"This summary of 29 studies involving 63,000 people taking traditional rock based calcium supplements with vitamin D, SLOWS bone loss. It does not INCREASE bone density as the AlgaeCal formulations have in two clinical

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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Summary

Background Whether calcium supplementation can reduce osteoporotic fractures is uncertain. We did a meta-analysis to include all the randomised trials in which calcium, or calcium in combination with vitamin D, was used to prevent fracture and osteoporotic bone loss.

Methods We identified 29 randomised trials (n=63 897) using electronic databases, supplemented by a hand-search of reference lists, review articles, and conference abstracts. All randomised trials that recruited people aged 50 years or older were eligible. The main outcomes were fractures of all types and percentage change of bone-mineral density from baseline. Data were pooled by use of a random-effect model.

Findings In trials that reported fracture as an outcome (17 trials, n=52 625), treatment was associated with a 12% risk reduction in fractures of all types (risk ratio 0·88, 95% CI 0·83–0·95; p=0·0004). In trials that reported bone-mineral density as an outcome (23 trials, n=41 419), the treatment was associated with a reduced rate of bone loss of 0·54% (0·35–0·73; p<0·0001) at the hip and 1·19% (0·76–1·61%; p<0·0001) in the spine. The fracture risk reduction was significantly greater (24%) in trials in which the compliance rate was high (p<0·0001). The treatment effect was better with calcium doses of 1200 mg or more than with doses less than 1200 mg (0·80 *vs* 0·94; p=0·006), and with vitamin D doses of 800 IU or more than with doses less than 800 IU (0·84 *vs* 0·87; p=0·03).

Interpretation Evidence supports the use of calcium, or calcium in combination with vitamin D supplementation, in the preventive treatment of osteoporosis in people aged 50 years or older. For best therapeutic effect, we recommend minimum doses of 1200 mg of calcium, and 800 IU of vitamin D (for combined calcium plus vitamin D supplementation).

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Introduction

The social and economic burden of osteoporotic fractures is increasing worldwide, as the population ages. In the USA, osteoporosis affects more than 10 million individuals,[1] and the yearly expenditure on osteoporotic fractures has exceeded that on breast cancer.[2] The prevention of fractures has therefore become a major public-health priority. However, preventive drugs can be as expensive as the treatment of fractures themselves, albeit far less painful to the patients.[3] Furthermore, as the demographic trend of ageing shifts to Asia, Africa, and Latin America, much of the rising cost of prevention of fractures will be disproportionately borne by some of the poorest health-care systems in the world. As a result, the development of an affordable preventive therapy will have a great effect on health, and its economic management, worldwide.

Calcium alone, or in combination with vitamin D, has been suggested as an inexpensive treatment to prevent osteoporotic bone loss and fractures, costing as little as €0·41 per day in one European study.[4] However, there has been substantial uncertainty about its efficacy in lowering the fracture rate. Data from earlier clinical trials showed that it reduced the fracture rate,[5,6] but this finding was not confirmed in subsequent multicentre trials.[7–9] Moreover, results from meta-analyses have been inconsistent.[10–13] All meta-analyses have included a different subset of the available trials, but none has offered a comprehensive review of all the relevant evidence. Consequently, the role of calcium supplementation in the preventive treatment of osteoporotic fractures has remained uncertain.

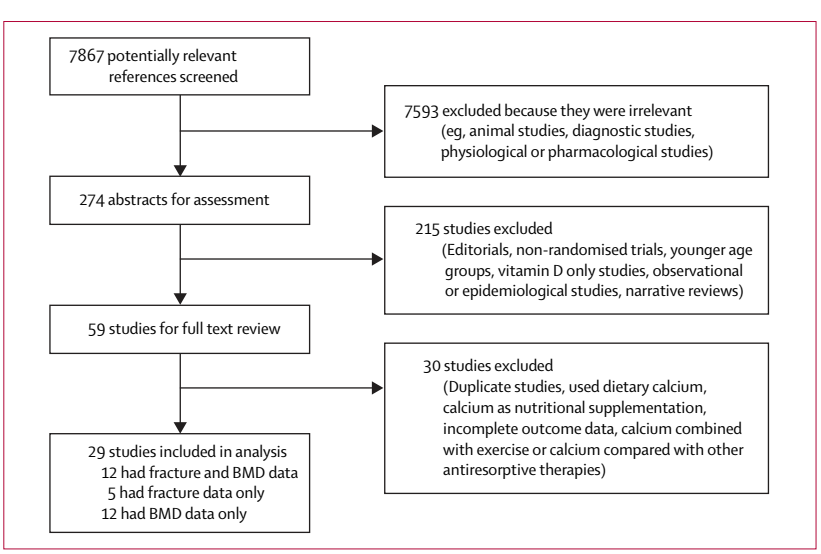

Figure 1: **Study selection**
BMD=bone-mineral density.

For the **National Institute of Health repository** see http://www.clinicaltrials.gov

For the **National Research Register repository** see http://www.nrr.nhs.uk

For the **Current Controlled Trials repository** see http://www.controlled-trials.com

For the **Trials Central repository** see http://www.trialscentral.org

For the **International Osteoporosis Foundation** see http://www.osteofound.org

For the **National Guideline Clearinghouse** see http://www.guideline.gov

For the **American College of Physicians** see http://www.acpjc.org

We aimed to do a systemic review to quantitatively assess all the published randomised controlled trials that assessed the effect of calcium, or calcium in combination with vitamin D supplementation, on osteoporotic fractures and bone-mineral density, in adults aged 50 years and older.

Methods

Search strategy and selection criteria

The study was done with a prospectively developed protocol, which prespecified the research objective, search strategy, study eligibility criteria, and the methods of data extraction and statistical analysis. All subgroup variables were defined before analysis. The reporting of the study's findings was in accordance with the Quality of Reporting of Meta-analyses (QUOROM) conference statement.[14]

We searched, without language restrictions, for all publications on calcium and vitamin D between January, 1966, and January, 2007, using electronic databases, including Medline, Embase, Current Content, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews. We also searched for unpublished trials and those in progress using clinical trials repositories, including that of the National Institute of Health, the National Research Register, Current Controlled Trials, and Trials Central. The search was supplemented by use of resource websites, including those of the International Osteoporosis Foundation, National Guideline Clearinghouse, American College of Physicians, and Computer Retrieval of Information on Scientific Projects.

The search strategy used the following MeSH search terms: (1) "osteoporosis"; (2) "bone density", "bone strength", or "bone loss"; (3) "fracture" or "bone fracture"; (4) "calcium carbonate", "calcium", or "dietary calcium"; (5) "vitamin D"; and (6) "cholecalciferol" or "colecalciferol".

	Year	Country	Total (n)	Mean age (years)*	Participants	Treatment	Dose(Ca/Vit D)	Outcomes	Trial quality†
Chapuy-1[5]	1992	France	2790	84 (6)	Mobile elderly women in nursing homes	Ca+vit D	1200 mg/800 IU	Fracture & BMD	B,R
Reid-1[27]	1993	New Zealand	122	58 (5)	Healthy, postmenopausal women	Ca	1000 mg	Fracture & BMD	B,C
Chevalley[28]	1994	Switzerland	156	72 (7)	Healthy, elderly men and women	Ca	800 mg	Fracture & BMD	B,C
Recker[29]	1996	USA	197	74 (7)	Independent postmenopausal women	Ca	1200 mg	Fracture	B,C
Dawson-Hughes-1[6]	1997	USA	389	71	Healthy, ambulatory men and women	Ca+vit D	500 mg/700 IU	Fracture & BMD	B,C,R
Riggs[30]	1998	USA	236	66 (3)	Healthy, postmenopausal women	Ca	1600 mg	Fracture & BMD	B,C
Peacock[31]	2000	USA	261	75 (8)	Independent, mobile elderly men and women	Ca	750 mg	Fracture & BMD	R
Chapuy-2[25]	2002	USA	583	85	Ambulatory, institutionalised women	Ca+vit D	1200 mg/800 IU	Fracture & BMD	None reported
Larsen[24]	2004	Denmark	9605	74 (66–103)	Elderly men and women	Ca+vit D	1000 mg/400 IU	Fracture	None reported
Harwood[32]	2004	U.K.	150	81 (67–92)	Elderly women with previous fractures	Ca+vit D	1000 mg/800 IU	Fracture & BMD	R
Fujita[26]	2004	Japan	19	81	Elderly, institutionalised women	Ca	900 mg	Fracture & BMD	None reported
RECORD-1[7]	2005	UK	2638	78 (6)	Elderly men and women with previous fractures	Ca	1000 mg	Fracture	B,C,R
RECORD-2[7]	2005	UK	2643	77 (6)	Elderly men and women with previous fractures	Ca+vit D	1000mg / 800IU	Fracture	B,C,R
Porthouse[33]	2005	UK	3314	77 (5)	Women with risk factors for hip fracture	Ca+vit D	1000mg / 800IU	Fracture	R
Jackson[8]	2006	USA	36 282	62 (7)	Healthy, postmenopausal women	Ca+vit D	1000 mg/400 IU	Fracture & BMD	B,R
Reid-2[34]	2006	New Zealand	1471	74 (4)	Healthy, postmenopausal women	Ca	1000 mg	Fracture & BMD	B,C,R
Prince-1[9]	2006	Australia	1460	75 (3)	Healthy, elderly women	Ca	1200 mg	Fracture & BMD	C,R
Prince-2[46]	1995	Australia	84	62 (5)	Healthy, postmeopausal women	Ca	1000 mg	BMD	None reported
Lamke[35]	1978	Sweden	40	60 (3)	Elderly women with previous fractures	Ca	1000 mg	BMD	None reported
Orwell[36]	1990	USA	77	58 (12·5)	Healthy men	Ca+vit D	1000 mg	BMD	None reported
Dawson-Hughes-2[37]	1990	USA	301	58 (5)	Healthy, postmenopausal women	Ca	500 mg	BMD	None reported
Elders[38]	1991	Netherlands	295	50 (46–55)	Healthy, postmenopausal women	Ca	1500 mg	BMD	None reported
Lau[39]	1992	Hong Kong	60	76	Elderly women from nursing home	Ca	800 mg	BMD	R
Aloia[40]	1994	USA	118	52	Healthy, postmenopausal women	Ca+vit D	600 mg/400 IU	BMD	B,C,R
Strause[41]	1994	USA	59	66 (7)	Healthy, postmenopausal women	Ca	1000 mg	BMD	None reported
Storm[42]	1998	USA	60	72 (6)	Healthy, postmenopausal women	Ca	1000 mg	BMD	None reported
Baeksgaard[43]	1998	Denmark	240	62 (6)	Healthy, postmenopausal women	Ca+vit D	1000 mg/560 IU	BMD	None reported
Grados[44]	2003	France	192	75 (68–79)	Female outpatients	Ca+vit D	500 mg/400 IU	BMD	None reported
Meier[45]	2004	Germany	55	56 (11)	Healthy men and women	Ca+vit D	200 mg/200 IU	BMD	None reported

R=randomisation. C=allocation concealment. B=blinding of outcome assessment. BMD=bone-mineral density. Ca=calcium. Vit=vitamin. *The SD or the range of the age is shown in parantheses for studies that have this information available. †Reported in the study or confirmed by the author.

Table 1: **Study and participant summary characteristics**

We hand-searched the reference lists of every primary study for additional publications. Further searches were done by reviewing abstract booklets and review articles.

We included all randomised trials that used calcium, or calcium with vitamin D supplementation, versus placebo, reported fracture or bone-mineral density as an outcome, and included patients aged 50 years or older.

Studies were excluded if they were duplicated studies, did not use a placebo or control group, used dietary calcium as an intervention, used calcium as part of a complex nutritional supplementation regimen, used calcium in combination with other treatment (eg, fluoride, hormones, or antiresorptive therapy), enrolled patients with secondary osteoporosis (eg, long-term glucocorticoid use), or used vitamin D without calcium.

The primary outcome was fracture of any site, including hip, vertebra, and wrist. The secondary outcome was bone-mineral density, expressed as percentage change from baseline. For the purpose of analysis, more than one fracture suffered by the same patient was counted as one event, with the first fracture regarded as the primary outcome.

Data extraction

Data were extracted independently by two reviewers; disagreements were resolved by consensus. To quantify the level of agreement between reviewers, a κ statistic was calculated. The κ statistic is a chance-corrected proportional index, with values ranging from +1 (perfect agreement) to –1 (complete disagreement). Information extracted included year of publication, country of origin, clinical setting, trial duration, participant demographics, sample size, calcium and vitamin D doses, baseline calcium intake, serum 25-(OH)-vitamin D_3 concentration, and drug formulation. Authors were contacted if further study details were needed, discrepancies or inaccuracies were detected, or duplicate publication was suspected.

Quality assessment

We assessed the method of every study using a four-item checklist—namely, reporting of randomisation method, allocation concealment, blinding of outcome assessment, and completeness of follow-up. The criteria were drawn from the Cochrane Collaboration guidelines.[15] To assess the effect of trial quality on the effect size, sensitivity analysis was done by comparison of studies that fulfilled quality criteria with those that did not.

Statistical analysis

In every study, we calculated the risk ratio (RR) for the primary outcome (the fracture rate) and the mean percentage difference between groups for the secondary outcome (bone-mineral density), along with the 95% CIs. The outcome measures were pooled by use of the random-effects model. On the basis of pooled RR and the baseline risk, the number needed to treat was calculated, along with its 95% CI.[16] Heterogeneity was assessed with Cochran's Q statistic and quantified using the I^2 statistic, which indicated the proportion of variability across studies that was due to heterogeneity rather than sampling error. Metaregression was used to assess the effect of age, baseline fracture risk, bodyweight, trial duration, and compliance on treatment efficacy. The baseline fracture risk—ie, that in the control group—was calculated. The effect of individual studies on the pooled effect size was assessed with influence analysis, in which the analysis was repeated omitting one study at a time, to establish the contribution of each study to the effect size.

We anticipated the presence of clinical heterogeneity, based on the findings that the effects of calcium, or calcium with vitamin D, seemed to vary depending on dose and various treatment factors (eg, treatment duration, previous fractures), and since participant demographics and clinical settings differed greatly between studies. Since the test for heterogeneity had low statistical power, we assumed the presence of heterogeneity a priori, and used the random effects model in all analyses.

To assess whether the treatment effect (reduction in fracture risk) of calcium, or calcium with vitamin D, was modified by clinical and demographic variables, we prespecified a list of 12 variables for subgroup analysis. Variables were chosen on the basis of either biological plausibility (eg, age, baseline vitamin D concentration, or drug dose) or known risk factors (eg, institutional settings or history of previous fractures). We choose 1200 mg calcium and 800 IU vitamin D as threshold levels based on the following reasons. For calcium, the recommended dietary intake is 1200 mg for both men and women older than 50 years, according to the US Department of

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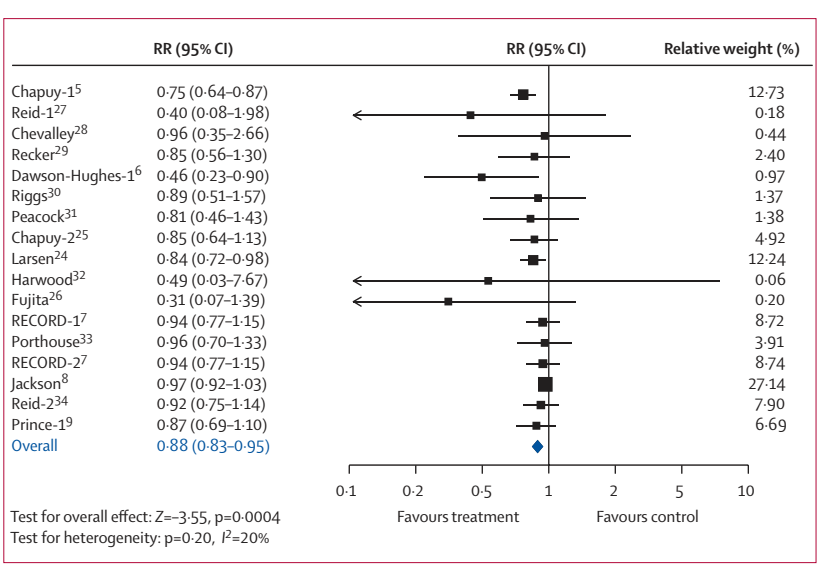

Figure 2: **Effect of calcium and calcium in combination with vitamin D on fracture risk**
RR=risk ratio. Size of data markers are proportional to the weight of every study in the forest plot. Horizontal bars=95% CI.

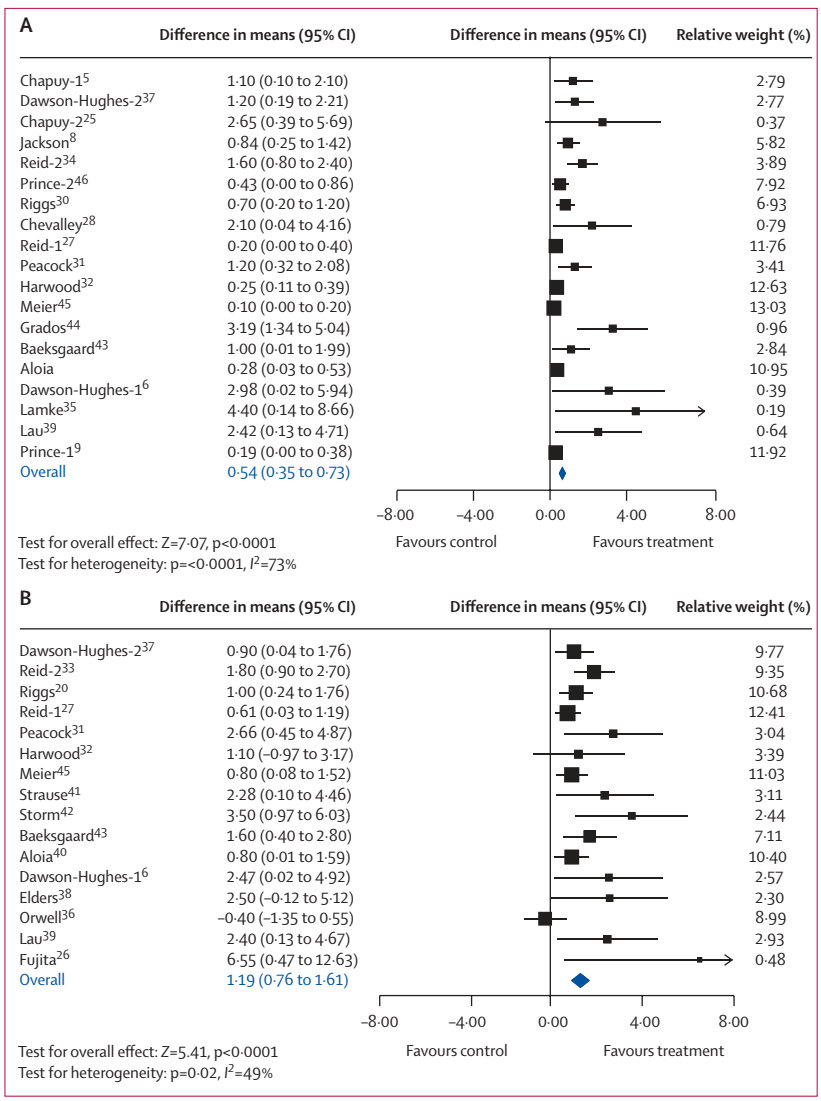

Figure 3: **Effect of calcium and calcium in combination with vitamin D on hip (A) and vertebral (B) bone-mineral density**

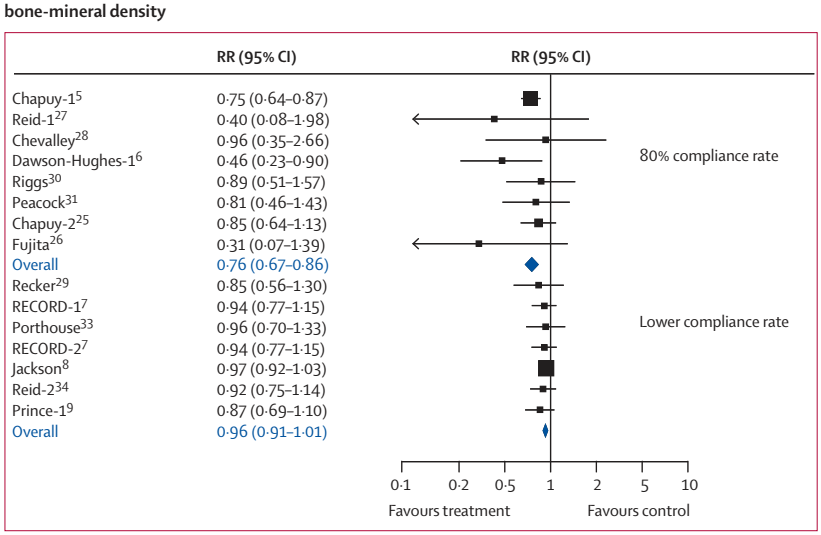

Figure 4: **Effect of compliance on fracture risk reduction**

Agriculture's dietary reference intakes guidelines.[17] Furthermore, most of the trials included in our analysis had a threshold level between 1000 mg and 1200 mg. For vitamin D, the lowest dose thought to have an effect is 800 IU per day. A recent meta-analysis showed that for a lower dose of 400 IU per day, there was no significant treatment benefit.[18] However, a higher dose (eg, 800 IU per day) reduced fractures in both ambulatory and institutionalised elderly people.[19] A test of interaction was done on all subgroups, to establish if the difference in effect size between subgroups was statistically significant.

We did cumulative meta-analysis by undertaking sequential random-effects pooling, starting with the earliest studies.[20] Each successive meta-analysis then summarised all the trials in the preceding years. Results were presented as a series of mini meta-analyses, which were ordered chronologically in a forest plot to show the consequence of adding studies on the effect size.

We assessed publication bias using the Egger's regression model.[21] If publication bias was detected, the effect of such bias was assessed with the fail-safe number method.[22,23] The fail-safe number was the number of unpublished studies that would be needed to nullify the observed result to statistical non-significance at the α=0·05 level. Publication bias is generally regarded as a concern if the fail-safe number is less than 5n+10, where n is the number of studies included in the meta-analysis.

Results were regarded as statistically significant if p<0·05. All analyses were done with Comprehensive Meta-analysis (version 2.0) and GraphPad Prism.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 7867 references screened, 29 studies were included in the final analysis (figure 1).[5–9,24–46] 17 trials reported fractures as an outcome,[5–9,24–34] and 24 reported bone-mineral density.[5,6,8,9,25–28,30–32,34–46] Some trials reported both outcomes (table 1). One study[7] had a four-group trial, with one placebo and three experimental groups. Its calcium group, and calcium in combination with vitamin D group, were analysed separately and therefore treated as two studies; as a result, the placebo group was counted twice.

In total, 63 897 individuals were analysed, most of whom were women (n=58 785 [92%]) with a mean age of 67·8 years (SD 9·7). The median baseline risk for fracture was 16% (10–22). In 13 trials, participants received calcium and vitamin D combination supplementation, whereas in all other trials they received calcium-only supplementation (table 1).

Trial quality was better in studies reporting fractures as outcome than it was in those reporting bone-mineral

	Subtotal (n)*	RR (95% CI)	p value
Supplementation			
Calcium	6517	0·90 (0·80–1·00)	0·63
Calcium and vitamin D	46 108	0·87 (0·77–0·97)	
Previous fractures			
No	46 919	0·86 (0·78–0·95)	0·85
Yes	5706	0·93 (0·82–1·06)	
Clinical setting			
Community	49 233	0·94 (0·90–0·99)	0·003
Institutionalised	3392	0·76 (0·66–0·88)	
Serum 25(OH) vitamin D_3 concentration†			
Low	10 144	0·86 (0·78–0·93)	0·06
Normal	39 167	0·94 (0·90–0·99)	
Fracture sites			
Hip	51 935	0·87 (0·75 – 0·99)	0·72
Vertebral	45 184	0·87 (0·75 – 1·01)	
Dietary calcium intake‡			
Low	7272	0·80 (0·71–0·89)	0·008
Normal	45 241	0·95 (0·91–1·00)	
Calcium dose			
<1200 mg	47 359	0·94 (0·89–0·99)	0·006
≥1200 mg	5266	0·80 (0·72–0·89)	
Vitamin D dose			
<800 IU	36 671	0·87 (0·71–1·05)	0·03
≥800 IU	9437	0·84 (0·75–0·94)	
Sex			
Women-only studies	46 586	0·88 (0·80–0·97)	0·33
Men and women studies	6039	0·88 (0·80–0·96)	
Percentage change in BMD			
<1%	38 212	0·96 (0·91–1·02)	0·007
≥1%	5621	0·80 (0·70–0·91)	
Age (years)			
50–69	36 640	0·97 (0·92–1·02)	0·003
70–79	12 481	0·89 (0·82–0·96)	
≥80	3504	0·76 (0·67–0·87)	
Compliance§			
≥80%	4508	0·76 (0·67–0·86)	0·002
60–69%	3511	0·92 (0·71–1·19)	
50–59%	44 494	0·96 (0·91–1·01)	

BMD=bone-mineral density. *Number may not add up to 100% of total because of missing data in some variables. †A serum 25(OH) vitamin D_3 concentration <25 nmol/L was regarded as below normal. Results were similar on higher cut-off points. ‡Dietary intake was regarded as low if <700 mg per day. Result was similar on higher cut-off point (1000–1200 mg/day). §Compliance means the use of 80% or more of the study drug. There was no study that had less than 50% compliance, and there was no study in the 70–80% subgroup.

Table 2: **Subgroup analysis for fracture**

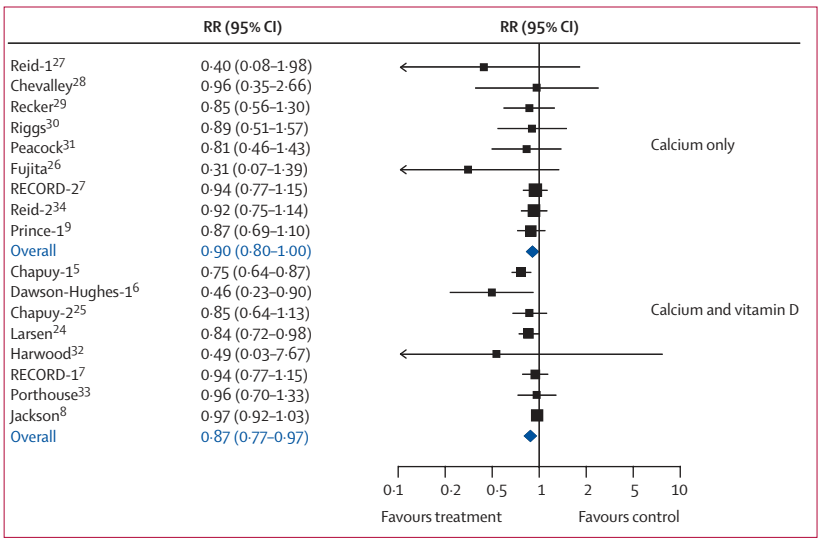

Figure 5: **Effect of calcium and calcium in combination with vitamin D on fracture risk reduction**

density only. In fracture trials, 14 of the 17 trials (82%) reported data for methodological quality, whereas in bone-mineral density only trials, only two of the 11 trials (18%) reported such data (table 1).

Of the 17 trials reporting fracture as an outcome (n=52 625), calcium and calcium in combination with vitamin D were associated with a 12% risk reduction in fractures of all types (RR 0·88, 95% CI 0·83–0·95; p=0·0004; figure 2). The direction of effect was consistent in all studies, with all favouring treatment in its effect on fractures. Of the 24 trials reporting bone-mineral density, calcium and calcium in combination with vitamin D were associated with a reduced bone loss of 0·54% (0·35–0·73; p<0·0001) at the hip and 1·19% (0·76–1·61; p<0·0001) in the spine (figure 3). A positive treatment effect on bone-mineral density was evident in most studies.

Trials with higher compliance showed a significantly greater risk reduction than did those with lower compliance rates (figure 4). Of the eight trials (n=4508) that reported a compliance rate of 80% or more, the treatment was associated with a 24% risk reduction in fractures of all types (p<0·0001). We found no relation between compliance and an increased dose of calcium (p=0·57).

We found that the treatment effect was similar across fracture sites and sex, all showing a risk reduction of 12–13% (table 2). Similarly, a history of previous fractures did not change the treatment effect (p=0·85).

The addition of vitamin D to calcium did not change treatment effect significantly (figure 5). The difference in RR between calcium-only supplementation and calcium with vitamin D combination was very small (0·87 *vs* 0·90) and was not significant (p=0·63).

People with low vitamin D serum concentration (25-(OH)-vitamin D_3<25 nmol/L), had a greater risk reduction compared with those whose serum 25-(OH)-vitamin D_3 was normal (RR 0·86 *vs* 0·94); however, the result was not significant (p=0·06). Results were the same at 35 nmol/L. At an even higher cut-off point (50 nmol/L) there was no longer a difference in risk reduction (RR 0·82 *vs* 0·89; p=0·46). The treatment effect was greater in people who were institutionalised than in those living in the community (RR 0·76 *vs* 0·94; p=0·003).

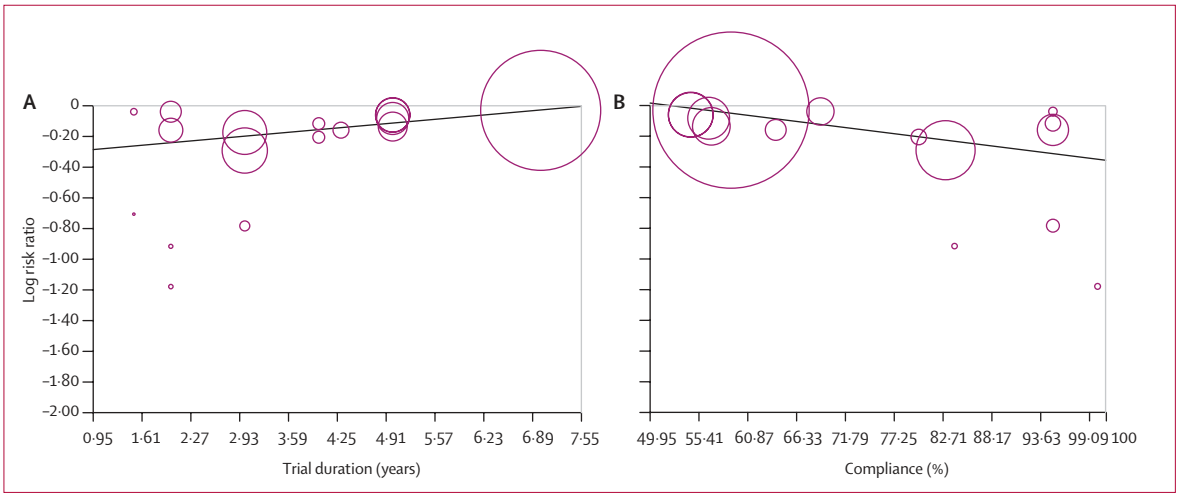

Figure 6: **Meta-regression analysis of trial duration (A) and compliance (B)**
Size of the circles corresponds to the weight of each study.

The treatment effect was also greater in participants whose daily calcium intake was low (defined as less than 700 mg per day) (0·80 *vs* 0·95; p=0·008). There was a non-significant association between being institutionalised and having a low daily calcium intake (p=0·08).

The treatment effect was significantly better in trials with high compliance rate than in those with a rate lower than 80% (table 2). The treatment effect was also best with calcium doses of 1200 mg or more, or vitamin D doses of 800 IU or more (table 2).

Age was an important determinant of treatment efficacy. Risk reduction was less in people aged 50–70 years than in those who were older than 70 years (table 2). For people older than 70 years, the extent of risk reduction was statistically significant. As we expected, a lesser reduction in bone-mineral density was associated with a greater treatment effect (table 2).

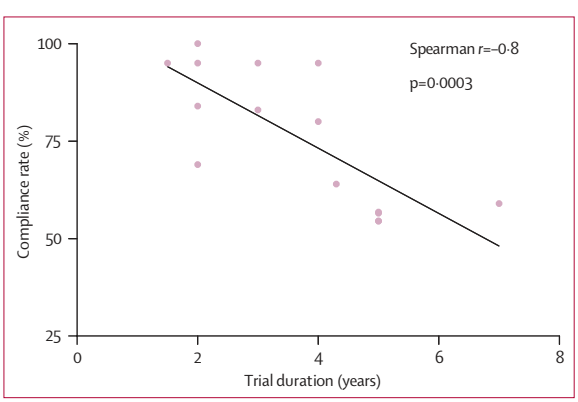

Figure 7: **Relation between compliance rate and trial duration**

	Slope (95% CI)	p value
Trial duration	0·045 (0·02 to 0·07)	0·002
Compliance	0·007 (0·003 to 0·01)	0·001
Age	−0·01 (−0·013 to −0·003)	0·002
Bodyweight	0·01 (0·004 to 0·017)	0·002
Baseline risk	−0·01 (−0·02 to −0·002)	0·02

Table 3: **Summary of metaregression analysis**

We used metaregression analysis to examine the variation in treatment effect (reduction in fracture risk) attributable to prespecified variables. We noted that a smaller treatment effect was associated with an increased trial duration and lower participant compliance (figure 6). There was a strong correlation between trial duration and participant compliance, with reduced compliance recorded in trials of long duration (figure 7), suggesting that the reduced treatment effect in these trials may well have been related to poor participant compliance. We also found a greater treatment effect with older patients, a lower bodyweight, and a higher baseline risk (table 3).

Egger's regression analysis showed that publication bias was present (p=0·01; figure 8). We therefore used the fail-safe methods to estimate the number of potential missing studies needed to significantly change the conclusion of our findings. This analysis showed that, to nullify our estimated effect size, 100 studies with non-significant findings or 22 studies showing harmful treatment effect would be needed. In view of the fact that there have been no more than 30 studies published over the past 15 years, it is highly improbable that such a large number of similar studies would have gone unpublished or have been missed by our extensive search strategy. Furthermore, the missing studies are likely to be small, the effect of which is probably very negligible.

The influence analysis showed that no particular trial affected the pooled effect size (figure 9). Cumulative meta-analysis showed that the evidence was consistent over time (figure 10). The point estimates and their CIs stabilised over the past year (2006) and remained unchanged, even when three large studies[8,9,31] were added. This result suggested that the addition of any future

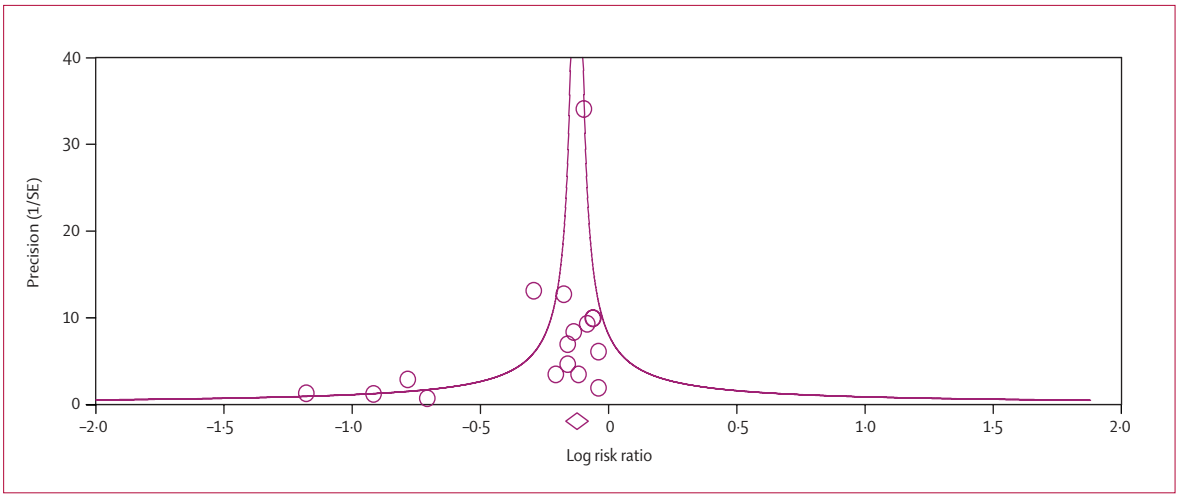

Figure 8: **Funnel plot to assess publication bias**
Circles indicate individual studies. Diamond indicates summary estimate. SE=standard error.

study, even if it included many thousands of participants, would add little to the cumulative body of evidence.

In a sensitivity analysis, we analysed separately the studies that did not meet methodological criteria and compared them with studies of better quality. For each of the four criteria, studies of lesser quality showed a slightly more optimistic estimate of the RR than did those of high quality (table 4). However, the results did not differ significantly. The κ statistic was 0·882, suggesting good agreement between reviewers in data extraction.

Discussion

Our meta-analysis has shown that calcium supplementation, alone or in combination with vitamin D, is effective in the preventive treatment of osteoporotic fracture. Over an average treatment duration of 3·5 years, the risk of fracture was reduced and was accompanied by a reduction of bone loss at the hip and spine. The fracture risk reduction was greater in individuals who were elderly, lived in institutions, had a low bodyweight, had a low calcium intake, or were at a high baseline risk than it was in others. The treatment effect was consistent irrespective of sex, fracture sites, or history of previous fracture. Moreover, the treatment was similarly effective whether the person used calcium or calcium in combination with vitamin D supplementation. However, the treatment was less effective if compliance was poor. For calcium-only supplementation, a minimum dose of 1200 mg is needed for best therapeutic effect. For calcium in combination of vitamin D supplementation, a minimum dose of 800 IU of vitamin D is recommended.

Although addition of vitamin D supplementation was not shown to offer additional risk reduction over and above the use of calcium alone, a significant difference was observed between the effects of different vitamin D doses. This discrepancy could be due to statistical artifact. However, we would like to point out that our analysis was

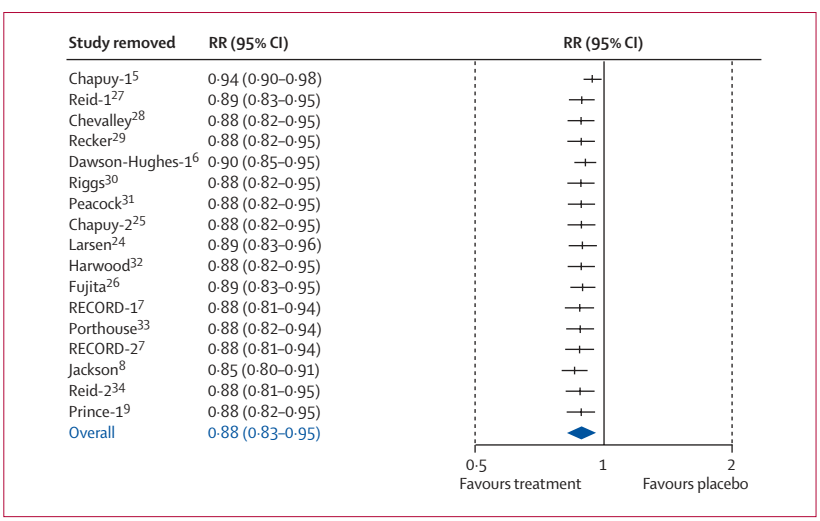

Figure 9: **Influence analysis**

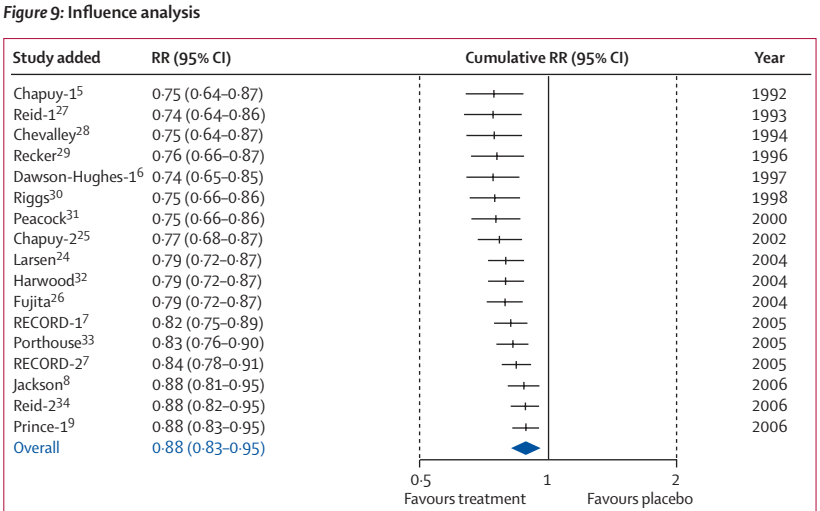

Figure 10: **Cumulative meta-analysis**

	Studies reported criteria RR (95% CI)	Studies not reported criteria RR (95% CI)	p value
Randomisation	0·89 (0·82–0·98)	0·84 (0·74–0·95)	0·12
Allocation concealment	0·91 (0·82–1·01)	0·87 (0·78–0·96)	0·79
Blind assessment of outcome	0·89 (0·80–0·98)	0·86 (0·77–0·95)	0·15
Loss to follow-up*	0·88 (0·81–0·95)	0·89 (0·73–1·08)	0·69

*Loss to follow-up was regarded as significan t if 30% or more.

Table 4: **Sensitivity analysis by methodological criteria**

limited by the scarcity of data for vitamin D doses higher than 800 IU. It is possible that vitamin D does have a beneficial effect when the dose is large enough (ie, >800 IU). In the absence of such data, we recommend that if vitamin D is to be used as an adjunct supplementation to calcium, its dose should be at least 800 IU or more.

Our study on calcium is a large and exhaustive meta-analysis. An earlier meta-analysis by Shea and colleagues[10] included studies on calcium-only supplementation. However, it was restricted to postmenopausal women and had a substantially smaller sample size (n=1806) than our study. Two other meta-analyses[12,13] included studies on calcium in combination with vitamin D supplementation. The first, by Avenell and co-workers,[12] had only 10 376 participants.[12] The more recent trial, by Boonen and colleagues,[13] was restricted because it reported only data for hip fracture and had omitted a large trial[24] of 9605 people. By contrast, our study reported on fracture rate and bone-mineral density, and contained all relevant trials, including those omitted by previous meta-analyses. It therefore includes all the available evidence for the efficacy of calcium supplementation in the treatment of osteoporotic fracture.

Poor compliance is a major obstacle to obtaining the full benefit of calcium supplementation. When we analysed trials with a compliance rate of at least 80% separately, the risk reduction was doubled. We also noted that there was a substantially greater number of people enrolled in trials that reported a low compliance rate than in those with a high compliance rate. Therefore, the pooled risk reduction we reported is probably an underestimation of the treatment efficacy; the risk reduction associated with a high compliance rate may show more accurately the therapeutic efficacy of calcium.

We noted a greater treatment effect in individuals with low dietary calcium intake than in those whose dietary intake was high. This result is important since inadequate dietary calcium is prevalent throughout the world, especially in elderly people and women.[47,48] It is also consistent with what is understood about the pathophysiology of osteoporosis. After midlife there is an age-related yearly loss of bone in both sexes of about 1%,[49] which is accelerated to 2% for up to 14 years in women around the age of menopause.[50] This bone loss is characterised by the loss of calcium from bone. To keep bone loss to a minimum, increased dietary calcium is needed to offset the continuing loss. It is possible that the role of supplementation might diminish with increased intake. It can be difficult, however, for many elderly people to maintain a calcium intake above 1000 mg per day, especially when energy intake falls with increasing age.

The treatment effect was previously reported to be higher for patients in institutionalised care,[12] and this result was confirmed by our study. Some investigators have suggested that the greater treatment effect could be attributed to an increased prevalence of vitamin D deficiency in elderly people who are institutionalised.[13,51] Although a lower concentration of serum 25-(OH)-vitamin D_3 was noted in institutionalised people in our study, it is unlikely to be the only cause. On the basis of the strong relation between treatment effect and compliance, as shown by our data, the supervised care in institutions could feasibly have contributed to increased compliance, and hence a greater treatment effect. In fact, of the three studies using institutionalised patients, two reported the presence of nursing staff to ensure compliance[5,25] and one was undertaken in a hospital[26] in which drugs were routinely given by nurses.

Our study has implications for both clinicians and policymakers. The estimated number needed to treat shows that 63 patients will need to be treated over 3·5 years to prevent one fracture. This result is comparable to other preventive treatments such as statins, in which 40 people would need to be treated for 5 years to prevent one major cardiovascular event,[52] and it is substantially better than aspirin treatment, in which more than 270 participants would need to be treated for 6 years to prevent one cardiovascular event.[53] Furthermore, the number needed to treat decreased to 30 or fewer in individuals who were elderly, had low dietary calcium intake, or were compliant with calcium supplementation.

On the basis of our recommended minimum dose of 1200 mg of calcium or 800 IU of vitamin D, many formulations of calcium or combined calcium with vitamin D tablets that are available contain insufficient quantities of the active ingredients. In view of the large number of calcium supplementation tablets sold worldwide, adequate dosage is an important issue to address if best possible public-health benefits are to be realised. Our study also has implications for future studies of cost-effectiveness. Although our findings confirmed that therapeutic effect generally increased with age, it also suggested that the effect becomes much greater and clinically significant after the age of 70 years. The cost-effectiveness of selecting a specific age group, such as people aged 70 years or older, will therefore need to be addressed in future studies.

Our study has several strengths. First, the large number of patients provided us with adequate statistical power to

detect a treatment effect, whereas most individual trials were unable to do so because of their small sample size. Second, we undertook extensive analysis in exploring important variables that could affect clinical management, hence providing clinicians with an evidence base for their decisionmaking. Third, our results are robust and consistent, as shown by our extensive search for potential bias by use of influence analysis, publication bias analysis, cumulative meta-analysis, and sensitivity analysis.

Our study also has limitations. We have excluded trials that studied calcium as part of a dietary intake or nutritional supplementation regimen. However, these studies have been reviewed elsewhere.[54] We did not include any observational studies, in which evidence suggests an association between low dietary calcium intake and increased fracture risk, since these studies were beyond the scope of our review. Similarly, there were trials investigating the use of calcium in secondary osteoporosis, or patients with major comorbidities, which we omitted since our entry criteria excluded them. Furthermore, there were no men-only trials. Hence, our findings on the effect of sex on treatment efficacy were inferred indirectly by comparison of women-only to mixed-sex trials. Additionally, we did multiple comparisons in our subgroup analysis. Caution is therefore needed in the interpretation of our findings, in view of the increased likelihood of type 1 error. Lastly, we were unable to assess the interaction of physical exercise on the treatment effect, because trials reporting physical exercise used widely differing units, so we could not calculate a summary estimate.

Contributors

BMPT had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. AB and CN organised the study concept and design. BMPT acquired, analysed, and interpreted the data. BMPT, GDE, CN, CS, and AB drafted the manuscript. BMPT did statistical analysis.

Conflict of interest statement

We declare that we have no conflict of interest.

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