calcium 1000 mg *vs.* placebo	2	BMD: Lumbar spine, proximal femur, total body Fractures: symptomatic vertebral fractures	13/135 (9.6%)
Elders[c] 1991 (26) (primary and secondary)	198/97	46–55 0.88 g/cm^2 (0.13) −1.5 Independent of fracture prevalence	1150 (1082) mg/d	Calcium carbonate 1000 mg or 2000 mg *vs.* placebo	2	BMD: Lumbar spine	47/295 (15.9%)
Nelson, 1991 (21) (secondary)	19/22	60.2 (6.5) 0.93 g/cm^2 (0.06) −1.1 Independent of fracture prevalence	879 (534) mg/d	Calcium 831 mg and exercise, calcium 831 mg alone, exercise alone or placebo	1	BMD: Lumbar spine, proximal femur, and distal radius	5/41 (12.2%)
Prince, 1991 (22) (secondary)	39/41	56.0 (4.0) 272 mg/mm (31) Independent of fracture prevalence –	781 (300) mg/d	Calcium gluconate 1000 mg plus exercise *vs.* exercise alone	2	BMD: Distal, median and proximal forearm	10/80 (12.5%)
Dawson-Hughes, 1990 (15) (primary and secondary)	238/123	58.4 (4.8) 0.91 g/cm^2 (0.02) −1.3 0% non traumatic fracture prevalence	406 (84) mg/d	Calcium carbonate 500 mg Calcium citrate malate 500 mg *vs.* placebo	2	BMD: Lumbar spine, femoral neck, 1/3 radius	46/361 (12.7%)
Smith, 1989 (17) (primary)	44/38	55 (4.7) 0.68 g/cm^2 Independent of fracture prevalence –	679 (237) mg/d	Calcium 500 mg *vs.* placebo	4	BMC and BMD: Radius, ulna, and humerus	15/82 (18.3%)

TABLE 1. Continued

Study (first author/ year/Ref.) (primary/secondary prevention)[a]	No. of participants (treatment/control)	Study sample Mean age (SD) BMD g/cm^{2b} T-score	Baseline dietary calcium intake (SD)	Intervention (Vitamin D supplementation)	Duration (years)	Outcomes measured	Lost to follow-up (%)
Hansson, 1987 (25) (secondary)	25/25	66.0 (6.0) 273 mg/mm – 100% vertebral fracture prevalence	Not available	Calcium gluconate 1000 mg daily *vs.* placebo	3	BMC: Lumbar spine Fractures: vertebral	9/50 (18%)
Riis, 1987 (13) (primary)	15/13	50 (2.8) 0.72 g/cm^2 (0.15)–3.0 Independent of fracture prevalence	Not collected (800 mg national average)	Calcium carbonate 2000 mg *vs.* placebo	2	BMD: Lumbar Spine, total body, distal forearm, proximal forearm	3/28 (10.7%)
Lamke, 1978 (18) (secondary)	20/20	60.0 (3.0) 256 mg/mm (42) – 100% forearm fracture prevalence	Not collected	Calcium 1000 mg *vs.* placebo	1	BMC: Femoral neck and femoral shaft	4/40 (10%)

BMC, Bone mineral content.
[a] Refer to *a priori* hypotheses regarding heterogeneity defining primary and secondary prevention.
[b] BMD g/cm^2 lumbar spine, corrected to Hologic measurements with SD *in parenthesis*.
[c] Perimenopausal women randomized, only postmenopausal women included in analysis, forearm BMC mg/mm, T-score not available.

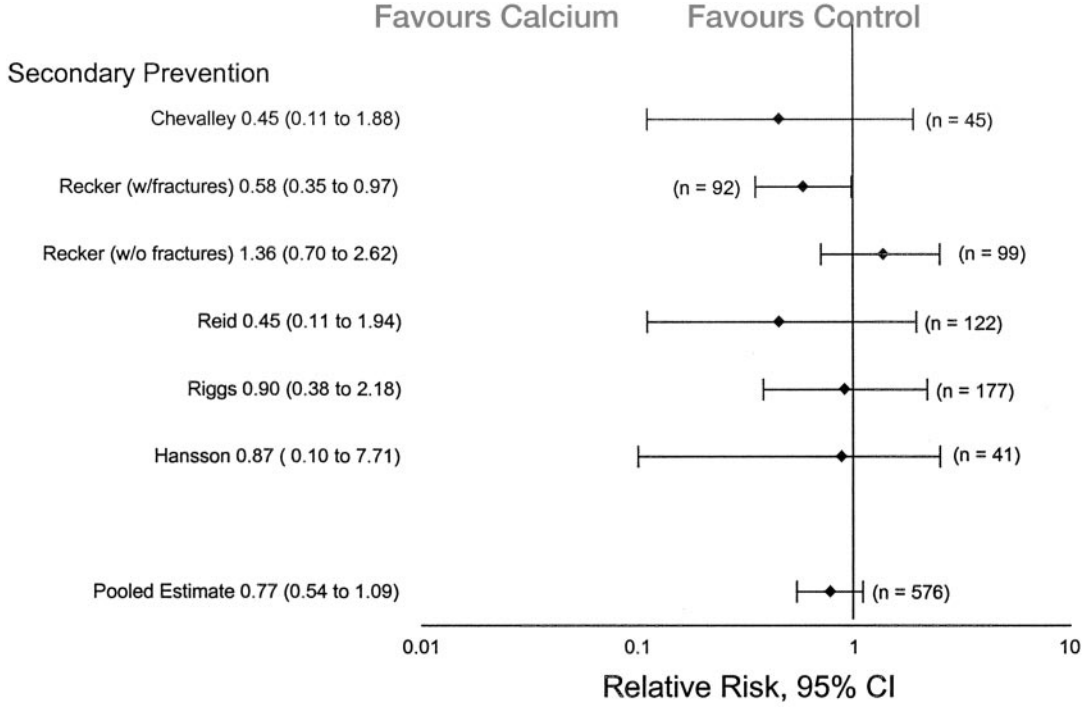

FIG. 2. RR of vertebral fracture after treatment with calcium.

TABLE 2. Weighted RR of fracture After treatment with calcium

Fracture site	No. of trials	Sample size	RR (95% CI)	RR *P* value	Heterogeneity *P* value
Vertebral	5	576	0.77 (0.54,1.09)	0.14	0.40
Non vertebral	2	222	0.86 (0.43,1.72)	0.66	0.54

We interpreted $P \leq 0.05$ as indicating important between-study differences in results.

change from baseline in the treatment and placebo groups and the associated SD values. We constructed regression models in which the independent variables were year and dose, and the dependent variable the effect size, and we used this regression to determine the years across which pooling was appropriate. To assess whether the magnitude of heterogeneity (differences in apparent treatment effect across studies) was greater than one might expect by chance, we conducted a test based on the χ^2 distribution with N-1 degrees of freedom, where N is the number of studies (11).

TABLE 3. Weighted mean difference of bone density after treatment with calcium

Bone density site	No. of trials	Sample size (n)	Weighted mean difference (95% CI)	*P* value	Test of heterogeneity *P* value
Total body	4	358	2.05 (0.24, 3.86)	0.03	<0.01
Lumbar spine (2 yr)	9	845	1.66 (0.92, 2.39)	<0.01	0.02
Lumbar spine (3 or 4 yr)	2	218	1.13 (−0.11, 2.38)	0.07	0.71
Combined hip	8	830	1.64 (0.70, 2.57)	<0.01	0.04
1/3 Distal radius	6	615	1.91 (0.33, 3.50)	0.02	<0.01

We interpreted $P \leq 0.05$ as indicating important between study-differences in results.

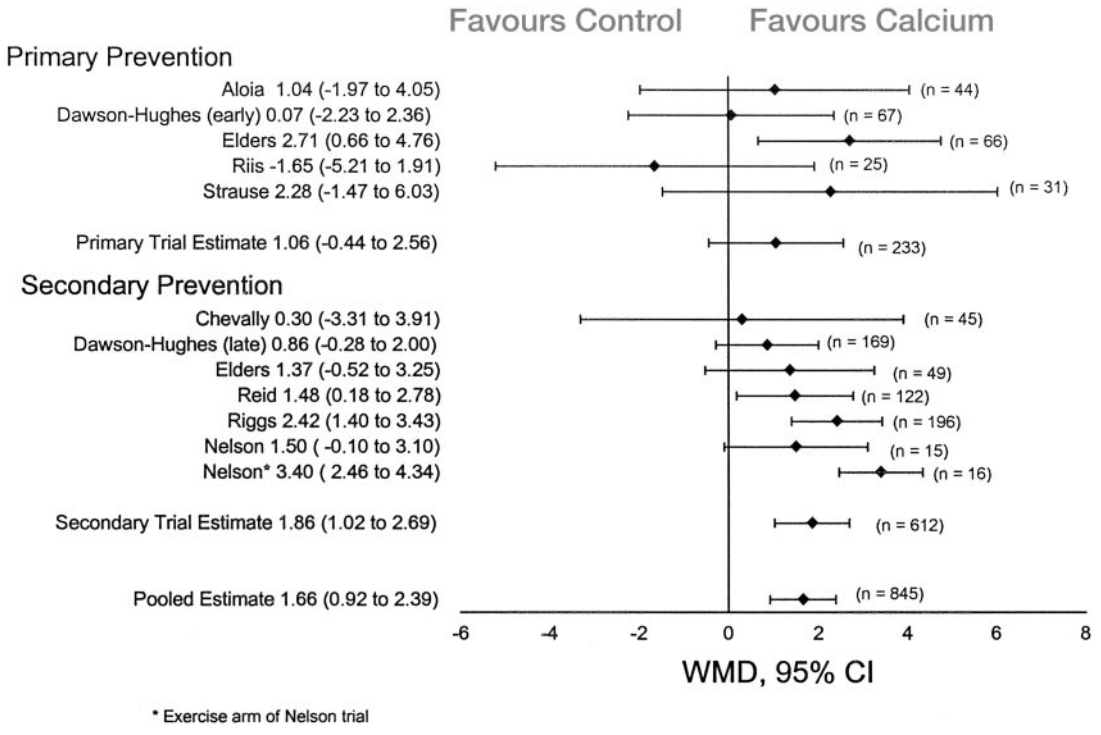

FIG. 3. Weighted mean difference for lumbar spine after treatment with calcium at 2 yr.

For each fracture analysis, we calculated a risk ratio (a RR) using methods described by Fleiss (11). We derived risk ratios by constructing two-by-two tables for vertebral and nonvertebral fractures. We tested for heterogeneity using a χ^2 procedure (12).

We tested whether our *a priori* hypotheses could explain variability in the magnitude of treatment effects across studies using a procedure described by Hedges and Olkin (12). To test for publication bias, we constructed plots of the relationship between sample size and the magnitude of the treatment effect.

D. Results

1. Search results. Figure 1 presents the results of our search for eligible studies. Electronic and hand searching uncovered a total of 66 published papers that addressed the relationship between calcium intake and bone mineral density. Twenty-three described RCTs (6, 7, 13–33), of which 7 were excluded for various reasons including combination with vitamin D (29, 33), male participants (31), trial duration less then 1 yr (30, 32), or measurement of bone density exclusively at the ultra-distal forearm site (27, 28).

Of the 16 authors of eligible studies whom we contacted for missing data, 13 provided additional data (6, 7, 13–23). We had to exclude one study due to lack of the data regarding error terms for the analysis (24), and we were unable to contact one investigator (26), although the study provided sufficient data for inclusion. Thus, 15 RCTs both fulfilled our eligibility criteria and provided useful data for pooling (6, 7, 13–23, 25, 26). Of the 13 investigators who did provide additional data, 11 were able to provide us with all the information we sought (6, 7, 14–20, 22, 23), whereas the other 2 provided us with some of the information we requested (13, 21).

2. Study characteristics. The 15 RCTs included 1806 patients, of whom 953 patients received calcium supplementation. Table 1 summarizes the characteristics of these studies. Of the 15 studies, 13 investigators confirmed that the randomization was concealed (6, 7, 13–23); 13 investigators confirmed that patients, caregivers, and those measuring outcome were blind to allocation (6, 7, 13–23). None of the trials had between 1% and less than 5% loss to follow-up, 13 trials had a loss to follow-up between 5% and 20%, and 2 trials lost

TABLE 4. Heterogeneity of difference of bone mineral density

Bone density site	Heterogeneity *P* value	Primary, secondary/ difference (95% CI) *P* value	Loss to follow-up (≤15%/>15%)	Calcium supplementation (800 mg+ *vs.* ≤800 mg)	Baseline daily calcium intake (750 mg+ *vs.*750 mg)	Site measured (Total hip *vs.* femoral Neck)
Total body	<0.01	4.50; 0.59 3.91 (1.18, 6.64) *P* = 0.01	2.91; 0.37 2.54 (−1.06, 6.14) *P* = 0.17	0.63; 5.50 −4.87 (−6.80, −2.93) *P*<0.01	0.82; 2.86 −2.05 (−7.12, 3.02) *P* = 0.43	One site only
Lumbar spine (2 yr)	0.02	1.06; 1.86 −0.80 (−2.51, 0.92) *P* = 0.36	1.32; 2.17 −0.35 (−2.24, 0.53) *P* = 0.23	2.00; 0.74 1.27 (0.02, 2.51) *P* = 0.05	1.87; 1.39 0.48 (−0.94, 1.90) *P* = 0.51	One site only
Lumbar spine (3–4 yr)	0.71	0.65; 1.25 −0.60 (−3.76, 2.57) *P* = 0.71	0.65; 1.25 −0.60 (−3.76, 2.57) *P* = 0.71	1.25; 0.65 0.60 (−2.57, 3.76) *P* = 0.71	Only 1 subgroup	One site only
Combined hip	0.04	2.78; 1.51 1.27 (−4.04, 6.57) *P* = 0.64	1.78; 1.45 0.33 (−1.43, 2.10) *P* = 0.71	1.53; 2.11 0.57 (−3.28, 2.14) *P* = 0.68	1.55; 1.70 −0.14 (−2.15, 1.86) *P* = 0.89	1.37; 1.87 −0.50 (−2.16, 1.16) *P* = 0.55
1/3 Distal radius	<0.01	2.51; 1.71 0.81 (−1.80, 3.41) *P* = 0.54	1.70; 3.44 −1.74 (−4.55, 1.06) *P* = 0.22	2.30; 1.18 1.12 (−1.54, 3.78) *P* = 0.41	1.05; 2.35 −1.30 (−4.70, 2.10) *P* = 0.45	One site only

We interpreted $P \leq 0.05$ as indicating important between-study differences in results.

TABLE 5. Difference of bone mineral density by calcium type

Bone density site	Heterogeneity *P* value	Calcium citrate; calcium carbonate/ difference (95% CI) *P* value	Calcium citrate; calcium gluconate/ difference (95% CI) *P* value	Calcium carbonate; calcium gluconate/ difference (95% CI) *P* value
Total body	<0.01	0.37; 4.50 −4.13 (−6.93, −1.33) *P* < 0.01		
Lumbar spine (2 yr)	0.34	2.41; 1.24 1.17 (−0.43, 2.77) *P* = 0.15		
Lumbar spine (3 or 4 yr)	0.71	1.25; 0.65 0.60 (−2.57, 3.76) *P* = 0.71		
Combined hip	0.15	1.15; 4.19 −3.03 (−5.92, −0.15) *P* = 0.04	1.15; 1.61 −0.46 (−2.17, 1.26) *P* = 0.60	4.19; 1.61 2.58 (−0.33, 5.48) *P* = 0.08
1/3 Distal radius	0.16	–; 2.83 (Only 1 subgroup)		

more that 20% of their patients. We were unable to obtain the methodology information for two of the trials (25, 26).

3. Fractures. Five studies including 576 women reported fractures as an outcome (6, 16, 20, 23, 25). All five trials investigated the influence of calcium supplementation on vertebral fractures. The pooled RR indicated a nonsignificant trend toward reduction in vertebral fractures in the calcium group (RR 0.77, 95% CI 0.54–1.09, $P = 0.14$; Fig. 2). The two trials (6, 23) that reported nonvertebral fractures had very few events, and the CI on the pooled estimate is therefore very wide (RR 0.86, 95% CI 0.43–1.72, $P = 0.66$). For both vertebral and nonvertebral fractures, the effect of calcium was consistent across trials (heterogeneity $P = 0.40$, 0.54, respectively; Table 2). The funnel plots provided no evidence of publication bias.

4. Bone mineral density. Table 3 summarizes the impact of calcium on bone mineral density at the four sites we examined. Our initial analyses suggested that we could pool across years in all instances but one, the lumbar spine. Here, the estimated effect of calcium for yr 3 and 4 was actually less than for yr 1 and 2 (Table 3). For all sites but lumbar spine at 2 yr of follow-up (Fig. 3), calcium showed an effect of between 1.6 and just over 2% in bone density.

At all sites, we found considerable variability in estimates of effect across trials reflected in statistically significant tests of heterogeneity. Funnel plots provided no persuasive evidence of publication bias.

Our search for explanations of this heterogeneity proved largely fruitless (Table 4). For the total body measurement, we observed a statistically significantly greater effect in primary than secondary studies, and with smaller doses of calcium than larger doses. For lumbar spine at 2 yr, the effect was in the opposite direction, suggesting a larger impact of higher doses.

We did find an apparently greater effect of calcium carbonate than calcium citrate on total body bone density and on the hip site (Table 5). However, the trend for the lumbar spine measurements was in the opposite direction (larger effects with calcium citrate). Moreover, the total body and hip site analyses were based on only a single RCT using calcium citrate and two RCTs using calcium carbonate. Thus, any inferences based on this analysis are extremely weak. No other subgroup analysis showed statistically significant results.

E. Discussion

This systematic review is restricted to calcium supplementation with minimal vitamin D. Large studies of vitamin D have shown conflicting results (29, 33). We summarize the data from all randomized trials of vitamin D in *Section VIII*.

Our data suggest a relatively small, but possibly important, effect of calcium supplementation on bone density in postmenopausal women. The inference that calcium increases bone density is strengthened by the consistency of the finding across four sites of measurement (Table 3). The inference is, however, weakened by the large loss to follow-up in most studies (Table 1) and by the unexplained heterogeneity of results across studies (Tables 3 and 4).

To establish the effect of calcium supplementation on fractures would require large, relatively long trials measuring fracture incidence. We found only five RCTs that measured fracture rate. The point estimate from the meta-analysis of these five studies suggested a potentially important reduction in vertebral fractures (RR 0.77, 95% CI 0.54–1.09, $P = 0.14$, RR 0.77), and a smaller reduction in risk of nonvertebral fractures (RR 0.86, 95% CI 0.43–1.72, $P = 0.66$). Thus, even for vertebral fractures, a true underlying substantial reduction in the RR of fractures (46%) or small increase in the RR of fractures (10%) both remain plausible.

The estimates provided by our analysis are limited by problems inherent in the original studies, including a lack of uniformity in outcome measures. In 1996, during the Conference on Outcome Measures in Rheumatology Clinical Trials (OMERACT 3), participants agreed on a potential core set of outcome measures for osteoporosis (34). A core set will permit the comparison of data across all trials to perform accurate meta-analyses. The primary outcomes will be the number of women experiencing new nonvertebral and vertebral fractures (clinical and radiographic), bone mineral density, and toxicity (measured by withdrawals and side effects), as recommended by the OMERACT group in 1997 (34).

As well as considering these issues, future investigations should take care with the selection of study patients, the dose and formulation of calcium administration, and the measures of outcome. When they select study populations, investigators should also consider factors that may influence the effectiveness of calcium supplementation, including age, years since menopause, dietary calcium intake, and vitamin D status, in selecting study populations. Site of bone density measurement, type and precision of the instruments, and definition of fracture may also influence the apparent magnitude of treatment effects.

In summary, we found small but statistically significant and potentially important effects of calcium supplementation in bone loss over a 2-yr period. Ensuring adequate calcium intake may be important for a variety of reasons, including its role as part of an intervention that includes another agent such as vitamin D or bisphosphonates. The magnitude of reduction in fracture risk with calcium supplementation alone remains an open question.

F. Acknowledgments

The authors thank Dr. Graeme Jones for reviewing earlier versions of this paper and Candyce Hamel for her administrative support, and also express thanks to the authors who were instrumental in obtaining the additional data: J. F. Aloia, E. Flaster, M. Feuerman, T. Chevally, R. Rizzoli, B. Dawson-Hughes, E. Khral, B. Lamke, R. Prince, R. Recker, I. Reid, B. L. Riggs, K. Egan, B. J Riis, E. Smith, L. Strause, M. Andon of Procter & Gamble, and M. E. Nelson. We thank Dr. A. J. Yates for helpful comments on the manuscript. This work was supported in part by grants from Merck and Procter & Gamble.

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