Calcium intake and risk of fracture: systematic review

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ABSTRACT

OBJECTIVE

To examine the evidence underpinning recommendations to increase calcium intake through dietary sources or calcium supplements to prevent fractures.

DESIGN

Systematic review of randomised controlled trials and observational studies of calcium intake with fracture as an endpoint. Results from trials were pooled with random effects meta-analyses.

DATA SOURCES

Ovid Medline, Embase, PubMed, and references from relevant systematic reviews. Initial searches undertaken in July 2013 and updated in September 2014.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Randomised controlled trials or cohort studies of dietary calcium, milk or dairy intake, or calcium supplements (with or without vitamin D) with fracture as an outcome and participants aged >50.

RESULTS

There were only two eligible randomised controlled trials of dietary sources of calcium (n=262), but 50 reports from 44 cohort studies of relations between dietary calcium (n=37), milk (n=14), or dairy intake (n=8) and fracture outcomes. For dietary calcium, most studies reported no association between calcium intake and fracture (14/22 for total, 17/21 for hip, 7/8 for vertebral, and 5/7 for forearm fracture). For milk (25/28) and dairy intake (11/13), most studies also reported no associations. In 26 randomised controlled trials, calcium supplements reduced the risk of total fracture (20 studies, n=58 573; relative risk 0.89, 95% confidence interval 0.81 to 0.96) and vertebral fracture (12 studies, n=48 967. 0.86, 0.74 to 1.00) but not hip (13 studies, n=56 648; 0.95, 0.76 to 1.18) or forearm fracture (eight studies, n=51 775; 0.96, 0.85 to 1.09). Funnel plot inspection and Egger's regression suggested bias toward calcium supplements in the published data. In randomised controlled trials at lowest risk of bias (four studies, n=44 505), there was no effect on risk of fracture at any site. Results were similar for trials of calcium monotherapy and co-administered calcium and vitamin D. Only one trial in frail elderly women in residential care with low dietary calcium intake and vitamin D concentrations showed significant reductions in risk of fracture.

CONCLUSIONS

Dietary calcium intake is not associated with risk of fracture, and there is no clinical trial evidence that increasing calcium intake from dietary sources prevents fractures. Evidence that calcium supplements prevent fractures is weak and inconsistent.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Older men and women are recommended to take at least 1000-1200 mg/day of calcium to prevent fractures, and many people take calcium supplements to meet these recommendations

Recent trials have raised concerns about the safety of calcium supplements

Experts have therefore encouraged older people to increase their calcium intake through food rather than by taking supplements, but it is not known whether increasing dietary calcium intake prevents fractures

WHAT THIS STUDY ADDS

Dietary calcium intake is not associated with risk of fracture, and there is currently no evidence that increasing calcium intake prevents fractures

Calcium supplements have small inconsistent benefits on fracture prevention

Increasing calcium intake, through calcium supplements or dietary sources, should not be recommended for fracture prevention

Introduction

Older men and women are recommended to take at least 1000-1200 mg/day of calcium for bone health and prevention of fractures.[1] The average intake in the diet in Western countries is 700-900 mg/day, and lower in Asia and Africa, meaning that most older people would need to take calcium supplements to meet these recommendations. These guidelines for calcium intake have been widely implemented, and, in some Western countries, more than 30-50% of older women take calcium supplements.[2-5] Clinical trials of calcium supplements at doses of 1000 mg/day, however, have reported adverse effects, including cardiovascular events,[6-8] kidney stones,[9] and hospital admissions for acute gastrointestinal symptoms.[10] Consequently, older people have been encouraged to improve bone health by increasing their calcium intake through food rather than by taking supplements.[11] This advice assumes that increasing dietary calcium intake to the recommended level of >1200 mg/day prevents fractures without causing the adverse effects of calcium supplements.

We assessed the evidence supporting the recommendation to increase dietary calcium intake to prevent fractures and compared the anti-fracture efficacy of increasing calcium intake through dietary sources with the anti-fracture efficacy of calcium supplements. We undertook a systematic review of studies of dietary sources of calcium or calcium supplements in older adults (>50) with fracture as an endpoint. We primarily focused on the results of randomised controlled trials, but when insufficient evidence from such trials was available, we considered results of observational studies.

Methods

Literature search

In July 2013, we searched Ovid Medline and Embase since inception for English language studies of calcium, milk, or dairy intake, or calcium supplements

that reported on a broad range of skeletal and non-skeletal endpoints including fracture. The full text of the search was designed with assistance from a professional librarian and is shown in appendix 1. From this search, we also identified 120 systematic reviews or meta-analyses on these topics and hand searched these articles, any other articles included in our review, and recent review articles on fracture risk for other relevant articles. In September 2014, we updated the results with a focused search (no language restrictions) of PubMed (appendix 1) and Embase for studies with fracture or bone mineral density as an endpoint.

Study selection

We included randomised controlled trials and cohort, case-control, or cross sectional studies with fracture as an outcome in which participants were aged >50 at baseline, or for cohort studies, where most follow-up occurred in participants aged >50. We excluded studies where most participants had a major systemic pathology at baseline other than osteoporosis, such as renal failure or malignancy. We included studies of calcium supplements used in combination with other treatment provided that the other treatment was given to both arms (for example, calcium plus oestrogen *v* placebo plus oestrogen), and included studies of co-administered calcium and vitamin D supplements (CaD). We classified milk, dairy products, and dietary calcium intake from food as dietary sources of calcium. We treated hydroxyapatite as a dietary source of calcium, though it is not a food because hydroxyapatite supplements are made from bone and contain other minerals, hormones, protein, and amino acids in addition to calcium. Several cohort studies reported analyses of calcium intake and fracture risk in more than one publication. We included the results from the publication that reported the longest duration of follow-up for the cohort. Superseded publications are listed in appendix 1. Titles and abstracts were screened by one author (WL or MJB) and the full text of potentially relevant studies reviewed by two authors independently (WL, MJB, VT, or SB). The flow of articles is shown in appendix 2.

Data extraction

From each study we extracted information on characteristics of participants, study design, funding source and conflicts of interest, and numbers of participants with total, hip, forearm, and vertebral fractures. When data were reported for non-vertebral fracture but not total fracture, we treated non-vertebral fractures as total fractures. A single author (WL, MJB, or VT) extracted data, which were checked by a second author (MJB or SB). Risk of bias was assessed as recommended in the Cochrane Handbook,[12] and we planned a subgroup analysis for each fracture outcome stratified by risk of bias. Any discrepancies were resolved through discussion.

Incorporation of studies

In one randomised controlled trial[13] it was not clear whether the data reported were total number of fractures or number of participants with a fracture. Another was described as a cluster trial of three different fracture prevention programmes: CaD, an environmental programme, or both.[14] Treatment was randomly assigned to each cluster, however, which was based on location of residence and there were only four clusters (one cluster per treatment group), so in effect participants were quasi-randomised by location. The CaD and environmental programmes included an intervention—a home visit by a nurse to review treatment—which was not offered to the control group. Thus, the best estimate of the effect of CaD in the study is a comparison of both programmes (CaD and environmental) with the environmental programme, whereas the comparison of CaD versus no CaD assesses a multifactorial intervention. For these reasons, we considered these two randomised controlled trials to be at high risk of bias and included them only in sensitivity analyses. One trial was described in the methods as a cluster randomised controlled trials but was analysed as individually randomised.[15 16] We analysed the trial as a cluster trial in the primary analyses, using the approach recommended in the Cochrane handbook[12] with an intracluster correlation coefficient of 0.023[17 18] and an estimated average cluster size of 3.5. In sensitivity analyses we analysed the trial as individually randomised. In one trial[9] there was an interaction between oestrogen treatment, CaD treatment, and risk of hip fracture.[19] In women taking oestrogen, CaD reduced risk of hip fracture (relative risk 0.59, 95% confidence interval 0.38 to 0.93), whereas in women not taking oestrogen, CaD had no effect on risk (1.20, 0.85 to 1.69).[19] We included the data for all participants in the trial in the primary analyses but used results of participants not taking oestrogen from this reanalysis in sensitivity analyses.

Statistics

For randomised controlled trials, data were pooled with random effects meta-analyses and heterogeneity was assessed with the I^2 statistic (I^2 >50% was considered significant heterogeneity). We used funnel plots and Egger's regression model to assess for bias. For the primary analyses, we assessed the effects of calcium with or without vitamin D, and in subgroup analyses we assessed calcium monotherapy and co-administered CaD separately. Randomised controlled trials of CaD versus vitamin D, in which the groups differed only in treatment by calcium, were included in subgroup analyses of calcium monotherapy, while trials of CaD versus placebo or controls were included in the CaD subgroup analyses. For trials with factorial designs or more than two arms, in which multiple comparisons can occur, we included all available data from the study. Thus, for factorial randomised controlled trials we included all study arms that allowed a comparison of calcium versus no calcium in the primary analyses and the calcium monotherapy subgroup analysis, but only arms comparing CaD with controls in the CaD subgroup analysis. For multi-arm

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Table 1 | Study design and selected baseline characteristics of randomised controlled trials of calcium intake that reported on fractures. Data are means (SD) unless stated

Trial	Design	Calcium dose (mg/day)	Vitamin D dose	Duration	Care setting	Primary endpoint	Participants Ca/controls	Age (years)	% Female
Dietary calcium trials									
Chevalley 1994[21]	3 arm RCT OMC/D; CaD; P/D	800	300 000 IU IM stat	18 m	Community	BMD	62/31	72 (6)	88
Lau 2001[20]	2 arm RCT milk powder; control	800	240 IU/d	2 y	Community	BMD	100/100	57 (6)	100
Calcium supplement trials									
Inkovaara 1983[13]	2*3 factorial RCT Ca; D; M; CaD; CaM; DM; CaDM; P	1200	1000 IU/d	12 m	Residential care	Biochemistry	171/156	80 (7)	83
Hansson 1987[73]	4 arm RCT 30 mg NaF/Ca; 10 mg NaF/Ca; Ca; P	1000	—	3 y	Community	BMC	25/25	66 (6)	100
Chapuy 1992,1994[15 16]	2 arm cluster RCT CaD; P	1200	800 IU/d	3 y	Residential care	Fracture	1634/1636	84 (6)	100
Reid 1993,1995[74 75]	2 arm RCT Ca; P	1000		4 y	Community	BMD	68/67	58 (5)	100
Chevalley 1994[21]	3 arm RCT CaD; OMC/D; P/D	800	300,000 IU IM stat	18 m	Community	BMD	62/31	72 (6)	88
Recker 1996[76]	2 arm RCT Ca; P	1200	—	4.3 y	Community	Fracture	95/102	73 (7)	100
Dawson-Hughes 1997[77]	2 arm RCT CaD; P	500	700 IU/d	3 y	Community	BMD	187/202	71 (5)	55
Riggs 1998[78]	2 arm RCT Ca; P	1600	—	4 y	Community	BMD	119/117	66 (3)	100
Baron 1999[79 80]	2 arm RCT Ca; P	1200	—	4 y	Community	Colorectal adenoma	464/466	61 (9)	28
Ruml 1999[81]	2 arm RCT Ca; P	800	—	2 y	Community	BMD	29/34	52 (4)	100
Peacock 2000[82]	3 arm RCT Ca; 25OHD; P	750	—	4 y	Community	BMD	126/135	74 (8)	72
Chapuy 2002[83]	3 arm RCT CaD; CaD; P	1200	800 IU/d	2 y	Residential care	25OHD	389/194	85 (7)	100
Avenell 2004[84]	2*2 factorial RCT Ca; D; CaD; control	1000	800 IU/d	46 m	Community	Compliance/ retention	64/70	77 (5)	82
Fujita 2004[85]	3 arm RCT Ca; Ca; P	900	—	2 y	Residential care	BMD	38/20	80 (7)	100
Harwood 2004[86]	4 arm RCT CaD; CaD; D; control	1000	300 000 IU IM stat or 800 IU/d	12 m	Community	Biochemistry	75/75	81	100
Larsen 2004[14]	4 arm cluster RCT Env; CaD; Env/CaD; control	1000	400 IU/d	42 m	Community	Fracture	4957/4648	75	60
Grant 2005[87]	2*2 factorial RCT Ca; CaD; D; P	1000	800 IU/d	45 m	Community	Fracture	2617/2675	77 (6)	85
Porthouse 2005[88]	2 arm RCT CaD; control	1000	800 IU/d	25 m	Community	Fracture	1321/1993	77 (5)	100
Jackson 2006[9]	2 arm RCT CaD; control	1000	400 IU/d	7 y	Community	Fracture	18176/18106	62 (7)	100
Prince 2006[89]	2 arm RCT Ca; control	1200	—	5 y	Community	Fracture	730/730	75 (3)	100
Reid 2006[90]	2 arm RCT; Ca; control	1000	—	5 y	Community	Fracture	732/739	74 (4)	100
Bolton-Smith 2007[91]	2*2 factorial RCT CaD; CaD/vit K; vit K; P	1000	400 IU/d	2 y	Community	BMD	62/61	68 (6)	100
Bonnick 2007[92]	3 arm RCT CaD/alend; CaD; Alend/D	1000	—	2 y	Community	BMD	282/281	66 (9)	100
Reid 2008[93]	3 arm RCT Ca; Ca; P	600 or 1200	—	2 y	Community	BMD	216/107	56 (10)	0
Salovaara 2010[94]	2 arm RCT CaD; control	1000	800 IU/d	3 y	Community	Fracture	1718/1714	67 (2)	100
Sambrook 2012[18]	3 arm cluster RCT Ca/UV; UV; control	600	UV exposure	1 y	Residential care	Falls	207/190	86 (6)	69

RCT=randomised controlled trial; OMC=ossein-mineral complex (hydroxyapatite); D=vitamin D; CaD=co-administered calcium and vitamin D; P=placebo; Ca=calcium; M=methanedione; NaF=sodium fluoride; BMC=bone mineral content; BMD=bone mineral density; IM=intramuscular; 25OHD=25-hydroxyvitamin D; Env=environmental programme; vit K=vitamin K; alend= alendronate; UV=ultraviolet light.

randomised controlled trials, we pooled data from the separate treatment arms for the primary analyses, but each treatment arm was used only once. We undertook analyses of prespecified subgroups (risk of bias, calcium monotherapy versus CaD, participants living in the community versus residential care, and baseline dietary calcium intake <800 mg/day) with a random effects model and performed a test for interaction between subgroups. Sensitivity analyses were performed to explore the effects of incorporating different study designs and risk of bias. All tests were two tailed and P<0.05 was considered significant. All analyses were performed with Comprehensive Meta-Analysis (Version 2, Biostat, Englewood, NJ, USA).

For prospective cohort studies, authors reported their data in four different ways: the risk of fracture by group with the cohort divided into two to five groups by baseline dietary intake; pooled risk of fracture per unit of dietary intake; mean baseline dietary intake in individuals with or without subsequent fracture; or a written description of any association. We used only one association from each study for each fracture outcome with priority assigned in the order listed. These four different types of data cannot be combined in a meta-analysis and therefore we did not pool the results of different studies. Instead, we assessed whether there was an association between dietary intake and risk of fracture for each study. We classified associations into four groups: no association, inverse association (where a higher intake was associated with a lower risk of fracture, or a lower intake with a higher risk), a positive association (where a higher intake was associated with a higher risk of fracture or a lower intake with a lower risk), or a U shaped association (where both higher and lower intakes were associated with a higher risk of fracture). We considered associations to be present when there were significant differences between mean baseline dietary intakes (assessed by *t* tests either reported in the paper or calculated post hoc with OpenEpi; www.OpenEpi.com) or when the confidence interval for a group excluded 1. For studies that reported data from three or more groups of dietary intake, we assessed the results for the group furthest from the reference group. Thus, when the reference group had the lowest dietary intake, we assessed results from the group with the highest intake; when the reference group had the highest dietary intake, we assessed results from the group with the lowest intake; and when the reference group had intermediate dietary intake, we assessed results from the groups with both highest and lowest intake.

Results

Dietary sources of calcium

Randomised controlled trials

We identified two randomised controlled trials of dietary sources of calcium: milk powder in one (n=200, calcium dose 800 mg/day, vitamin D dose 240 IU/day)[20] and a preparation of hydroxyapatite in the other (n=62, calcium dose 800 mg/day).[21] Table 1 and table A in appendix 3 show the study designs and selected baseline characteristics. For the randomised controlled trial of milk powder, there was one fracture in the milk group and three in the controls (relative risk 0.33, 95% confidence interval 0.04 to 3.2; P=0.34). For the trial of the hydroxyapatite preparation, fracture data were not reported separately for the hydroxyapatite arm (n=31 participants) but were reported for the 62 participants receiving hydroxyapatite or calcium supplements and are included in the analyses of calcium supplements.

Cohort studies

As there were too few randomised controlled trials of dietary calcium intake that reported fracture to draw conclusions, we analysed observational studies. We identified 50 publications[22-71] from 44 cohort studies reporting relations between dietary calcium (n=37), milk (n=14), dairy intake (n=8), or calcium supplements (n=11) and fracture outcomes. There were sufficient cohort studies to analyse, so we did not analyse case-control or cross sectional studies, which are considered a lower level of evidence. Table 2 and table C in appendix 3 show the study design and selected characteristics of the cohort studies.

Tables 3-5 and tables E-F in appendix 3 summarise the results of these cohort studies. For dietary calcium, 14/22 studies (32 853 with fracture/291 273 participants) reported no relation between calcium intake and total fracture (table 3), 17/21 no relation with hip fracture (2629 with fracture/329 414 participants) (table 4), 7/8 no relation with vertebral fracture (711 with fracture/54 140 participants) (table 5), and 5/7 no relation with forearm fracture (1065 with fracture/65 268 participants) (table 5). Thus, 43 of the 58 (74%) reported associations between dietary calcium intake and fracture outcomes were neutral. When relations were reported, they were usually inverse (13/15 associations), with one study describing a positive relation and one study a U shaped relation. Of these 15 associations, 14 reported a numerical relative risk estimate, and 11 of these 14 estimates were between 0.5 and 2.0, which are considered weak associations in observational studies.[72] For milk and dairy intake (tables D and E in appendix 3), nearly all studies reported no association with fracture risk, with 25/28 neutral associations for milk intake and fracture risk and 11/13 for dairy intake.

Calcium supplements

Randomised controlled trials

We identified 26 randomised controlled trials (n=69 107 participants) of calcium supplements that reported fracture outcomes.[9 13-16 18 21 73-94] Table 1 and table A in appendix 3 shows the study design and selected baseline characteristics of the randomised controlled trials. Fourteen studied calcium monotherapy, eight studied CaD, and four were multi-arm or factorial studies of both agents. Twenty trials used a dose of ≥1000 mg/day of calcium; 21 were in individuals living in the community; 15 had a duration of three or more years; in 16, the mean age of participants at baseline was ≥70; in

Table 2 | Study design and selected characteristics of cohort studies reporting fractures. Data are mean (SD) or range unless stated. For dietary calcium, milk, and dairy intake, and calcium supplement, "yes" indicates data reported for this variable in article

Author	No in group	% Female	Duration	Age (years)	Dietary calcium intake	Milk intake	Dairy intake	Calcium supplement	No with fracture			
									Total	Hip	Vertebra	Forearm
Riggs 1982[22]	72	100	5 y	64	—	—	—	Yes	—	—	107*	—
Holbrook 1988[23]	957	55	14 y	50-79	Yes	—	—	—	—	33	—	—
Wickham 1989[24]	1419	49	15 y	≥65	Yes	—	—	—	—	44	—	—
Paganini-Hill 1991[25]	13 649	NS	7 y	73	Yes	—	—	Yes	—	418	—	—
Looker 1993[26]	2226†	100	14.6 y	50-74	Yes	—	—	—	—	122	—	—
Huang 1996[27]	2513†	100	13.4 y	62 (9)	—	—	Yes	—	—	130	—	—
Cumming 1997[28]	9704	100	6.6 y	72	Yes	Yes	—	Yes	1950	332	389	467
Fujiwara 1997[29]	4573	65	14 y	59 (12)	—	Yes	—	—	—	55	—	—
Meyer 1997[30]	39 787	50	11.4 y	47 (5)	Yes	Yes	—	—	—	213	—	—
Owusu 1997[31]	43 063	0	8 y	54 (10)	Yes‡	Yes	—	Yes‡	—	56	—	201
Mussolino 1998[32]	2879†	0	22 y	61	Yes	—	—	—	—	71	—	—
Munger 1999[33]	32 050	100	3.3 y	61 (4)	Yes	Yes	Yes	Yes	—	44	—	—
Honkanen 2000[34]	11 798†	100	5 y	52 (3)	Yes	—	—	—	—	—	—	368
Huopio 2000[35]	3068†	100	3.6 y	53	Yes	—	—	—	257	—	—	—
Kato 2000[36]	6250	100	7.6 y	58	Yes	—	—	—	1025	—	—	193§
Nguyen 2001[37]	1844†	60	7.6 y	70 (7)	Yes	—	—	—	—	—	—	121
Dargent-Molina 2002[38]	1588	100	3.7 y	81	Yes	—	—	—	—	NS	—	—
Albrand 2003[39]	672	100	5.3 y	59	Yes	—	—		75	—	—	—
Feskanich 2003[40]	72 337	100	18 y	60	Yes	Yes	—	Yes		603	—	—
Michaelsson 2003[41]	60 689†	100	11 y	54	—	Yes	Yes	—	3986	1535	—	—
Melton 2003[42]	225	100	14 y	68	Yes	—	—	—	126	—	—	—
Roy 2003[43]	6575	52	3.8 y	63 (8)	—	Yes	—	—	—	—	224	—
van def Klift 2004[44]	3001	54	6.3 y	66 (7)	Yes	—	—	—	—	—	157	—
Kanis 2005[45]	39 563**	69	3.8 y	64	—	Yes	—	—	2469	413	—	—
Papaioannou 2005[46]	5143	100	3 y	63 (10)	Yes¶	—	—	—	280	—	34	—
Cauley 2007[47]	159 579	100	8 y	63 (7)	Yes¶	—	—	—	23 270	—	—	—
Diez-Perez 2007[48]	5146	100	3 y	72 (5)	Yes	—	—	—	311	49	—	104
Key 2007[49]	34 696	77	5.2 y	47	Yes	—	—	—	1898	—	—	—
Kung 2007[50]	1435	100	5 y	63 (8)	Yes	—	—	—	80	—	—	—
Lewis 2007[51]	5876	0	4.1 y	74	Yes¶	—	—	—	275	—	—	—
Nguyen 2007[52]	924†	100	10 y	69 (6)	Yes	—	—	—	221	24	76	—
Van Geel 2007[53]	2367	100	10 y	62 (7)	Yes	—	—	—	380	—	—	—
Dargent-Molina 2008[54]	36 217	100	8.4 y	56 (6)	Yes	—	—	Yes	2408	—	—	—
Meier 2008[55]	609†	0	5.8 y	73 (6)	Yes	—	—	—	113	27	55	—
Nieves 2008[56]	52 144	100	3.3 y	65	Yes	—	—	—	2205	337	—	—
Koh 2009[57]	63 154	56	7.1 y	56	Yes¶	—	—	Yes	—	968	—	—
Nakamura 2009[58]	75 879	54	10 y	52 (8)	Yes	Yes	—	—	—	—	364	—
Thomas-John 2009[59]	257	0	3 y	77 (4)	—	—	Yes	Yes	41	—	—	—
Gronskag 2010[60]	4851	100	9.3 y	73	—	Yes	—	—	—	391	—	—
Benetou 2011[61]	29 122	64	8 y	64	Yes	—	Yes	—	—	275	—	—
Nakamura 2011[62]	773	100	5.5 y	75 (4)	Yes	—	—	—	51	—	—	—
Warensjo 2011[63]	61 433†	100	19 y	54	Yes	—	—	—	14 738	3871	—	—
Khan 2012[64]	12 528	NS	13-14 y	45-64	Yes	—	—	—	824	—	—	—
Rouzi 2012[65]	707	100	5.2 y	61 (7)	Yes	—	—	—	138	—	—	—
Feart 2013[66]	1482†	63	8 y	76 (5)	—	Yes	Yes	—	155	57	43	73
Prentice 2013[67]	46 892	100	7.2 y	50-79	—	—	—	Yes	6640	451	—	—
Samieri 2013[68]	1482†	63	8 y	76 (5)	Yes	—	—	Yes	155	—	—	—
Sahni 2013[69]	3212	56	12 y	55 (10)	—	Yes	Yes	—	—	43	—	—
Domiciano 2014[70]	707	64	4.3 y	73 (5)	—	—	Yes	—	—	—	111	—
Sahni 2014[71]	764	NS	11.6 y	77 (5)	—	Yes	—	—	—	97	—	—

NS=not stated, IF=funding by grants from independent funders; Ind=funded by grants from industry and/or run by industry.
*Data are number of vertebral fractures not number of participants with vertebral fractures.
†Reports from same cohort studies. Report with longest duration of follow-up and/or most number of fractures for each association included.
‡Reported total calcium intake divided into dairy and non-dairy intake. Dairy calcium intake treated as dietary intake, and non-dairy intake treated as supplemental calcium intake.
§Data for forearm and hip fracture not reported separately; includes 34 hip fractures.
¶Reported total calcium intake only. Treated as dietary calcium intake because most total calcium intake was from dietary sources.
**Individual patient meta-analysis of six cohort studies.

Table 3 | Association between dietary calcium intake and risk of total fracture in cohort studies

Study	Fracture*/ participants	Association	Groups	Risk or daily calcium intake†		Group 3 risk	Group 4 risk	Group 5 risk	Cut points between each group (mg/d)‡ or unit for pooled risk
				Group 1	Group 2				
Cauley 2007[47]	23 270/159 579	Nil	—	NR§	NR§	NR§	—	—	—
Lewis 2007[51]	275/5876	Nil	—	NR§	NR§	NR§	—	—	—
Albrand 2003[39]	75/672	Nil	2	824 (313)	804 (270)	—	—	—	No fracture; fracture
Nguyen 2007[52]	221/924	Nil	2	583 (284)	555 (300)	—	—	—	No fracture; fracture
Samieri 2013[68]	155/1482	Inverse	2	871 (439)	796 (398)	—	—	—	No fracture; fracture
Huopio 2000[35]	257/3068	Nil	—	1.10 (0.99 to 1.23)	—	—	—	—	Per quartile decrease
Melton 2003[42]	126/225	Inverse	—	1.29 (1.06 to 1.56)	—	—	—	—	Per SD decrease
Papaioannou 2005[46]	280/5143	Nil	—	1.005 (0.925 to 1.093)	—	—	—	—	Per 500 mg/d increase
Meier 2008[55]	113/609	Nil	—	1.43 (1.17 to 1.78)	—	—	—	—	Per SD (322 mg/d) decrease
Diez-Perez 2007[48]	311/5146	Inverse	2	1.92 (1.30 to 2.86)	1	—	—	—	250
Kung 2007[50]	80/1435	Inverse	2	3.1 (1.9 to 5.2)	1	—	—	—	400
Van Geel 2007[53]	380/2367	Nil	2	1.0 (0.8 to 1.2)	1	—	—	—	900
Khan 2012[64]	824/12 528	Inverse	2	1	0.75 (0.60 to 0.94)	—	—	—	Lowest quintile; highest quintile
Rouzi 2012[65]	138/707	Inverse	2	1.66 (1.08 to 2.53)	1	—	—	—	391
Cumming 1997[28]	1950/9704	Nil	4	1	1.0 (0.9 to 1.1)	0.9 (0.7 to 1.1)	0.9 (0.7 to 1.1)	—	400; 800; 1200
Kato 2000[36]	1025/6250	Nil	5	1	1.06 (0.9 to 1.3)	0.93 (0.8 to 1.1)	1.10 (0.9 to 1.3)	0.92 (0.8 to 1.1)	569; 689; 799; 949
Key (F>50 y) 2007[49]	888/NS	Inverse	5	1.53 (1.05 to 2.23)	1.31 (0.98 to 1.77)	1.10 (0.87 to 1.39)	1.05 (0.87 to 1.27)	1	525; 700; 900; 1200
Key (M) 2007[49]	343/7947	Nil	5	1.15 (0.63 to 2.09)	0.94 (0.59 to 1.49)	0.91 (0.62 to 1.32)	1.02 (0.76 to 1.37)	1	525; 700; 900; 1200
Dargent-Molina 2008[54]	2408/36 217	Nil	4	1	1.05 (0.94 to 1.19)	1.00 (0.89 to 1.13)	0.91 (0.80 to 1.03)	—	829; 995; 1201
Nieves 2008[56]	2205/52 144	Nil	3	1	0.94 (0.80 to 1.10)	0.92 (0.81 to 1.06)	—	—	500; 800
Nakamura 2011[62]	51/773	Nil	4	0.64 (0.29 to 1.41)	0.81 (0.39 to 1.69)	0.73 (0.32 to 1.64)	1	—	410; 544; 722;
Warensjo 2011[63]	14 738/61 433	Inverse	5	1.18 (1.12 to 1.25)	1.04 (0.98 to 1.10)	1	1.02 (0.96 to 1.07)	1.00 (0.95 to 1.06)	751; 882; 996; 1137

Nil=no association between calcium intake and risk of fracture; inverse=higher calcium intake associated with decreased risk of fracture or lower calcium intake associated with higher risk of fracture; SD=standard deviation; M=male; F=female; Q=quartile (values not reported in paper); NS=not stated.
*Number of participants with fracture.
†Hazard ratio or relative risk (95% CI) or mean (SD) mg/d.
‡For example, cut point of 250 indicates 2 groups of <250 and ≥250 mg/d; cut points of 400; 800; and 1200 indicate 4 groups <400; 400-799; 800-1199; ≥1200 mg/d.
§No numerical data were reported, but it was stated that there was no association between calcium intake and risk of fracture.

24 most participants were women; and in 10 of 19 randomised controlled trials that reported baseline dietary calcium intake, the level was <800 mg/day. Table B in appendix 3 shows our assessment of the risk of bias: three trials were assessed as low risk of bias, one as high risk of bias for hip fracture but low risk for other outcomes, nine as moderate risk of bias, and 13 as high risk of bias.

Figures 1-4 show that calcium supplements reduced the risk of total fracture (20 studies, n=58 573; relative risk 0.89, 95% confidence interval 0.81 to 0.96; P=0.004; fig 1) and vertebral fracture (12 studies, n=48 967; 0.86, 0.74 to 1.00; P=0.04; fig 3) but not hip fracture (13 studies, n=56 648; 0.95, 0.76 to 1.18; P=0.63; fig 2) or forearm fracture (eight studies, n=51 775; 0.96, 0.85 to 1.09; P=0.54; fig 4). With Egger's regression model and visual inspection of funnel plots, data seemed biased toward reduction in risk with calcium supplements for total (P=0.006), vertebral (P=0.002), and forearm fracture (P=0.06), raising the possibility of publication bias. Furthermore, the pooled effect estimates for all fracture outcomes seemed related to the risk of bias. Figures 1, 3 and 4 and table 2 show that the effect size was smallest and not significant for total, forearm, and vertebral fracture in the subgroup of studies at lowest risk of bias, and that results also differed by risk of bias for hip fracture (fig 2).

Table 6 shows the results of the prespecified subgroup analyses. There was no evidence of a difference in the results between the subgroups of calcium monotherapy or CaD, or between the subgroups based on residential status and baseline dietary calcium intake for total, vertebral or forearm fracture. Fig 1 and table 6 show that there were differences in all subgroup analyses for hip fracture, which were largely because of the results of a single large trial of CaD with a 23% reduction in hip fractures that was carried out in women living in residential care with a low dietary calcium intake and low vitamin D concentrations.[15 16] In all four subgroup analyses (risk of bias, calcium or CaD, residential status, and baseline dietary calcium intake), whichever subgroup this study was in had markedly different results to the other subgroup, in which there were non-significant increases in risk of hip fracture.

Table 7 shows the results of the sensitivity analyses. Inclusion of two randomised controlled trials at high risk of bias[13 14] and analysis of one cluster randomised controlled trial[15 16] as an individually randomised trial did not alter the results. We used the result from the reanalysis of the Women's Health Initiative restricting participants to those not using oestrogen (relative risk 1.20, 95% confidence interval 0.85 to 1.69)[19] instead of the result for the entire cohort (0.88, 0.72 to 1.07).[9] This had a modest effect, moving the results toward those of the trials at low risk of bias. We repeated our analyses excluding the influential trial with the outlying results.[15 16] The relative risk was 0.90 (0.82 to 0.98) for total fracture and 1.02 (0.78 to 1.34) for hip fracture.

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Table 4 | Association between dietary calcium intake and risk of hip fracture in cohort studies

Study	Fracture*/ participans	Association	Groups	Risk or daily calcium intake†		Group 3 risk	Group 4 risk	Group 5 risk	Cut points between each group (mg/d)‡ or unit for pooled risk
				Group 1	Group 2				
Dargent-Molina 2002[38]	NS/1588	Nil	—	NR§	NR§	NR§	NR§	NR§	—
Munger 1999[33]	44/32 050	Nil	2	842 (322)	778 (267)	—	—	—	No fracture; fracture
Nguyen 2007[52]	24/924	Nil	2	583 (284)	489 (367)	—	—	—	No fracture; fracture
Holbrook 1988[23]	33/957	Inverse	—	0.6	—	—	—	—	Per 198 mg/1000 kcal/d increase
Meier 2008[55]	27/609	Nil	—	1.32 (0.81 to 2.16)	—	—	—	—	Per SD (322mg/d) decrease
Benetou 2011[61]	275/29 122	Nil	—	1.02 (0.91 to 1.13)	—	—	—	—	Per quintile increase
Diez-Perez 2007[48]	49/5146	Inverse	2	2.52 (1.07 to 5.92)	1	—	—	—	250
Wickham 1989[24]	44/1419	Nil	3	0.7 (0.1 to 3.9)	0.9 (0.2 to 4.3)	1	—	—	641; 901
Paganini-Hill (F) 1991[25]	332/8600	Nil	3	1	1.02 (0.77 to 1.33)	1.11 (0.85 to 1.44)	—	—	280; 500;
Paganini-Hill (M) 1991[25]	86/5049	Nil	3	1	0.87 (0.50 to 1.51)	1.25 (0.75 to 2.08)	—	—	280; 500;
Looker 1993[26]	122/2226	Nil	4	1	0.86 (0.5 to 1.5)	1.03 (0.6 to 1.7)	0.72 (0.4 to 1.3)	—	300; 501; 776
Cumming 1997[28]	332/9704	Nil	4	1	1.0 (0.7 to 1.3)	0.8 (0.5 to 1.2)	0.9 (0.5 to 1.6)	—	400; 800; 1200
Meyer (F) 1997[30]	150/19 752	Nil	4	1	0.86 (0.55 to 1.35)	0.87 (0.56 to 1.35)	0.67 (0.42 to 1.08)	—	435; 569; 718
Meyer (M) 1997[30]	55/20 035	Nil	4	1	0.96 (0.46 to 2.00)	1.08 (0.53 to 2.21)	0.64 (0.28 to 1.45)	—	623; 823; 1030
Owusu 1997[31]	56/43 063	Nil	5	1	1.47 (0.65 to 3.28)	1.14 (0.50 to 2.64)	0.86 (0.35 to 2.13)	0.64 (0.24 to 1.69)	134; 248; 364; 591
Mussolino 1998[32]	71/2879	Nil	4	1	0.83 (0.42 to 1.63)	0.76 (0.34 to 1.66)	0.76 (0.32 to 1.79)	—	417; 680; 1033
Feskanich 2003[40]	603/72 337	Nil	5	1	1.13 (0.87 to 1.49)	1.29 (0.98 to 1.71)	1.04 (0.76 to 1.42)	1.08 (0.78 to 1.49)	500; 625; 750; 900
Nieves 2008[56]	337/52 144	Nil	3	1	0.89 (0.61 to 1.31)	0.87 (0.63 to 1.21)	—	—	500; 800
Koh (F) 2009[57]	692/35 241	Positive	4	1	1.16 (0.92 to 1.47)	1.36 (1.07 to 1.73)	1.45 (1.16 to 1.82)	—	259; 327; 425
Koh (M) 2009[57]	276/27 913	Nil	4	1	1.23 (0.90 to 1.69)	0.87 (0.60 to 1.27)	1.24 (0.86 to 1.79)	—	259; 327; 425
Warensjo 2011[63]	3871/61 433	U shaped	5	1.29 (1.17 to 1.43)	1.09 (0.98 to 1.21)	1	1.13 (1.01 to 1.26)	1.19 (1.06 to 1.32)	751; 882; 996; 1137

Nil=no association between calcium intake and risk of fracture; inverse=higher calcium intake associated with decreased risk of fracture or lower calcium intake associated with higher risk of fracture; SD=standard deviation; M=male; F=female; Q=quartile (values not reported in paper); NS=not stated.
*Number of participants with hip fracture.
†Hazard ratio or relative risk (95% confidence interval) or mean (SD) mg/d.
‡For example, cut point of 250 indicates 2 groups of <250 and ≥250 mg/d; cut points of 400; 800; and 1200 indicate 4 groups <400; 400-799; 800-1199; ≥1200 mg/d.
§No numerical data were reported, but it was stated that there was no association between calcium intake and risk of fracture.

Cohort studies

Table 2 and table C in appendix 3 show the study design and selected characteristics of the 11 cohort studies that reported associations between calcium supplements and fracture outcomes. Most studies reported no association between calcium use and fracture (table F in appendix 3). Of the 20 reported associations, 13 were neutral, five were positive, and two were inverse.

Discussion

There is insufficient evidence to assess the effect of increasing calcium intake in the diet from randomised controlled trials as only two small trials of dietary sources of calcium have reported fracture outcomes. Some 42 cohort studies, however, have assessed relation between dietary calcium intake, milk or dairy intake and fracture. Most analyses (≥75%) found no associations, and where there were relations reported, most relative risks were between 0.5 and 2.0, which are considered weak associations in observational studies.[72] The recommended dietary calcium intake for older adults is 1200 mg/day.[1] Most studies, however, did not report reduced risk of fracture in individuals with this level of calcium intake compared with lower intakes. Thus, observational research does not support a hypothesis of dietary "calcium deficiency" in which there are reductions in fracture risk from increasing dietary calcium intake across the range of intakes (<300->1200 mg/day) in studies in this review.

In 26 randomised controlled trials, calcium supplements reduced the risk of total fracture by 11% and vertebral fracture by 14% but had no effect on forearm or hip fracture. The results, however, were not consistent. There was no effect of calcium supplements on any fracture outcome in the largest trials at lowest risk of bias. Only one trial in frail elderly women in residential care with low dietary calcium intake and vitamin D concentrations showed significant reductions in fracture risk. Funnel plots were also asymmetric with more small-moderate sized studies than expected reporting risk reductions in total, vertebral, and forearm fracture with calcium supplements, raising the possibility of publication bias. Results from randomised controlled trials of calcium monotherapy were similar to those with CaD, with no evidence of additional benefit of vitamin D on risk. These results suggest that widespread untargeted use of calcium supplements in older individuals is unlikely to result in meaningful reductions in incidence of fracture.

Strengths and limitations

The strength of this review is its comprehensive nature, including both randomised controlled trials and observational studies, and assessment of four fracture outcomes: total, hip, vertebral, and forearm. An important limitation is the difficulty of identifying all cohort studies that reported relations between calcium intake and fracture risk. Many of the reports of cohort studies included in our review were not

Table 5 | Association between dietary calcium intake and risk of vertebral or forearm fracture in cohort studies

Study	Fracture*/ participants	Association	Groups	Risk or daily calcium intake†		Group 3 risk	Group 4 risk	Group 5 risk	Cut points between each group (mg/d)‡ or unit for pooled risk
				Group 1	Group 2				
Vertebral fracture									
van def Klift (M) 2004[44]	44/1377	Nil	2	1162 (399)	1148 (341)	—	—	—	No fracture; fracture
van def Klift (F) 2004[44]	113/1624	Nil	2	1108 (333)	1089 (305)	—	—	—	No fracture; fracture
Papaioannou 2005[46]	34/5143	Nil	2	1133 (681)	1274 (823)	—	—	—	No fracture; fracture
Nguyen 2007[52]	76/924	Nil	2	583 (284)	559 (292)	—	—	—	No fracture; fracture
Meier 2008[55]	55/609	Nil	—	1.08 (0.77 to 1.51)	—	—	—	—	Per SD (322 mg/d) decrease
Cumming 1997[28]	389/9704	Nil	4	1	1.2 (0.9 to 1.6)	1.2 (0.8 to 1.8)	1.5 (0.9 to 2.5)	—	400; 800; 1200
Nakamura (M) 2009[58]	NS/34 759	Nil	4	1.46 (0.82 to 2.61)	1.20 (0.68 to 2.09)	1.68 (1.02 to 2.74)	1	—	Q1; Q2; Q3; Q4
Nakamura (F) 2009[58]	NS/41 120	Inverse	4	1.92 (1.28 to 2.88)	1.30 (0.86 to 1.98)	1.50 (0.99 to 2.26)	1	—	Q1; Q2; Q3; Q4
Forearm fracture									
Nguyen (M) 2001[37]	21/739	Inverse	—	1.98 (1.00 to 3.58)	—	—	—	—	Per 300 mg/d decrease
Nguyen (F) 2001[37]	100/1105	Nil	—	1.01 (0.82 to 1.25)	—	—	—	—	Per 300 mg/d decrease
Diez-Perez 2007[48]	104/5146	Nil	2	1.52 (0.74 to 3.12)	1	—	—	—	250
Cumming 1997[28]	467/9704	Nil	4	1	1.0 (0.8 to 1.3)	1.4 (1.0 to 2.0)	0.9 (0.6 to 1.6)	—	400; 800; 1200
Owusu 1997[31]	201/43 063	Nil	5	1	1.01 (0.66 to 1.55)	0.75 (0.47 to 1.20)	1.08 (0.70 to 1.68)	1.11 (0.71-1.75)	134; 248; 364; 591
Honkanen 2000[34]	368/11 798	Inverse	4	1	0.7 (0.53 to 0.92)	0.61 (0.43 to 0.85)	0.48 (0.25 to 0.92)	—	500; 1000; 1500
Kato 2000[36]	193/6250	Nil	5	1	1.11 (0.7 to 1.7)	0.93 (0.6 to 1.5)	1.12 (0.7 to 1.7)	0.78 (0.5-1.3)	569; 689; 799; 949

Nil=no association between calcium intake and risk of fracture; inverse=higher calcium intake associated with decreased risk of fracture or lower calcium intake associated with higher risk of fracture; SD=standard deviation; M=male; F=female; Q=quartile (values not reported in paper); NS=not stated.
*Number of participants with vertebral fracture.
†Hazard ratio or relative risk (95% confidence interval) or mean (SD) mg/d.
‡For example, cut point of 250 indicates 2 groups of <250 and ≥250 mg/d; cut points of 400; 800; and 1200 indicate 4 groups <400; 400-799; 800-1199; ≥1200 mg/d.

identified by the database searches because the relation between calcium intake and fracture was not the focus of the report, with the results reported in the text or tables of the article but not the abstract. This was more likely to occur when there was no association between calcium intake and fracture, so the current analysis might overestimate the relation between diet and fracture. We did not perform a quality assessment of the cohort studies, although we included only those studies with a prospective cohort design, considered to be the strongest observational methods.

Generally, observational studies are considered to have a higher risk of bias than large well conducted randomised controlled trials. Tools for assessing quality of observational studies are available, but they often focus on reporting of studies rather than topic specific issues, such as methods of assessment of dietary calcium intake, methods of fracture assessment, categorisation of dietary calcium intake in statistical models, and inclusion of covariates in those models. Such factors are likely to be extremely influential in the results of the cohort studies but are either not easily assessed or not able to be assessed. If we limited our results to cohort studies with more than 100 fractures in which fracture risk by baseline dietary calcium intake was reported for at least three groups, most studies reported no association between baseline dietary calcium and fracture (5/7 for total fracture, 6/8 for hip fracture, 1/1 for vertebral fracture, and 3/4 for forearm fracture). The results from these large studies are similar to the overall results, and each study has adequate power to detect clinically relevant effect sizes.

We did not perform meta-regression analyses because there were few studies that reported sufficient data for such an analysis. Individual patient data analyses might be of value in further exploring the relation between baseline calcium intake and fracture risk. Other important limitations include that many of the randomised controlled trials were of short duration and did not have fracture as the primary endpoint. The trials were generally carried out in healthy populations or those at risk of osteoporosis, and so the findings might not apply to other population groups.

Results in context

Overall, there is little evidence currently to suggest an association between calcium intake and fracture risk or that increasing calcium intake through dietary sources will alter risk. Although calcium supplements produced some small inconsistent reductions in fractures, the doses used of 500-1600 mg/day gave an average total daily calcium intake of 1780 mg/day (range 1230-2314 mg/day). This is considerably higher than the dietary calcium intake in the highest quarter or fifth in the prospective observational studies. If calcium supplements are correcting dietary "calcium deficiency" it might be necessary to increase dietary calcium intake to about 1800 mg/day to achieve equivalent effects to calcium

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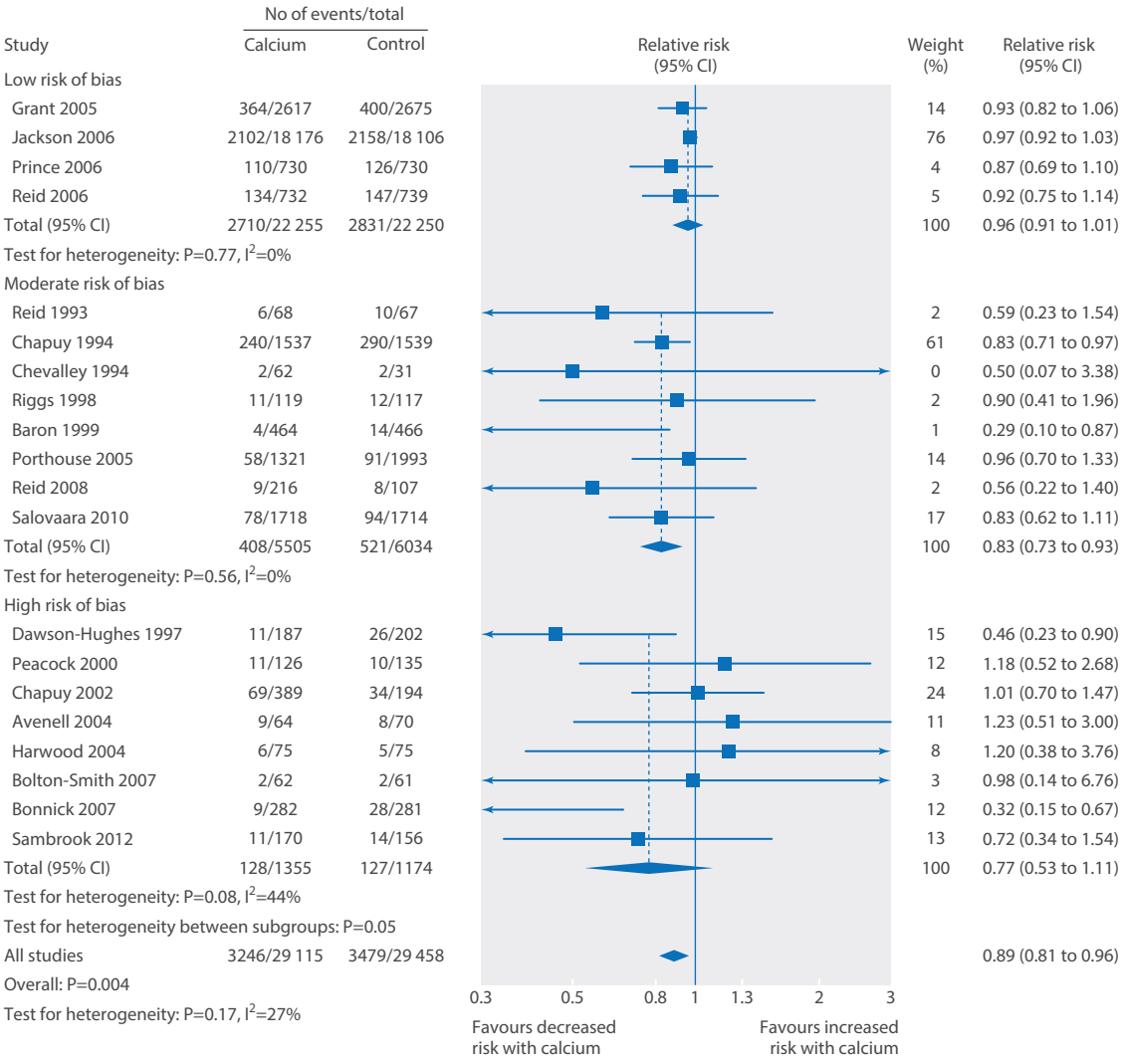

Fig 1 | **Random effects models of effect of calcium supplements on risk of total fracture. Trials with no events are not included in meta-analyses**

supplements. Dietary manipulation to increase calcium intake by ≥1000 mg/day or to achieve total daily intakes of this size is unlikely to be sustainable.

The pooled analyses of all randomised controlled trials showed reductions in risk with calcium supplements for all fractures (by 11%) and vertebral fractures (by 14%). The incidence of vertebral fracture and any fracture in the control groups in our pooled analyses was 1.5% and 12%, respectively, after a participant weighted average duration of follow-up of 6.2 and 5.5 years, respectively. With these values and the observed risk reductions from the meta-analyses, the number needed to treat (NNT) with calcium to prevent one vertebral fracture is 489 for 6.2 years and to prevent one fracture at any site is 77 for 5.5 years. These benefits are unlikely to be attractive for an individual and would be even smaller for individuals at lower risk of fracture, who are often advised to take calcium supplements, or if relative risks from the randomised controlled trials at lowest risk of bias were used in the calculations. There was no benefit from calcium supplements for hip fractures, which have the greatest clinical consequences.

Small benefits might be useful at a population level if calcium supplements were used widely, well tolerated, and safe. Persistence with calcium supplements in clinical trials is low, however, at about 40-60%,[9 87 89 90] and in one recent randomised controlled trial, there were 24 more women admitted to hospital for acute gastrointestinal symptoms in the calcium group than the placebo group, and 16 fewer women with a fracture.[10 89] In another randomised controlled trial, there were 68 more women with a kidney stone in the CaD group and 56 fewer women with a fracture.[9] In our randomised controlled trial and subsequent meta-analyses, the cardiovascular risks of calcium were similar to[6 7] or exceeded[8] the benefits of calcium on fracture prevention. In addition, 10-20% of people experience gastrointestinal side effects such as constipation, which cause a considerable number to stop taking the supplements. Thus, because of the small benefits of use and unfavourable risk:benefit

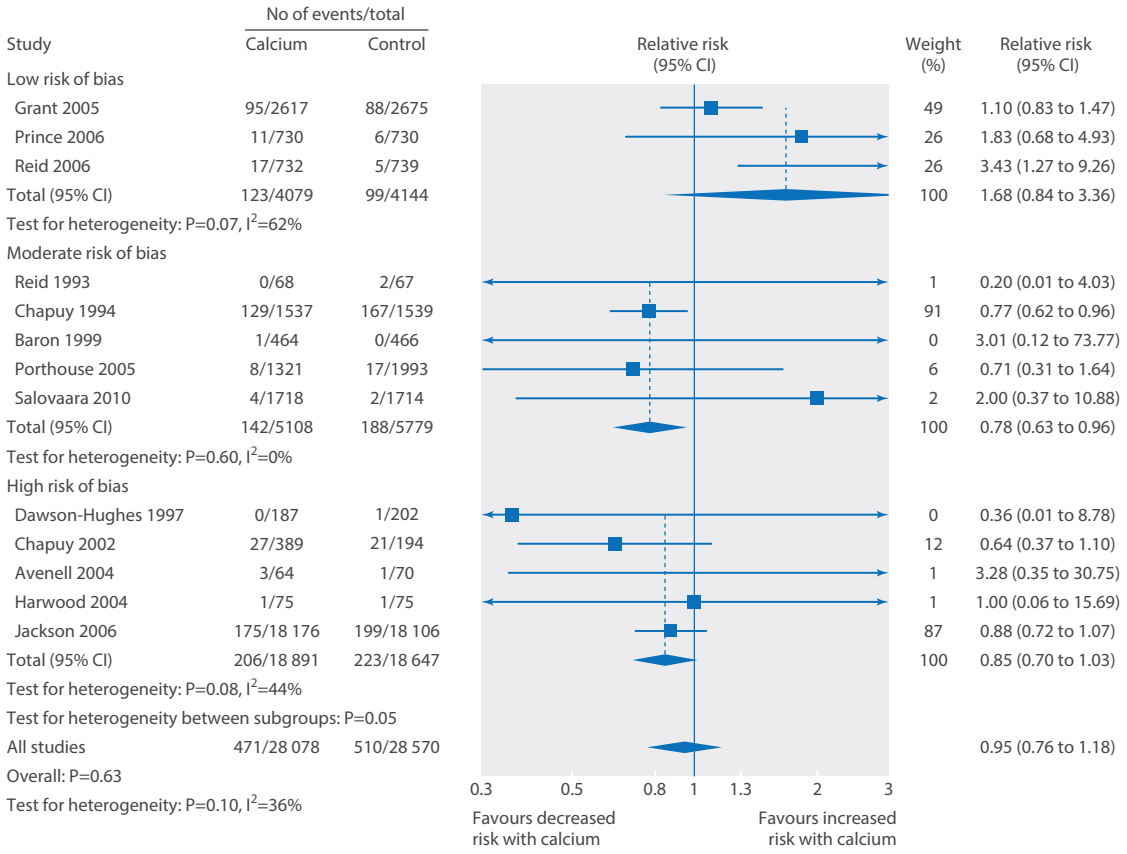

Fig 2 | **Random effects models of effect of calcium supplements on risk of hip fracture. Trials with no events are not included in meta-analyses**

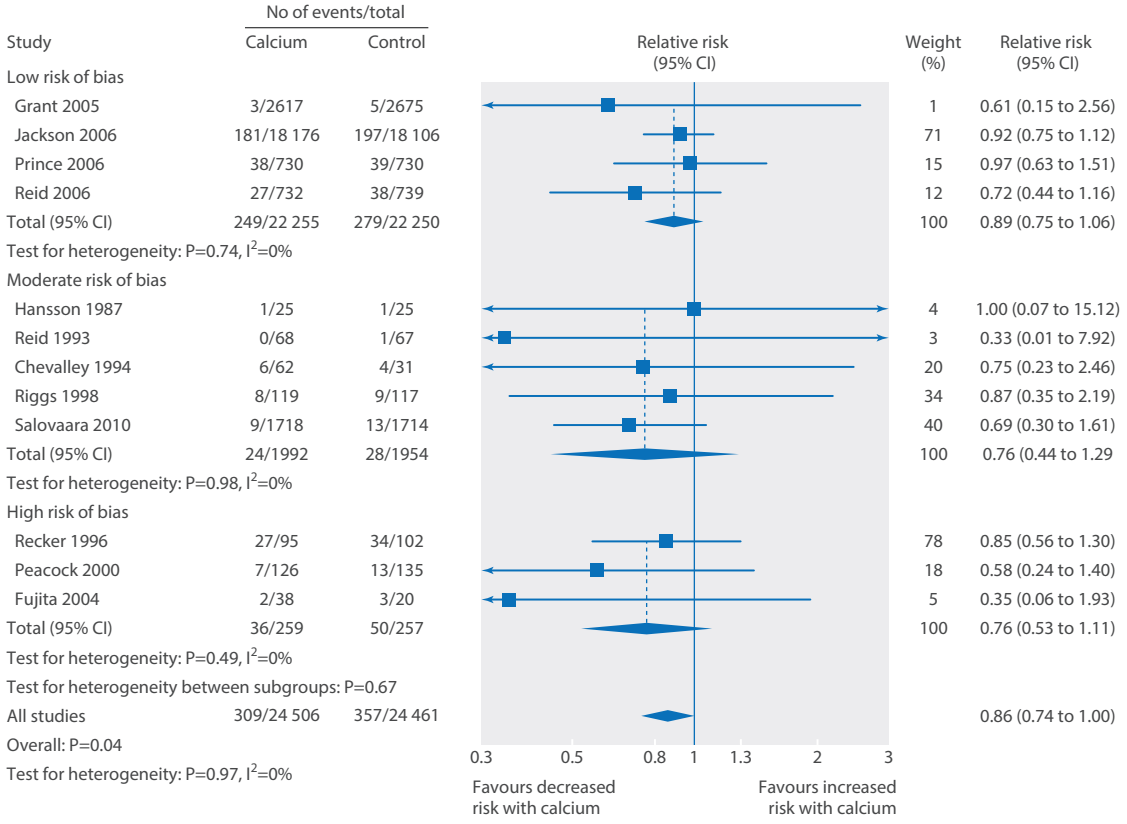

Fig 3 | **Random effects models of effect of calcium supplements on risk of vertebral fracture. Trials with no events are not included in meta-analyses**

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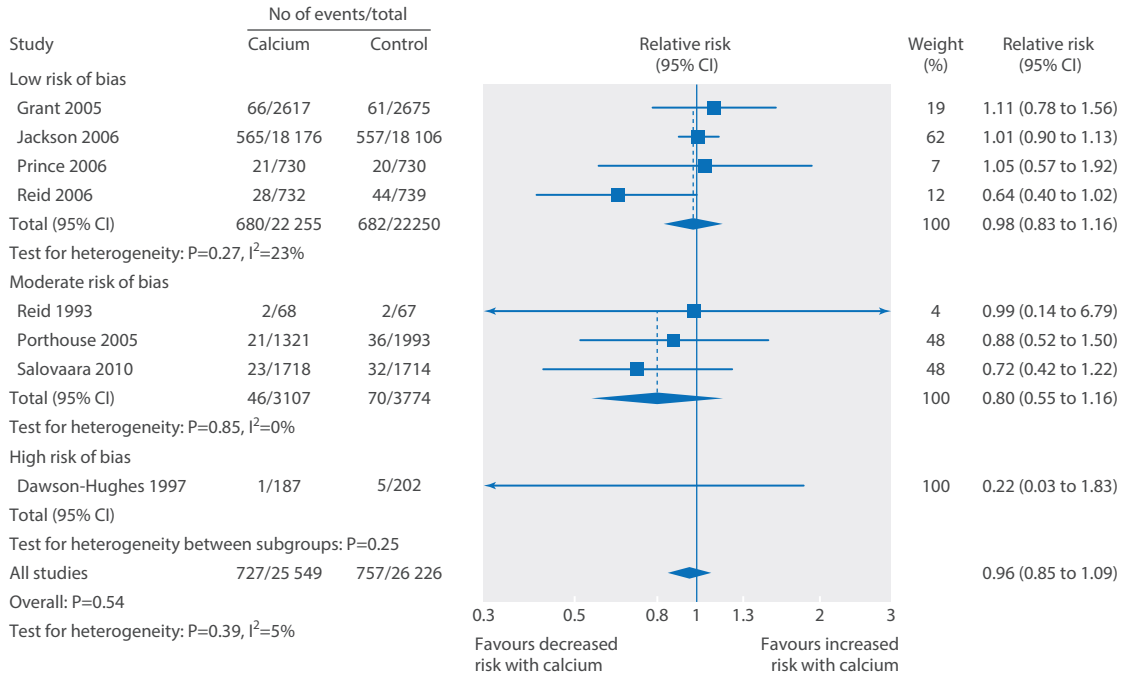

Fig 4 | **Random effects models of effect of calcium supplements on risk of forearm hip fracture. Trials with no events are not included in meta-analyses**

profile, calcium supplements should not be recommended for fracture prevention either at an individual or population level.

An important point emerging from our analyses is the impact of one randomised controlled trial[15] on previous meta-analyses. Chapuy and colleagues studied frail elderly French women (mean age 84) in residential care with low baseline dietary calcium intake (513 mg/day) and low baseline vitamin D concentrations (mean about 20 nmol/L in modern assays[83]). Of these participants, 16% died within 18 months of randomisation. Co-administered CaD (1200 mg/day, 800 IU/day) reduced hip fractures by 23% and all fractures by 17% at three years.[16] These results are in contrast to all six other large randomised controlled trials (n>1000) of calcium or CaD, none of which reported significant reductions in total or hip fracture risk (fig 1). Based on the average vitamin D concentrations in the Chapuy study (about 20 nmol/L), it is possible that many participants had unrecognised osteomalacia, the treatment of which might have led to the benefits observed. Therefore, the benefits of CaD in this study should not be expected to be reproduced in cohorts with higher vitamin D concentrations. In our subgroup analyses, whichever subgroup the Chapuy study was in had reductions in risk of hip fracture that were markedly different to the other subgroup (table 7). The influence of this single trial is also a feature of previous meta-analyses that concluded that high dose but not low dose vitamin D prevents fractures,[95] co-administered CaD but not vitamin D prevents fractures,[96] and CaD administered to people living in residential care but not in the community prevents fractures.[17] Our analyses highlight that the results from this study of a frail population with marked vitamin D deficiency are so different to those from other large randomised controlled trials and so influential in any pooled analysis that they should probably not be combined in pooled analyses with studies that enrolled different patient groups. Furthermore, recommendation of use of calcium and vitamin D supplements generally for older adults to prevent fracture based on results heavily influenced by this study of frail women in residential care is inappropriate.

On the basis of the trial data summarised here, we do not think further randomised controlled trials of calcium supplements with or without vitamin D with fracture as the endpoint in the general population are needed. In the population of frail elderly women with low dietary calcium intake and low vitamin D concentrations studied by Chapuy and colleagues,[15] co-administered CaD was clearly beneficial. Important adverse events such as cardiovascular events, however, were not reported, and it remains uncertain whether the benefit was due to vitamin D or calcium or both. Trials to compare the effects of CaD with vitamin D monotherapy in this population group and also to assess whether reduction in fracture risk with anti-resorptive agents requires co-administration of either vitamin D or CaD would be valuable. Surrogate endpoints, such as bone mineral density, allow biological effects of agents to be assessed in much smaller randomised controlled trials. The effects of increasing dietary calcium intake on bone mineral density in the general population and in specific subgroups considered most likely to benefit from this intervention should be examined before large trials with fracture as an endpoint are considered, though it should not be assumed that short term changes in

Table 6 | Subgroup analyses by fracture site in randomised controlled trials of calcium supplements

Subgroup	Total			Hip			Vertebral			Forearm		
	No of studies	RR (95% CI)	P value*	No of studies	RR (95% CI)	P value*	No of studies	RR (95% CI)	P value*	No of studies	RR (95% CI)	P value*
Risk of bias:												
Low	4	0.96 (0.91 to 1.01)	0.03	3	1.68 (0.84 to 3.36)	0.05	4	0.89 (0.75 to 1.06)	0.37	4	0.98 (0.83 to 1.16)	0.24
Moderate/high	16	0.80 (0.69 to 0.93)		10	0.82 (0.71 to 0.94)		8	0.76 (0.56 to 1.03)		4	0.77 (0.54 to 1.11)	
Treatment:												
Calcium monotherapy	13	0.85 (0.73 to 0.98)	0.25	7	1.51 (0.93 to 2.48)	0.02	10	0.80 (0.64 to 1.01)	0.47	4	0.92 (0.69 to 1.23)	0.70
Co-administered CaD†	10	0.92 (0.86 to 0.99)		9	0.84 (0.74 to 0.96)		3	0.90 (0.74 to 1.09)		5	0.98 (0.86 to 1.13)	
Residential status:												
Community	17	0.88 (0.80 to 0.98)	0.63	11	1.10 (0.83 to 1.46)	0.03	10	0.86 (0.75 to 1.00)	0.30	8	0.96 (0.85 to 1.09)	—
Residential care	3	0.85 (0.74 to 0.98)		2	0.75 (0.62 to 0.92)		1	0.35 (0.06 to 1.93)		0	—	
Calcium intake:												
<800 mg/d	7	0.83 (0.73 to 0.95)	0.78	4	0.75 (0.61 to 0.91)	0.05	6	0.77 (0.55 to 1.07)	0.45	2	0.50 (0.11 to 2.18)	0.42
>800 mg/d	9	0.86 (0.74 to 0.99)		6	1.32 (0.77 to 2.26)		4	0.89 (0.75 to 1.05)		5	0.92 (0.77 to 1.09)	

RR=relative risk.
*P value for interaction.
†Co-administered calcium and vitamin D.

Table 7 | Sensitivity analyses of randomised controlled trials of calcium supplements and risk of fracture

Analysis and fracture site	No of studies	Relative risk (95% CI)
Include Inkovaara 1983[13] and Larsen 2004[14]*		
Total fracture	22	0.90 (0.83 to 0.96)
Include Inkovaara 1983[13] and Larsen 2004[14]†		
Total fracture	22	0.89 (0.83 to 0.95)
Analyse Chapuy 1994[15 16] as individually randomised		
Total fracture	20	0.88 (0.81 to 0.96)
Hip fracture	13	0.95 (0.76 to 1.18)
Restrict Jackson 2006[9] to women not using oestrogen[19]		
Hip fracture-all studies	13	1.04 (0.80 to 1.34)
Hip fracture-CaD subgroup	9	0.90 (0.75 to 1.08)
Hip fracture-community dwelling	11	1.20 (0.97 to 1.48)
Hip fracture-calcium intake >800 mg/d	6	1.41 (0.92 to 2.18)
Exclude Chapuy 1994[15 16]		
Total fracture	19	0.90 (0.82 to 0.98)
Hip fracture	12	1.02 (0.78 to 1.34)

*Comparison of both environmental programme and calcium and vitamin D programme with environmental programme only.
†Comparison of any calcium and vitamin D versus no calcium and vitamin D.

bone density will be sustained or translate into fracture prevention.[97]

Conclusions

In summary, our analyses indicate that dietary calcium intake is not associated with risk of fracture, and there is no evidence currently that increasing dietary calcium intake prevents fractures. Calcium supplements have small inconsistent benefits on fracture reduction but probably have an unfavourable risk:benefit profile. There was no risk reduction in fracture at any site in pooled analyses of the randomised controlled trials of calcium supplements at lowest risk of bias, and there was evidence of publication bias in small-moderate sized trials. Collectively, these results suggest that clinicians, advocacy organisations, and health policymakers should not recommend increasing calcium intake for fracture prevention, either with calcium supplements or through dietary sources.

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Appendix 1: Literature searches and superseded reports of cohort studies
Appendix 2: Flow of articles
Appendix 3: Supplementary tables A-F

Calcium intake and bone mineral density: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To determine whether increasing calcium intake from dietary sources affects bone mineral density (BMD) and, if so, whether the effects are similar to those of calcium supplements.

DESIGN

Random effects meta-analysis of randomised controlled trials.

DATA SOURCES

Ovid Medline, Embase, Pubmed, and references from relevant systematic reviews. Initial searches were undertaken in July 2013 and updated in September 2014.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

Randomised controlled trials of dietary sources of calcium or calcium supplements (with or without vitamin D) in participants aged over 50 with BMD at the lumbar spine, total hip, femoral neck, total body, or forearm as an outcome.

RESULTS

We identified 59 eligible randomised controlled trials: 15 studied dietary sources of calcium (n=1533) and 51 studied calcium supplements (n=12 257). Increasing calcium intake from dietary sources increased BMD by 0.6-1.0% at the total hip and total body at one year and by 0.7-1.8% at these sites and the lumbar spine and femoral neck at two years. There was no effect on BMD in the forearm. Calcium supplements increased BMD by 0.7-1.8% at all five skeletal sites at one, two, and over two and a half years, but the size of the increase in BMD at later time points was similar to the increase at one year. Increases in BMD were similar in trials of dietary sources of calcium and calcium supplements (except at the forearm), in trials of calcium monotherapy versus co-administered calcium and vitamin D, in trials with calcium doses of ≥1000 versus <1000 mg/day and ≤500 versus >500 mg/day, and in trials where the baseline dietary calcium intake was <800 versus ≥800 mg/day.

CONCLUSIONS

Increasing calcium intake from dietary sources or by taking calcium supplements produces small non-progressive increases in BMD, which are unlikely to lead to a clinically significant reduction in risk of fracture.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Older people are recommended to take at least 1000-1200 mg/day of calcium to treat and prevent osteoporosis

Many people take calcium supplements to meet these recommendations

Recent concerns about the safety of such supplements have led experts to recommend increasing calcium intake through food rather than by taking supplements, but the effect of increasing dietary calcium intake on bone health is not known

WHAT THIS STUDY ADDS

Increasing calcium intake either by dietary sources or supplements has small non-progressive effects on bone density

These effects are unlikely to translate into clinically meaningful reductions in fractures

Introduction

Maintaining a calcium intake of at least 1000-1200 mg/day has long been recommended for older individuals to treat and prevent osteoporosis.[1 2] Calcium supplements are commonly taken to achieve such intakes, which are considerably higher than the average intake of calcium in the diet in older people in Western countries, around 700-900 mg/day. Recently, concerns have emerged about the risk-benefit profile of calcium supplements. The small reductions in total fractures[3] seem outweighed by the moderate risk of minor side effects such as constipation, coupled with the small risk of severe side effects such as cardiovascular events,[4-6] kidney stones,[7] and admission to hospital with acute gastrointestinal symptoms.[8] Consequently, some experts have recommended that older people increase their calcium intake through their diet and take supplements only when that is not feasible.[9] In a systematic review of calcium intake and fractures, we concluded that there was no evidence of an association between increased dietary calcium intake and lower risk of fracture.[10] We identified only two small randomised controlled trials of dietary calcium intake that reported fracture as an outcome. Numerous cohort studies, however, assessed the relation between dietary calcium, milk or dairy intake, and risk of fracture, and most reported neutral associations.[10]

The putative mechanism by which calcium intake affects bone health is by increasing bone mineral density (BMD). BMD is a surrogate endpoint for fracture risk that allows biological effects to be explored in randomised controlled trials of modest size. We investigated whether the results of randomised controlled trials with BMD as an endpoint support the recommendations to increase dietary calcium intake to prevent osteoporosis. We undertook a systematic review and meta-analysis of randomised controlled trials of dietary sources of calcium or calcium supplements in older adults (aged >50) to determine whether increasing intake from dietary sources has effects on BMD and, if so, whether they are similar to the effects of calcium supplements on BMD.

Methods

Literature search

As part of a broader search for studies of calcium intake and health, we searched Ovid Medline and Embase in

July 2013 and updated the search using Pubmed and Embase in September 2014 for randomised controlled trials of calcium, milk, or dairy intake, or calcium supplements with BMD as an endpoint. We also hand searched recent systematic reviews, meta-analyses, and any other articles included in our review for other relevant articles. Appendix 1 provided details of the searches.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in dissemination.

Study selection

Included studies were randomised controlled trials in participants aged >50 at baseline with BMD measured by dual energy x ray absorptiometry (DXA) or precursor technology such as photon absorptiometry. We included studies that reported bone mineral content (BMC) because BMD is obtained by dividing BMC by bone area and therefore the two are highly correlated. Studies in which most participants at baseline had a major systemic pathology other than osteoporosis, such as renal failure or malignancy, were excluded. We included studies of calcium supplements used in combination with other treatment provided that the other treatment was given to both arms (such as calcium plus vitamin K versus placebo plus vitamin K), and studies of co-administered calcium and vitamin D supplements (CaD). Randomised controlled trials of hydroxyapatite as a dietary source of calcium were included because it is made from bone and contains other minerals, hormones, protein, and amino acids in addition to calcium. One author (WL or MB) screened titles and abstracts, and two authors (WL, MB, or VT) independently screened the full text of potentially relevant studies. The flow of articles is shown in figure A in appendix 2.

Data extraction and synthesis

We extracted information from each study on participants' characteristics, study design, funding source and conflicts of interest, and BMD at the lumbar spine, femoral neck, total hip, forearm, and total body. BMD can be measured at several sites in the forearm, although the 33% (1/3) radius is most commonly used. For each study, we used the reported data for the forearm, regardless of site. If more than one site was reported, we used the data for the site closest to the 33% radius. A single author (VT) extracted data, which were checked by a second author (MB). Risk of bias was assessed as recommended in the Cochrane Handbook.[11] Any discrepancies were resolved through discussion.

The primary endpoints were the percentage changes in BMD from baseline at the five BMD sites. We categorised the studies into three groups by duration: one year was duration <18 months; two years was duration ≥18 months and ≤2.5 years; and others were studies lasting more than two and a half years. For studies that presented absolute data rather than percentage change from baseline, we calculated the mean percentage change from the raw data and the standard deviation of the percentage change using the approach described in the Cochrane Handbook.[11] When data were presented only in figures, we used digital callipers to extract data. In four studies that reported mean data but not measures of spread,[12-15] we imputed the standard deviation for the percentage change in BMD for each site from the average site and duration specific standard deviations of all other studies included in our review. We prespecified subgroup analyses based on the following variables: dietary calcium intake*v* calcium supplements; risk of bias; calcium monotherapy*v* CaD; baseline age (<65); sex; community*v* institutionalised participants; baseline dietary calcium intake <800 mg/day; baseline 25-hydroxyvitamin D <50 nmol/L; calcium dose (≤500*v* >500 mg/day and <1000*v* ≥1000 mg/day); and vitamin D dose <800 IU/day.

Statistics

We pooled the data using random effects meta-analyses and assessed for heterogeneity between studies using the I^2 statistic (I^2 >50% was considered significant heterogeneity). Funnel plots and Egger's regression model were used to assess for the likelihood of systematic bias. We included randomised controlled trials of calcium with or without vitamin D in the primary analyses. Randomised controlled trials in which supplemental vitamin D was provided to both treatment groups, so that the groups differed only in treatment by calcium, were included in calcium monotherapy subgroup analyses, while those comparing co-administered CaD with placebo or controls were included in the CaD subgroup analyses. We included all available data from trials with factorial designs or multiple arms. Thus, for factorial randomised controlled trials we included all study arms involving a comparison of calcium versus no calcium in the primary analyses and the calcium monotherapy subgroup analysis, but only arms comparing CaD with controls in the CaD subgroup analysis. For multi-arm randomised controlled trials, we pooled data from the separate treatment arms for the primary analyses, but each treatment arm was used only once. We undertook analyses of prespecified subgroups using a random effects model when there were 10 or more studies in the analysis and three or more studies in each subgroup and performed a test for interaction between subgroups. All tests were two tailed, and P<0.05 was considered significant. All analyses were performed with Comprehensive Meta-Analysis (version 2, Biostat, Englewood, NJ).

Results

Baseline characteristics

We identified 59 randomised controlled trials of calcium intake that reported BMD as an outcome.[7 12-70] Fifteen studied dietary sources of calcium (n=810 calcium, n=723 controls),[16-30] and 51 studied calcium supplements (n=6547 calcium, n=5710 controls).[7 12-15 17 19-22 26 28 31-70] Table 1 shows study design and selected baseline characteristics for included studies of dietary calcium. Tables 2 and 3 show the study design

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Table 1 | Design of randomised controlled trials and selected baseline characteristics of eligible trials of dietary calcium

Trial	Design	Calcium dose (mg/d)	Vitamin D dose (IU/d)	Duration	Care setting	Total No of participants*	No in Ca/controls group†	% women	Mean age (years)
Recker 1985[16]	2 arm: milk and control	NS	—	2 y	Community	30	16/14	100	59
Polley 1987[17]	4 arm: dairy, Ca, dairy/salt restrict, control	≥1250	—	9 mo	Community	269	58/52	100	57
Nelson 1991[18]	2×2 factorial: ex/milk, ex/control, sed/milk, sed/control	831	—	1 y	Community	41	18/18	100	60
Chevalley 1994[19]	3 arm: OMC/D, CaD, P/D	800	300 000 IM stat	18 mo	Community	93	31/31	85	72
Prince 1995[20]	4 arm: milk, Ca, Ca/ex, P	1000	—	2 y	Community	168	42/42	100	63
Storm 1998[21]	3 arm: milk, Ca, P	NS	—	2 y	Community	40	20/20	100	71
Castelo-Branco 1999[22]	3 arm: OHC, Ca, control	3320	—	2 y	Community	60	17/16	100	55
Cleghorn 2001[23]	2 arm: milk, control	700	—	1 y	Community	142	56/59	100	52
Lau 2001[24]	2 arm: milk, control	800	—	24 mo	Community	200	95/90	100	57
Chee 2003[25]	2 arm: milk, control	1200	—	24 mo	Community	200	91/82	100	59
Albertazzi 2004[26]	3 arm: OHC, Ca, P	500	—	6 mo	Community	153	52/50	100	68
Daly 2006[27]	2 arm: milk, control	1000	800	2 y	Community	167	85/82	0	62
Manios 2007[28]	3 arm: dairy, Ca, control	1200	300	12 mo	Community	112	39/36	100	61
Kukuljan 2009[29]	2×2 factorial: milk, milk/ex, ex, control	1000	800	12 mo	Community	180	90/90	0	61
Gui 2012[30]	3 arm: milk, soy milk, control	250	—	18 mo	Community	141	100/41	100	56

Ca=calcium; restrict=restriction; ex=exercise; sed=sedentary; OMC=ossein-mineral complex; D=vitamin D; CaD=co-administered Ca and vitamin D; P=placebo; IM=intramuscular; OHC=ossein-hydroxyapatite complex.
*Total number of randomised participants in all treatment arms.
†Number of participants in relevant arms from trial in whom bone mineral density was reported.

Table 2 | Design of randomised controlled trials and selected baseline characteristics of eligible trials of calcium supplements

Trial	Design	Calcium dose (mg/d)	Duration	Care setting	No of participants*	No in Ca/controls group†	% women	Mean age (y)
Recker 1977[31]	3 arm: Ca, HRT, control	1040	2 y	Community	60	22/20	100	57
Lamke 1978[32]	2 arm: Ca, P	1000	12 mo	Community	40	19/17	100	60
Hansson 1987[12]	4 arm: 30 mg NaF/Ca, 10 mg NaF/Ca, Ca, P	1000	3 y	NS	50	25/25	100	66
Polley 1987[17]	4 arm: Ca, dairy, dairy/salt restrict, control	1000	9 mo	Community	269	40/52	100	57
Riis 1987[34]	3 arm: Ca, HRT, P	2000	2 y	Community	43	14/11	100	51
Smith 1989[35]	2 arm: Ca, P	1500	4 y	Community	169	70/77	100	51
Dawson-Hughes 1990[36]	3 arm: Ca, Ca, P	500	2 y	Community	361	158/93	100	58
Fujita 1990[37]	2 arm: Ca, control	900	2 y	Institution	32	12/20	100	80
Elders 1991[39]	3 arm: Ca, Ca, P	1000 or 2000	2 y	Community	295	198/97	100	NS
Prince 1991[40]	3 arm: Ca/ex, ex, HRT	1000	2 y	Community	80	39/41	100	57
Lau 1992[42]	2×2 factorial: Ca, Ca/ex, ex/P, P	800	10 mo	Institution	50	27/23	100	76
Reid 1993[43]	2 arm: Cav P	1000	2 y	Community	135	61/61	100	58
Strause 1994[45]	2×2 factorial: Ca, Ca/minerals, minerals, P	1000	2 y	Community	113	27/32	100	66
Prince 1995[20]	4 arm: Ca, Ca/ex, milk, P	1000	2 y	Community	168	42/42	100	63
Fujita 1996[46]	3 arm: Ca, Ca, P	900	2 y	Institution	58	38/20	100	81
Perez-Jaraiz 1996[47]	4 arm: Ca, HRT, calcitonin, control	1000	1 y	Community	52	26/26	100	50
Recker 1996[48]	2 arm: Ca, P	1200	4.3 y	Community	197	91/100	100	74
Ricci 1998[51]	2 arm: Ca, P	1000	6 mo	Community	43	15/16	100	58
Riggs 1998[52]	2 arm: Ca, P	1600	4 y	Community	236	119/117	100	66
Storm 1998[21]	3 arm: Ca, milk, P	1000	2 y	Community	40	20/20	100	72
Castelo-Branco 1999[22]	3 arm: Ca, OHC, control	2500	2 y	Community	60	19/16	100	54
Ruml 1999[53]	2 arm: Ca, P	800	2 y	Community	63	25/31	100	52
Fujita 2000[54]	4 arm: Ca, Ca, Ca, P	900	4 mo	NS	38	32/6	100	55
Peacock 2000[13]	3 arm: Ca, 25OHD, P	750	4 y	Community	438	126/135	72	74
Son 2001[55]	3 arm: Ca, alphacalcidiol, P	1000	10 mo	Community	69	22/21	100	72
Albertazzi 2004[26]	3 arm: Ca, OHC, P	500	6 mo	Community	153	51/50	100	68
Prince 2006[61]	2 arm: Ca, P	1200	5 y	Community	1460	730/730	100	75
Reid 2006[62]	2 arm: Ca, P	1000	5 y	Community	1471	732/739	100	74
Manios 2007[28]	3 arm: Ca, dairy, control	600	12 mo	Community	112	26/36	100	62
Reid 2008[65]	3 arm: Ca, Ca, P	600 or 1200	2 y	Community	323	216/107	0	56
Chailurkit 2010[67,68]	2 arm: Ca, P	500	2 y	Community	404	178/165	100	66
Nakamura 2012[70]	3 arm: Ca, Ca, P	250 or 500	2 y	Community	450	281/137	100	60

Ca=calcium; HRT=hormone replacement therapy; P=placebo; ex=exercise; NaF=sodium fluoride; restrict=restriction; OMC=ossein-mineral complex; 25OHD=25-hydroxyvitamin D; NS=not stated.
*Total number of randomised participants in all treatment arms.
†Number of participants in relevant arms from trial in whom bone mineral density was reported.

Table 3 | Design of randomised controlled trials and selected baseline characteristics of eligible trials of calcium supplements that also used vitamin D supplements

Trial	Design	Calcium dose (mg/d)	Vitamin D dose (IU/d)	Duration	Care setting	No of participants*	No in Ca/control group†	% women	Mean age (y)
Smith 1981[33]	2×2 factorial: CaD, ex, ex/CaD, P	750	400	3 y	Institution	80	21/30	100	82
Orwoll 1990[38]	2 arm: CaD , P	1000	1000	3 y	Community	86	41/36	0	58
Chapuy 1992[41]	2 arm: CaD, P	1200	800	18 mo	Institution	3270	27/29	100	84
Aloia 1994[44]	3 arm: CaD, HRT/CaD, P/D	600	400	2.9 y	Community	118	34/36	100	52
Chevalley 1994[19]	3 arm: CaD, OMC/D, P/D	800	300 000 IM stat	18 mo	Community	93	31/31	89	72
Dawson-Hughes 1997[49]	2 arm: CaD, P	500	700	3 y	Community	445	187/202	55	71
Baeksgaard 1998[50]	3 arm: CaD, CaD/multivitamins, P	1000	560	2 y	Community	160	65/63	100	62
Chapuy 2002[56]	3 arm: CaD, CaD, P	1200	800	2 y	Institution	610	393/190	100	85
Grados 2003[57]	2 arm: CaD, P	500	400	12 mo	Community	192	95/97	100	75
Doetsch 2004[58]	2 arm: CaD, P	1000	800	12 w	Community	30	16/14	NS	NS
Harwood 2004[14]	4 arm: CaD, CaD, D, control	1000	300 000 IM stat or 800	12 mo	Community	150	75/75	100	81
Meier 2004[59]	2 arm: CaD, control	500	500	6 mo	Community	55	27/16	67	56
Riedt 2005[60]	3 arm: CaD/w-loss, D/w-loss, w-maintain	1200	400	6 mo	Community	55	23/24	100	61
Jackson 2006[7]	2 arm: CaD, P	1000	400	7 y	Community	2431	1230/1201	100	62
Bolton-Smith 2007[63]	2×2 factorial: CaD, CaD/vit K, vit K, P	1000	400	2 y	Community	244	99/110	100	68
Bonnick 2007[64]	3 arm: CaD/alend, CaD, alend/D	1000	400	2 y	Community	563	282/281	100	66
Hitz 2007[15]	2 arm: CaD, P	1200	1400	12 mo	Community	122	34/45	83	68
Zhu 2008[66]	3 arm: Ca, CaD, P	1200	1000	5 y	Community	120	79/41	100	75
Karkkainen 2010[69]	2 arm: CaD, control	1000	800	3 y	Community	593	287/306	100	67

Ca=calcium; HRT=hormone replacement therapy; P=placebo; CaD=co-administered calcium and vitamin D; ex=exercise; OMC=ossein-mineral complex; D=vitamin D; IM=intramuscular; w-loss=weight loss, w-maintain=weight maintenance; vit K=vitamin K; alend=alendronate; NS=not stated.
*Total number of randomised participants in all treatment arms.
†Number of participants in relevant arms from trial in whom bone mineral density was reported.

Table 4 | Summary of selected characteristics of eligible trials of calcium intake. Data are number (percentage) of trials

Characteristics of randomised controlled trials	Dietary sources of calcium (n=15)	Calcium supplements (n=51)
Agent studied:		
Calcium monotherapy	11 (73)	36 (71)
Calcium with vitamin D	4 (27)	13 (25)
Multi-arm study with calcium or calcium+vitamin D	0	2 (4)
Calcium dose ≥1000 mg/d	6 (40)	34 (67)
Calcium dose ≤500 mg/d	2 (13)	7 (14)
Duration ≤2 years	15 (100)	37 (73)
Duration ≥3 years	0	13 (25)
Participants living in community	15 (100)	45 (88)
Most participants women	13 (87)	48 (94)
Baseline mean age ≥70	2 (13)	18 (35)
Baseline mean dietary calcium intake <800 mg/d	9/13 (69)	26/39 (67)

and selected baseline characteristics for trials of calcium supplements, without and with additional vitamin D, respectively. Further details are in tables A-C in appendix 2. Of the 15 randomised controlled trials of dietary sources of calcium, 10 used milk or milk powder, two used dairy products, and three used hydroxyapatite preparations. Of the 51 trials of calcium supplements, 36 studied calcium monotherapy, 13 co-administered CaD, and two were multi-arm studies of both. Table 4 summarises other features of the trials. Most of them studied calcium without vitamin D in women aged <70 living in the community; the mean baseline dietary calcium intake was <800 mg/day; and most trials lasted ≤2 years. A calcium dose of >500 mg/day was used in most trials, but a higher proportion of trials of calcium supplements used a dose of ≥1000 mg/day. Table C in appendix 2 shows our assessment of risk of bias. Of the 15 trials of dietary sources of calcium, we assessed two as low risk of bias, six as moderate risk, and seven as high risk. Of the 51 trials of calcium supplements, we assessed 19 as low risk of bias, 12 as moderate risk, and 20 as high risk.

Primary analyses

Table 5 summarises the results of the meta-analyses. Increasing calcium intake from dietary sources increased BMD by 0.6-1.0% at the total hip and total body at one year and by 0.7-1.8% at these sites and the lumbar spine and femoral neck at two years (figs 1 and 2. There was no effect on BMD at the forearm.

When we restricted the analyses to the 12 randomised controlled trials of milk or dairy products, by excluding three trials of hydroxyapatite, there was little change in the results. Calcium supplements increased BMD at all five skeletal sites by 0.7-1.4% at one year (figs 3 and 4), by 0.8-1.5% at two years (figs 5 and 6), and by 0.8-1.8% at more than two and a half years (fig 7) (range of duration of trials was three to five years).

When we used Egger's regression model and visual inspection of funnel plots, data seemed skewed toward positive results with increased calcium intake from dietary sources or supplements in about half of analyses that included five or more studies. The asymmetry of the funnel plot was caused by more small-moderate sized studies reporting larger effects

Table 5 | Pooled analyses of trials of dietary sources of calcium and calcium supplements

	Trials of dietary sources of calcium				Calcium supplement trials				
Time point (years)	Studies	Participants	BMD difference* (95% CI)	P value	Studies	Participants	BMD difference* (95% CI)	P value	P (interaction)†
Lumbar spine									
1	11	1260	0.6 (−0.1 to 1.3)	0.08	27	3866	1.2 (0.8 to 1.7)	<0.001	0.13
2	8	816	0.7 (0.3 to 1.2)	0.001	21	6115	1.1 (0.7 to 1.6)	<0.001	0.19
>2.5	0	—	—	—	8	3861	1.0 (0.3 to 1.6)	0.003	—
Femoral neck									
1	8	1035	0.3 (−0.3 to 0.9)	0.30	19	2651	1.2 (0.7 to 1.8)	<0.001	0.02
2	7	783	1.8 (1.1 to 2.6)	<0.001	14	2415	1.0 (0.5 to 1.4)	<0.001	0.05
>2.5	0	—	—	—	5	2257	1.5 (0.2 to 2.9)	0.025	—
Total hip									
1	6	900	0.6 (0.3 to 1.0)	0.001	7	1159	1.4 (0.6 to 2.3)	0.001	0.08
2	5	689	1.5 (0.7 to 2.4)	<0.001	7	4366	1.3 (0.8 to 1.8)	<0.001	0.63
>2.5	0	—	—	—	6	3835	1.2 (0.5 to 1.9)	0.001	—
Forearm									
1	4	418	0.0 (−0.4 to 0.5)	0.85	10	791	1.0 (0.2 to 1.8)	0.014	0.04
2	2	171	0.1 (−0.3 to 0.4)	0.65	10	857	1.5 (0.5 to 2.6)	0.005	0.01
>2.5	0				5	437	1.8 (0.2 to 3.4)	0.025	
Total Body									
1	3	433	1.0 (0.3 to 1.8)	0.009	10	1255	0.7 (0.4 to 1.1)	<0.001	0.47
2	2	358	0.9 (0.5 to 1.3)	<0.001	6	3901	0.8 (0.5 to 1.1)	<0.001	0.67
>2.5	0	—	—	—	7	4164	0.8 (0.5 to 1.1)	<0.001	—

*Weighted mean difference between groups in percentage change in bone mineral density (BMD) from baseline.
†Test for interaction between subgroup of trials of dietary sources of calcium and subgroup of calcium supplement trials.

of calcium on BMD than expected, raising the possibility of publication bias. Seven multi-arm randomised controlled trials included a dietary source of calcium arm and a calcium supplement arm,[17 19-22 26 28] which allowed a direct comparison of the interventions. There were no significant differences between groups in BMD at any site in any individual trial, and there were also no significant differences between groups in BMD at any site or any time point in the pooled analyses (table D, appendix 2). We also tested for differences between the results of the trials of dietary sources of calcium and the trials of calcium supplements by comparing the two groups in subgroup analyses (table 4). There were no differences between the groups at any time point at the lumbar spine, total hip, or total body. At the femoral neck, there were greater increases in BMD at one year in the calcium supplement trials than in the dietary calcium trials, but at two years we found the opposite—that is, greater changes with dietary calcium than with calcium supplements. At the forearm, there were increases in BMD in the calcium supplement trials but no effect in the trials of dietary sources of calcium.

Subgroup analyses

We carried out additional subgroup analyses when there were 10 or more trials in an analysis and three or more trials in each subgroup. In the trials of dietary sources of calcium, these criteria allowed analyses to be carried out only on the one year results for the lumbar spine. For the calcium supplement trials, we carried out analyses on the one year and two year results for the lumbar spine, femoral neck, and forearm results, and the one year result for total body. Table E in appendix 2 shows that there were no consistent differences between subgroups based on calcium monotherapy versus CaD, age, risk of bias, calcium dose of ≥1000 mg/day versus <1000 mg/day, calcium dose of ≤500 mg/day versus >500 mg/day, vitamin D dose, baseline dietary calcium intake, or baseline 25-hydroxyvitamin D level. We did not find enough trials to carry out subgroup analyses based on sex and residence (community versus institution).

Discussion

Principal findings

Increasing calcium intake from dietary sources slightly increased bone mineral density (BMD) (by 0.6-1.8%) over one to two years at all sites, except the forearm where there was no effect. Calcium supplements increased BMD to a similar degree at all sites and all time points (by 0.7-1.8%). In the randomised controlled trials of calcium supplements, the increases in BMD were present by one year, but there were no further subsequent increases. Thus the increases from baseline at both two and over two and half years at each site were similar to the increases at one year. The increases in BMD with dietary sources of calcium were similar to the increases with calcium supplements, except at the forearm, in both direct comparisons of the two interventions in multi-arm studies and in indirect comparisons of the two interventions through subgroup analyses. The increases in BMD were similar in trials of calcium monotherapy and CaD, consistent with a recent meta-analysis reporting that vitamin D monotherapy had no effect on BMD.[71] There were no differences in changes in BMD in

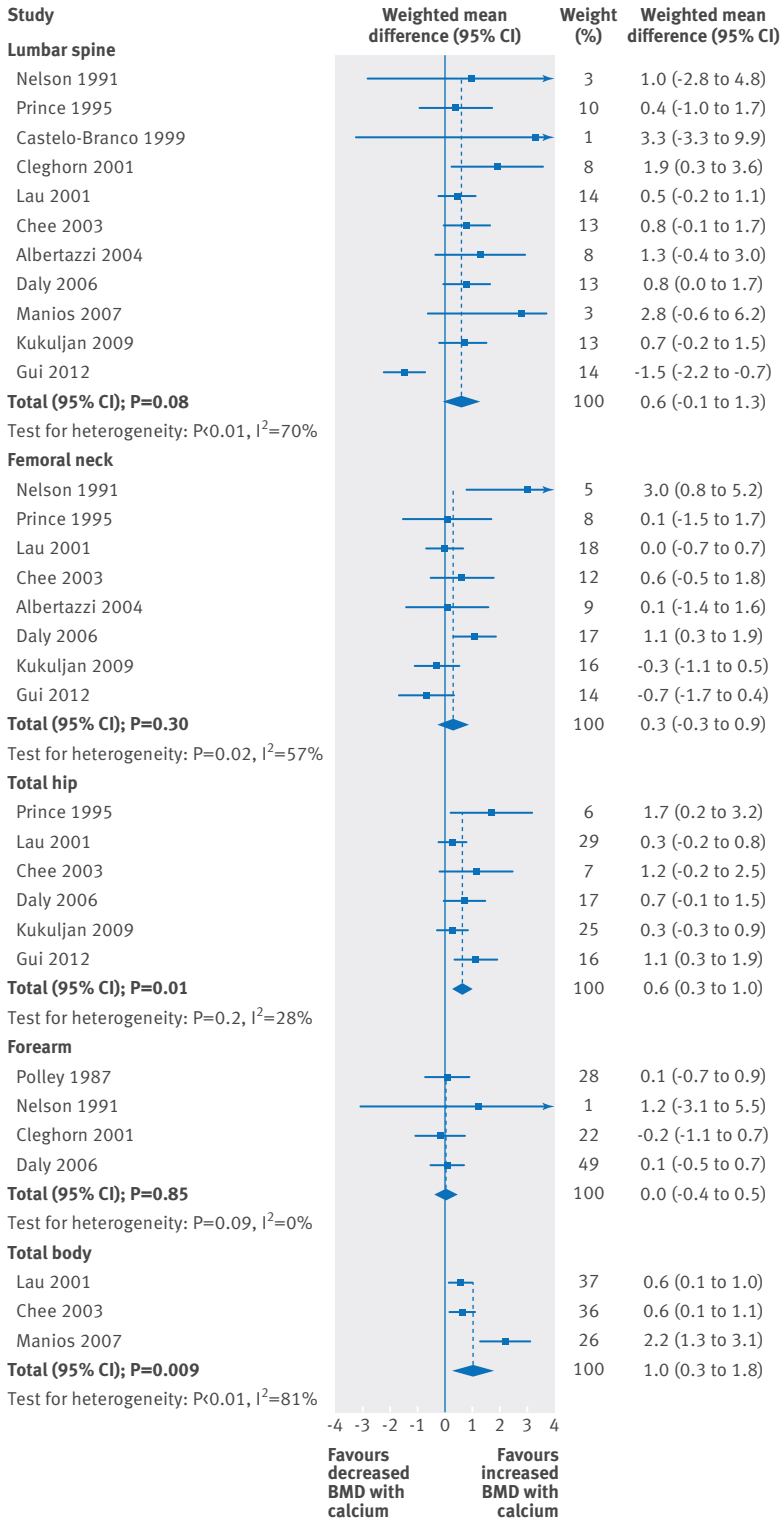

Fig 1 | **Random effects meta-analysis of effect of dietary sources of calcium on percentage change in bone mineral density (BMD) from baseline at one year**

our subgroup analyses between trials with calcium doses of ≥1000 mg/day and <1000 mg/day or doses of ≤500 mg/day and >500 mg/day, and in populations with baseline dietary calcium intake of <800 mg/day and ≥800 mg/day. Overall, the results suggest that increasing calcium intake, whether from dietary sources or by taking calcium supplements, provides a small non-progressive increase in BMD, without any ongoing reduction in rates of BMD loss beyond one year. The similar effect of increased dietary intake and supplements suggests that the non-calcium components of the dietary sources of calcium do not directly affect BMD.

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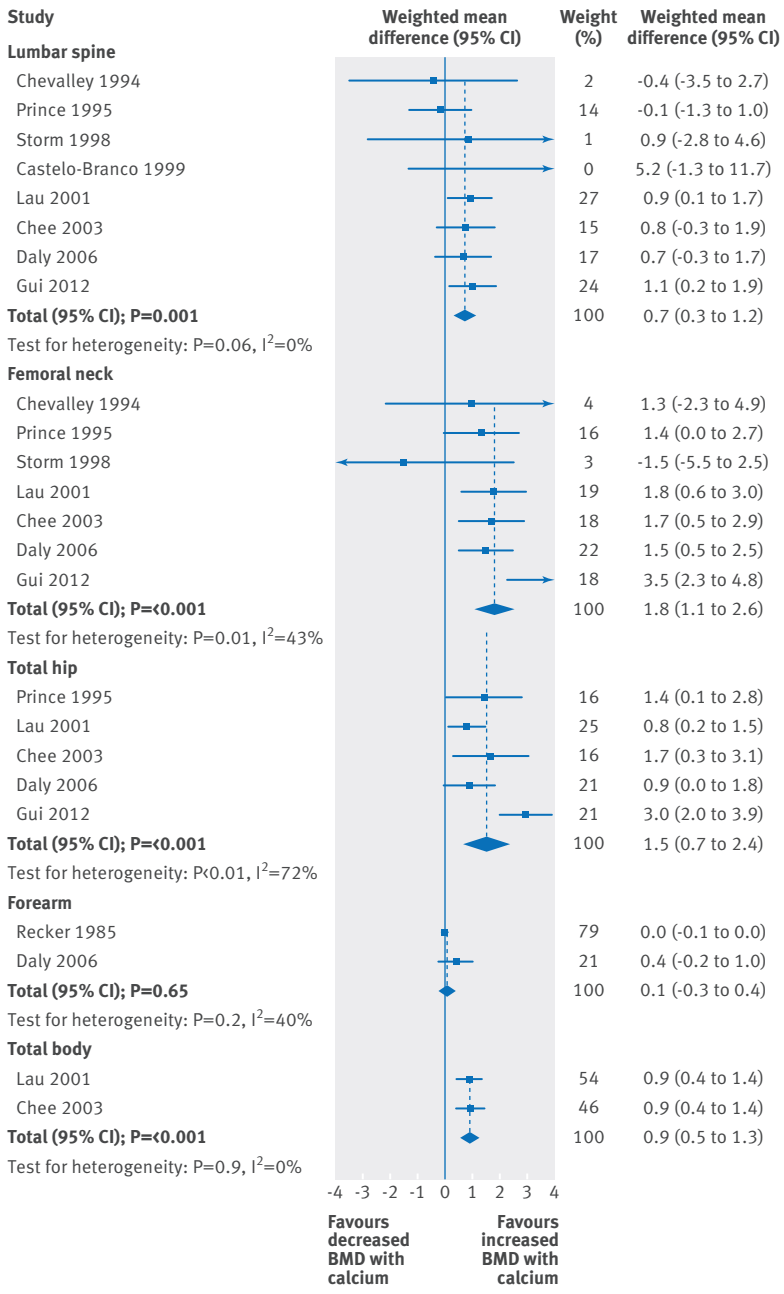

Fig 2 | **Random effects meta-analysis of effect of dietary sources of calcium on percentage change in bone mineral density (BMD) from baseline at two years**

Strengths and limitations of the study

The strength of this meta-analysis is its comprehensive nature. We included 59 randomised controlled trials and assessed the effects of both dietary calcium sources and calcium supplements on BMD at five skeletal sites and at three time points. The size of the review permitted a comparison of the effects on BMD of different sources of calcium—dietary sources or supplements—and also the effects in important subgroups such as those defined by dose of calcium, use of co-administered vitamin D, and baseline clinical characteristics. The results are consistent with those from an earlier meta-analysis of 15 randomised controlled trials of calcium supplements, which reported an increase in BMD of 1.6-2.0% over two to four years.[72]

An important limitation is that BMD is only a surrogate for the clinical outcome of fracture. We undertook the review, however, because many of the subgroup analyses in the dataset of trials with fracture as an endpoint have limited power,[10] and a comparison between randomised controlled trials of dietary sources of calcium and calcium supplements with fracture as the endpoint is not possible because only two small randomised controlled trials of dietary sources of calcium reported fracture data.[10] Another limitation is that in 60% of the meta-analyses, statistical heterogeneity between the studies was high (I^2>50%). This indicates

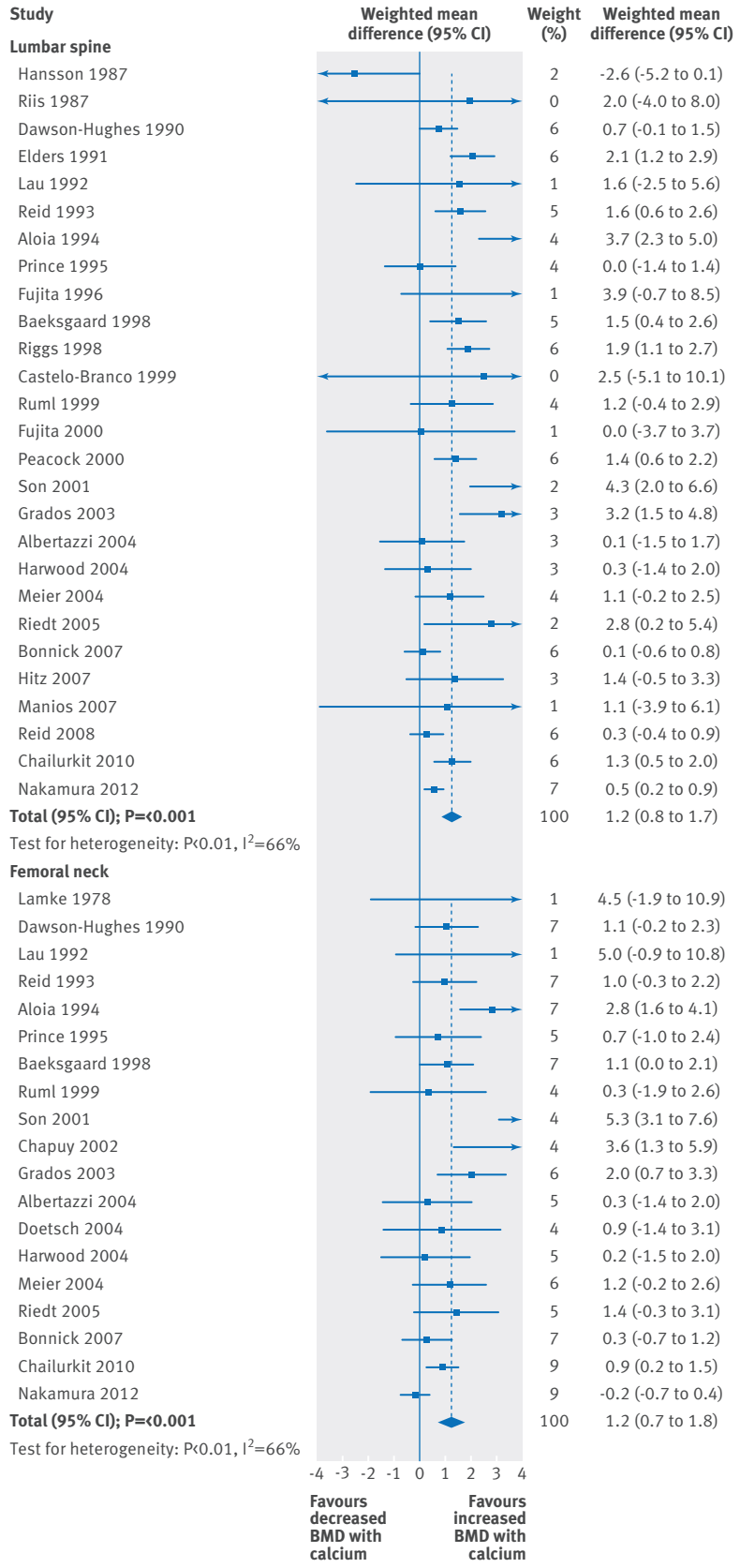

Fig 3 | Random effects meta-analysis of effect of calcium supplements on percentage change in bone mineral density (BMD) for lumbar spine and femoral neck from baseline at one year

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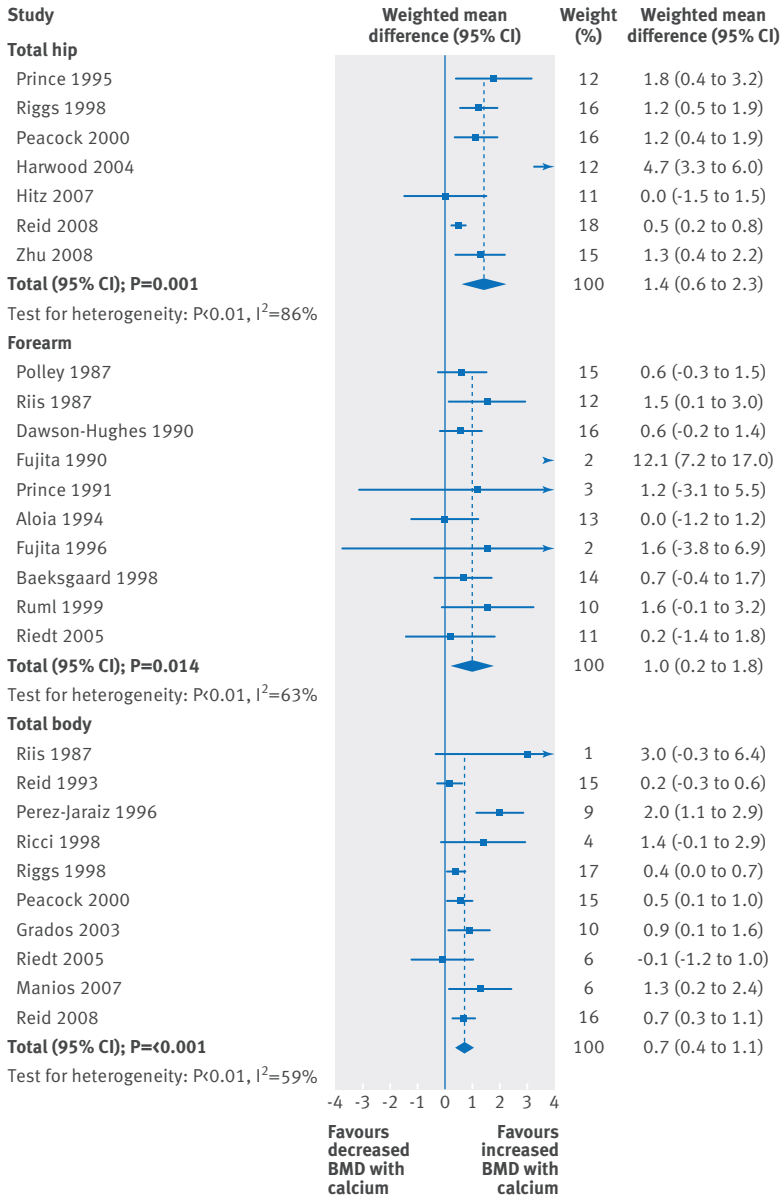

Fig 4 | **Random effects meta-analysis of effect of calcium supplements on percentage change in bone mineral density (BMD) for total hip, forearm, and total body from baseline at one year**

substantial variability in the results of included trials, although this was often because of the presence of a small number of outlying results. Subgroup analyses generally did not substantially reduce or explain the heterogeneity. We used random effects meta-analyses that take heterogeneity into account, and their results should be interpreted as reflecting the average result across the group of trials.

Implications of findings

The absence of any interaction with baseline dietary calcium intake or a dose-response relation suggests that increasing intake through dietary sources or through supplements does not correct a dietary deficiency (in which case greater effects would be seen in those with the lowest intakes or the highest doses). An alternative possibility is that increasing calcium intake has a weak anti-resorptive effect. Calcium supplements reduce markers of bone formation and resorption by about 20%,[62 65 73] and increasing milk intake also reduces bone turnover by a similar amount.[74] Suppression of bone turnover by this amount might lead to the small observed increases in BMD.

Increases in BMD of about 1-2% over one to five years are unlikely to translate into clinically meaningful reductions in fractures. The average rate of BMD loss in older post-menopausal women is about 1% a year. So the effect of increasing calcium intake is to prevent about one to two years of normal BMD loss, and if calcium intake is increased for more than one year it will slow down but not stop BMD loss. Epidemiological studies suggest that a decrease in BMD of one standard deviation is associated with an increase in the relative risk of fracture of about 1.5-2.0.[75] A one standard

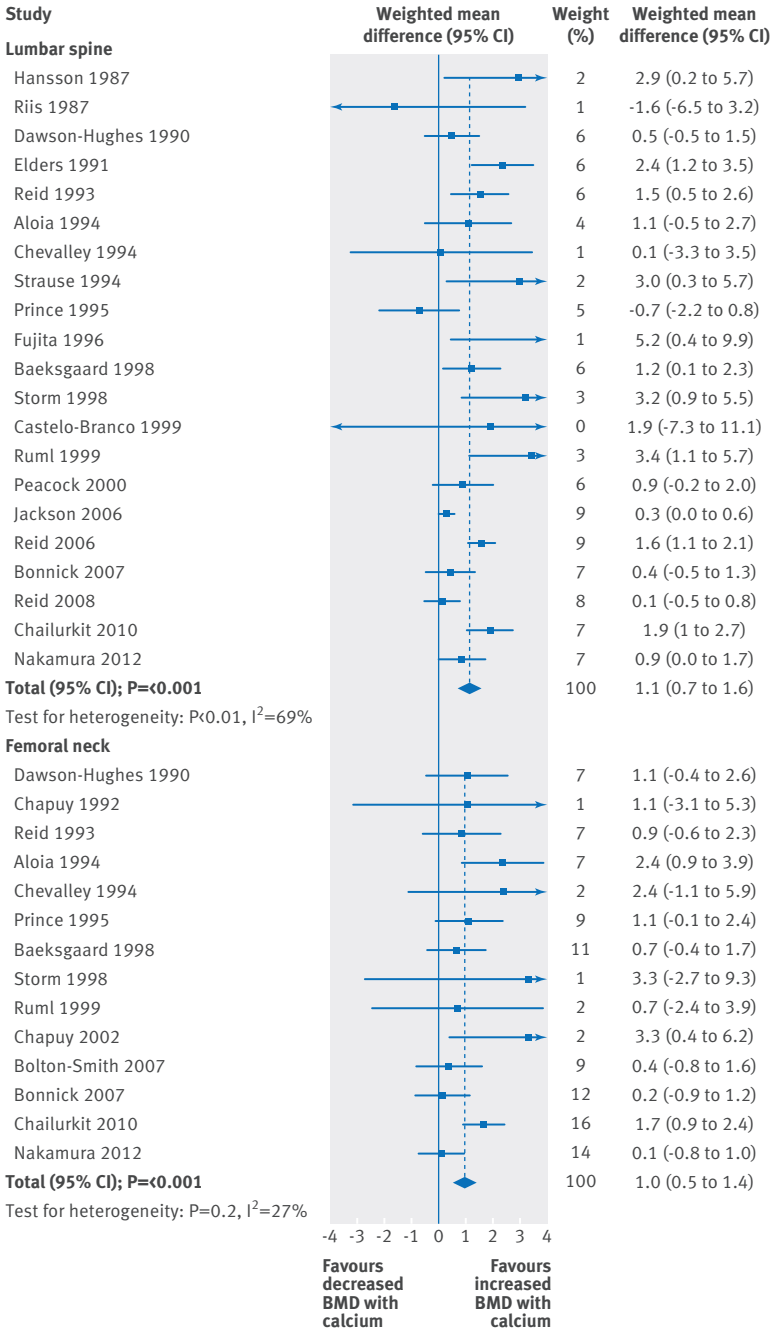

Fig 5 | **Random effects meta-analysis of effect of calcium supplements on percentage change in bone mineral density (BMD) for lumbar spine and femoral neck from baseline at two years**

deviation change in BMD is about equivalent to a 10% change in BMD. Based on these calculations, a 10% increase in BMD would be associated with a 33-50% reduction in risk of fracture. Therefore, the 1-2% increase in BMD observed with increased calcium intake would be predicted to produce a 5-10% reduction in risk of fracture. These estimates are consistent with findings from randomised controlled trials of other agents. The modest increases in BMD with increased calcium intake are smaller than observed with weak anti-resorptive agents such as etidronate[76] and raloxifene.[77] Etidronate, however, does not reduce vertebral or non-vertebral fractures, and raloxifene reduces vertebral but not non-vertebral fractures.[78] In contrast, potent anti-resorptive agents such as alendronate, zoledronate, and denosumab increase BMD by 6-9% at the spine and 5-6% at the hip over three years.[79-82] These changes are associated with reductions of 44-70% in vertebral fracture, 35-41% in hip fracture, and 15-25% in non-vertebral fractures.[78] The magnitude of fracture reduction predicted by the small increases in BMD we observed with increased calcium intake are also consistent with the findings of our systematic review of calcium supplements and fracture.[10] We observed small (<15%) inconsistent reductions in total and vertebral fracture overall but no reductions in fractures in the

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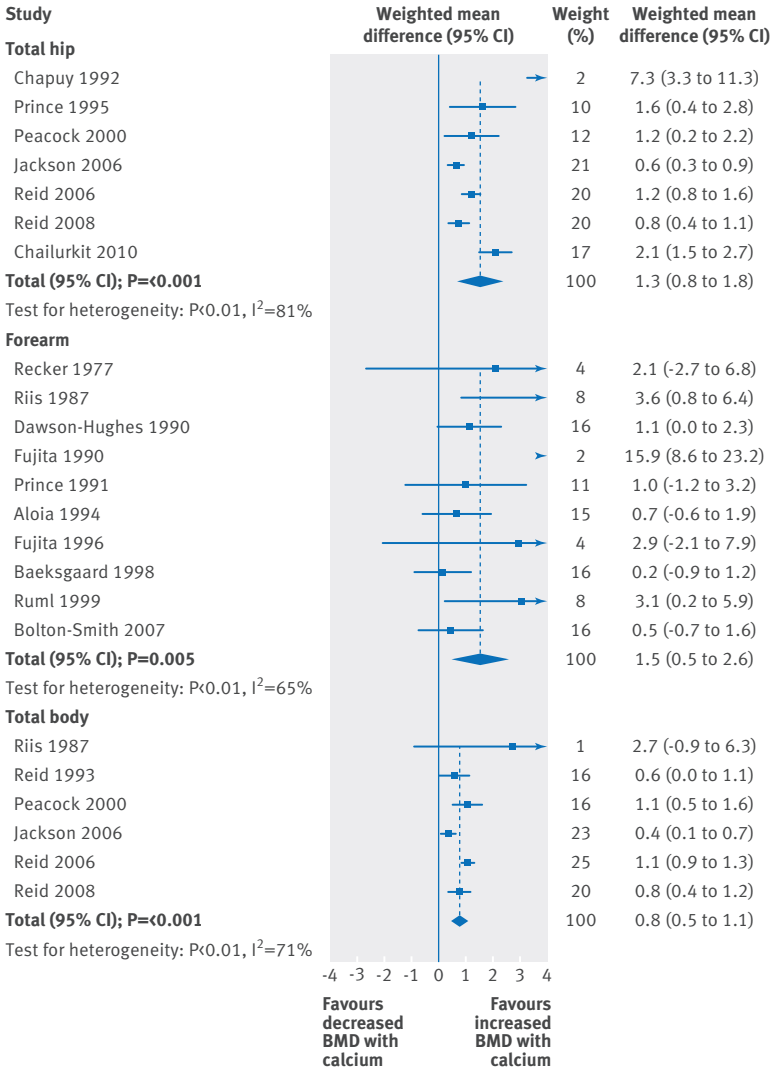

Fig 6 | **Random effects meta-analysis of effect of calcium supplements on percentage change in bone mineral density (BMD) for total hip, forearm, and total body from baseline at two years**

large randomised controlled trials at lowest risk of bias and no reductions in forearm or hip fractures.

The large number of randomised controlled trials that studied increased calcium intake and BMD and the consistency of the results across different populations in studies using higher or lower doses of calcium and in studies of dietary calcium sources or calcium supplements does not reveal any obvious gaps in the evidence. Any future trials conducted should have a strong rationale as to why the results are likely to differ from the large body of existing trial evidence. It is usually recommended that anti-resorptive agents are co-prescribed with calcium and vitamin D, although randomised controlled trials of such agents have shown reductions in risk of fracture[83-85] and the expected increases in BMD[64 86-88] without the co-administration of calcium and vitamin D. Randomised controlled trials clarifying the role of calcium and vitamin D in individuals using anti-resorptive agents might be valuable. In subgroup analyses, we stratified trials by thresholds of baseline dietary calcium intake (800 mg/day) and 25-hydroxyvitamin D (50 nmol/L). The clinical consequences of low calcium intake or vitamin D status such as osteomalacia, however, probably occur only at much lower thresholds, and there might also be interactions between calcium intake and vitamin D status. Analyses of individual patient data would be valuable in exploring these issues further.

Conclusions

In summary, increasing calcium intake from dietary sources increases BMD by a similar amount to increases in BMD from calcium supplements. In each case, the increases are small (1-2%) and non-progressive, with little further effect on BMD after a year. Subgroup analyses do not suggest greater benefits of increasing calcium intake on BMD in any subpopulation based on clinically relevant baseline characteristics. The small effects on BMD are unlikely to translate into clinically meaningful reductions in fractures. Therefore, for most individuals concerned about their bone density, increasing calcium intake is unlikely to be beneficial.

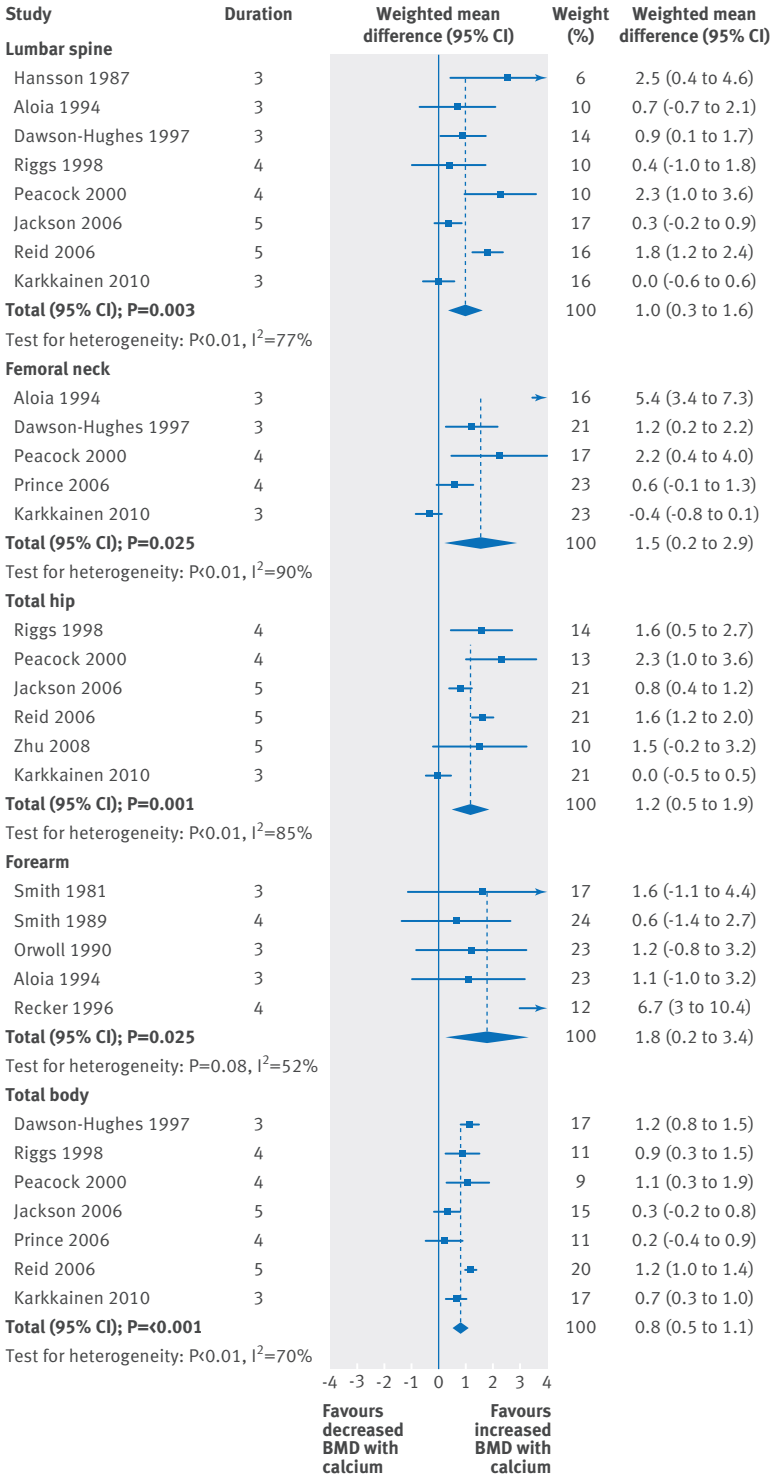

Fig 7 | Random effects meta-analysis of effect of calcium supplements on percentage change in bone mineral density (BMD) from baseline in studies that lasted more than two and a half years

Contributors: MJB, WL, VT, AG, and IRR designed the research. WL and MJB performed the literature searches. VT and MB extracted or checked data. MJB performed the analyses. MJB and VT drafted the paper. All authors critically reviewed and improved it. MJB is guarantor. All authors had access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethical approval: Not required.

Transparency statement: MB affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: No additional data available.

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Appendix 1: Literature searches

Appendix 2: Supplementary tables A-F and figure A