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

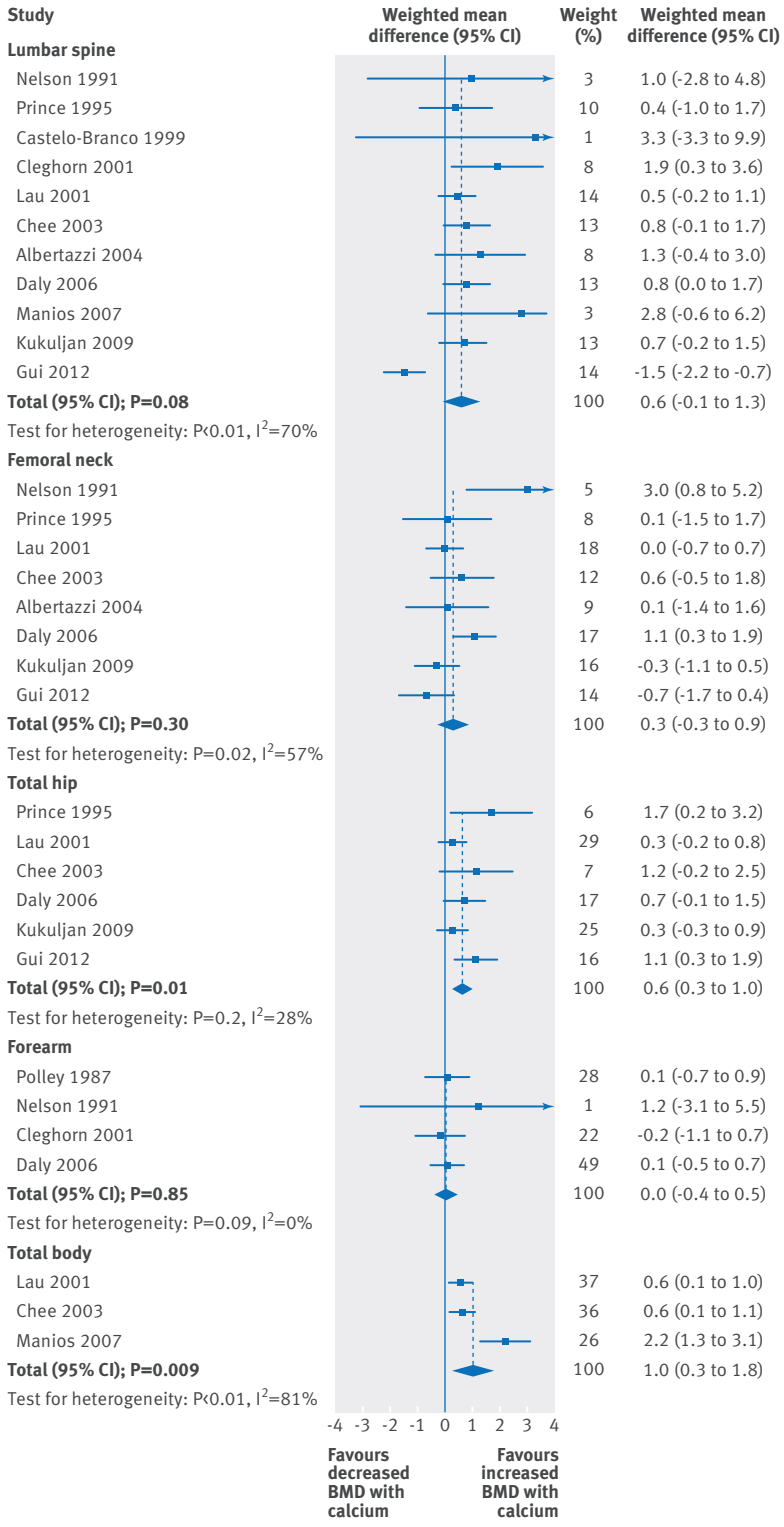

Fig 1 | **Random effects meta-analysis of effect of dietary sources of calcium on percentage change in bone mineral density (BMD) from baseline at one year**

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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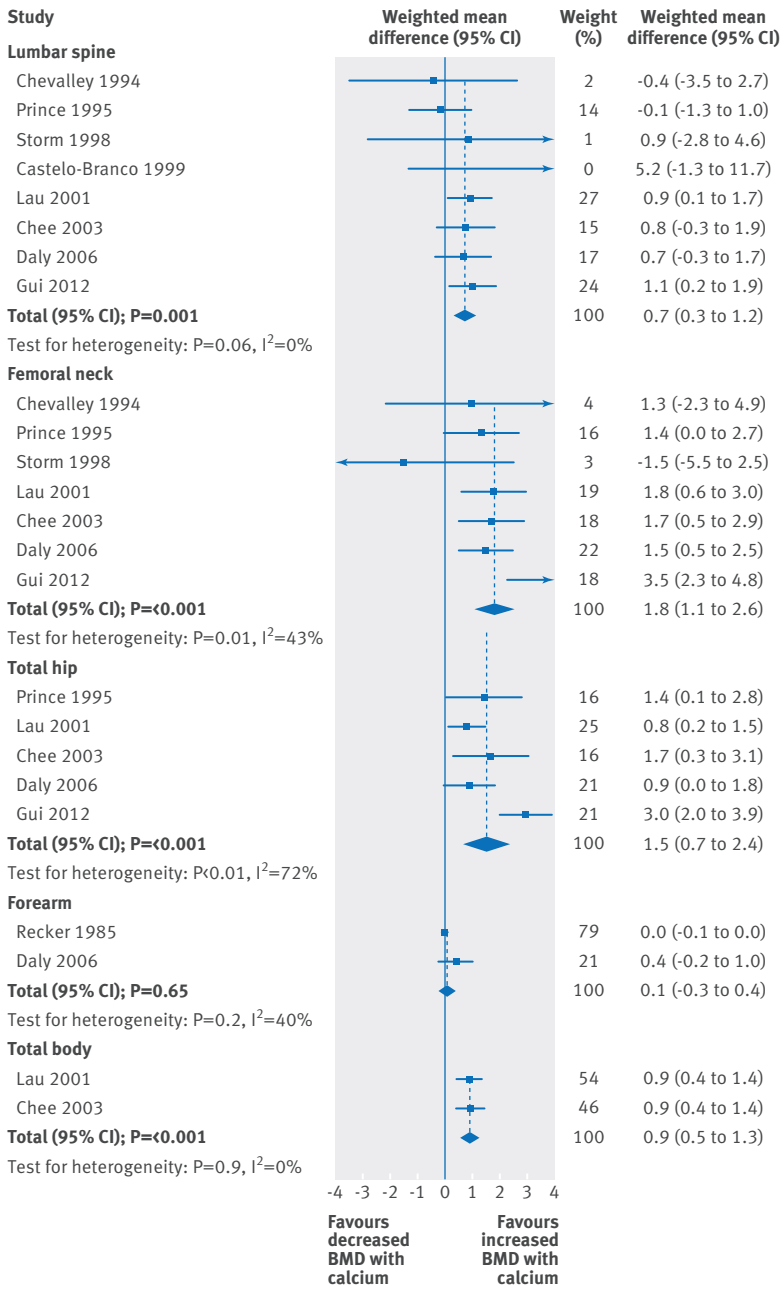

Fig 2 | **Random effects meta-analysis of effect of dietary sources of calcium on percentage change in bone mineral density (BMD) from baseline at two years**

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

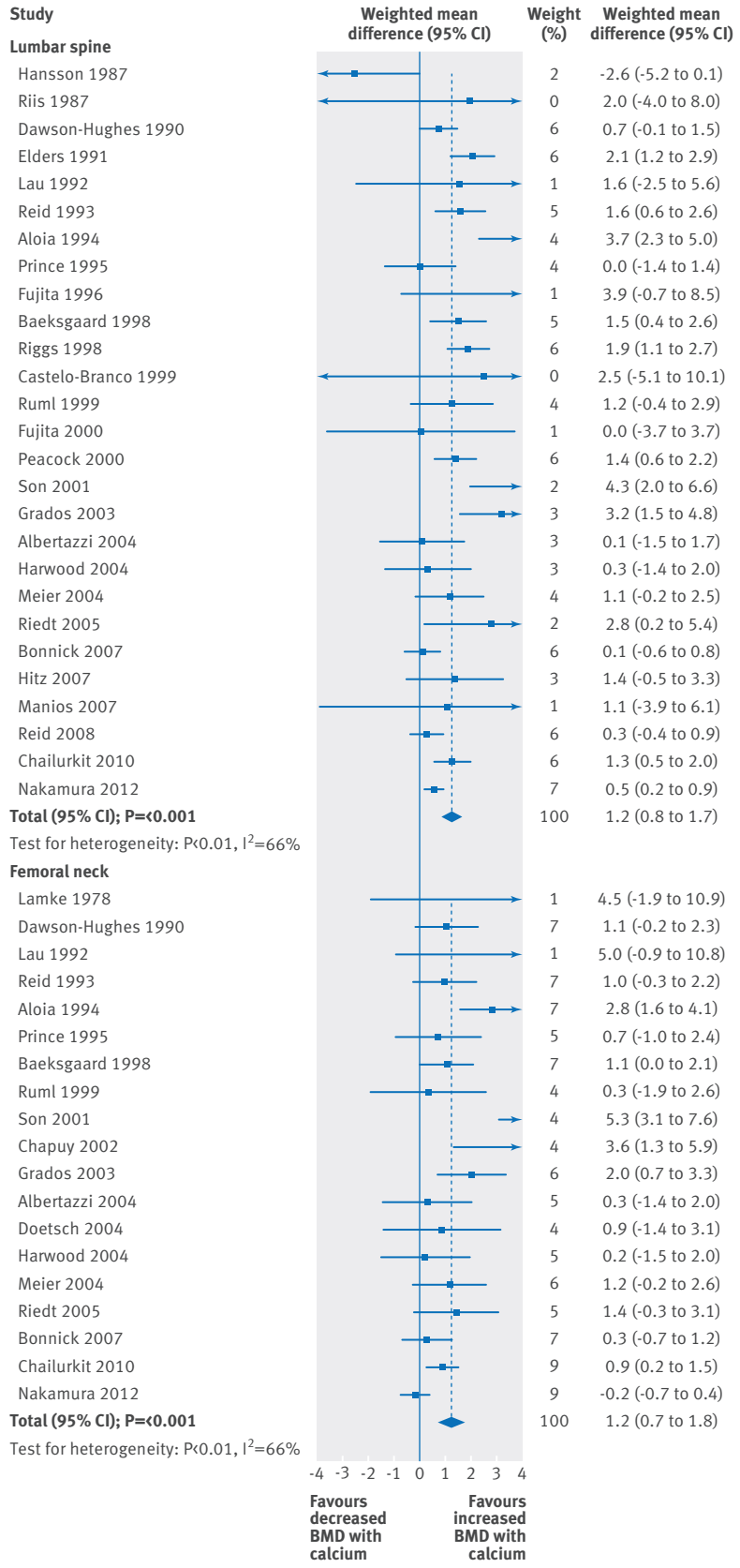

Fig 3 | Random effects meta-analysis of effect of calcium supplements on percentage change in bone mineral density (BMD) for lumbar spine and femoral neck from baseline at one year

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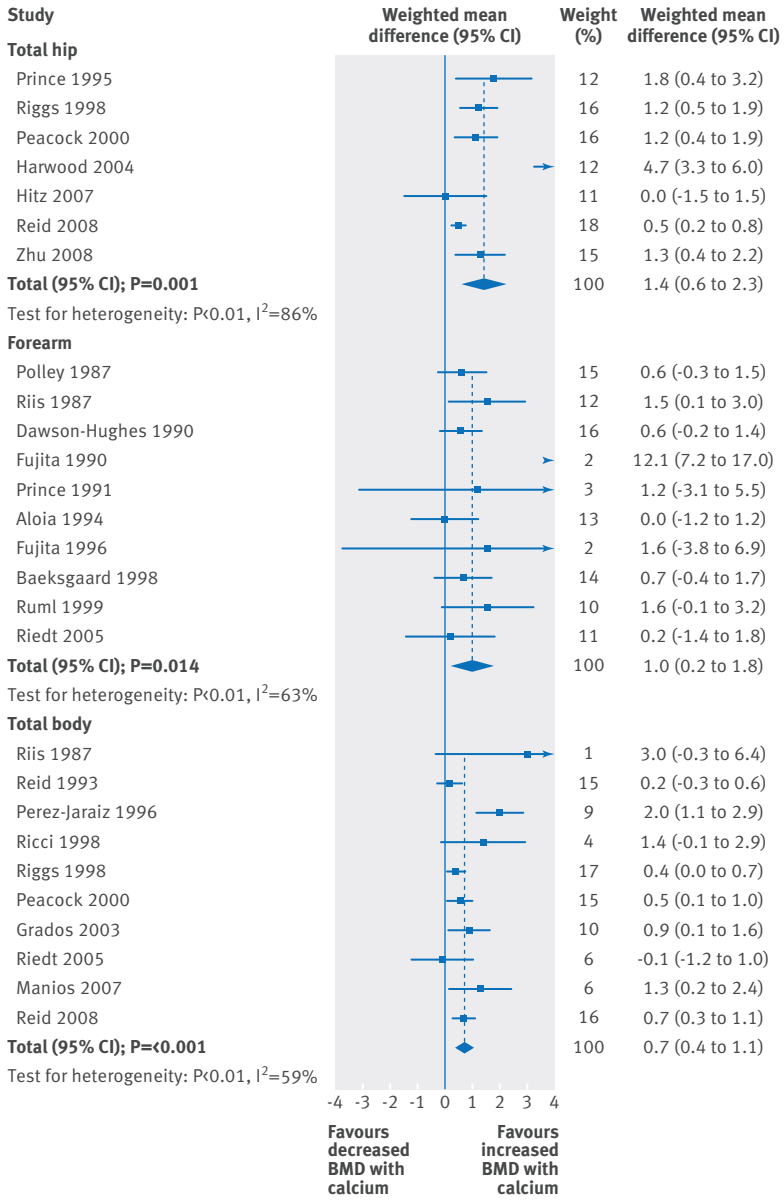

Fig 4 | **Random effects meta-analysis of effect of calcium supplements on percentage change in bone mineral density (BMD) for total hip, forearm, and total body from baseline at one year**

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

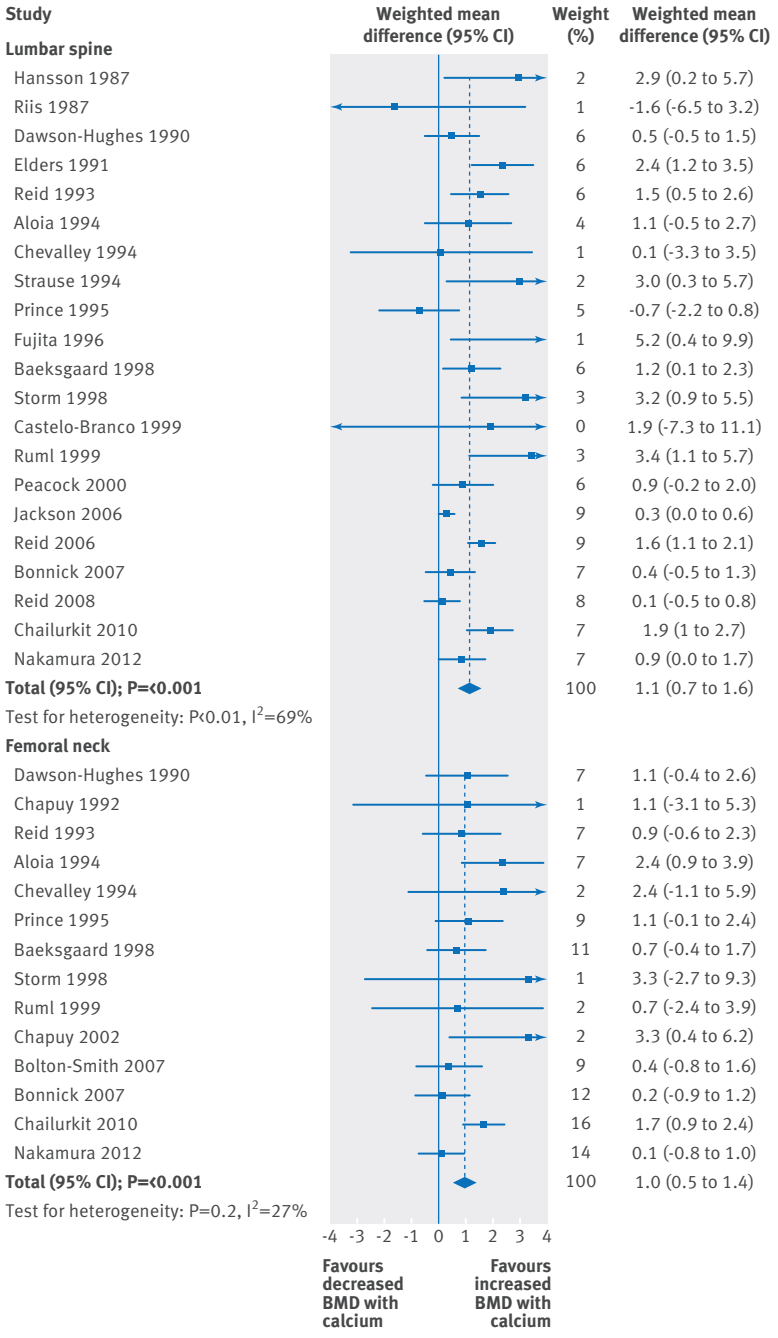

Fig 5 | **Random effects meta-analysis of effect of calcium supplements on percentage change in bone mineral density (BMD) for lumbar spine and femoral neck from baseline at two years**

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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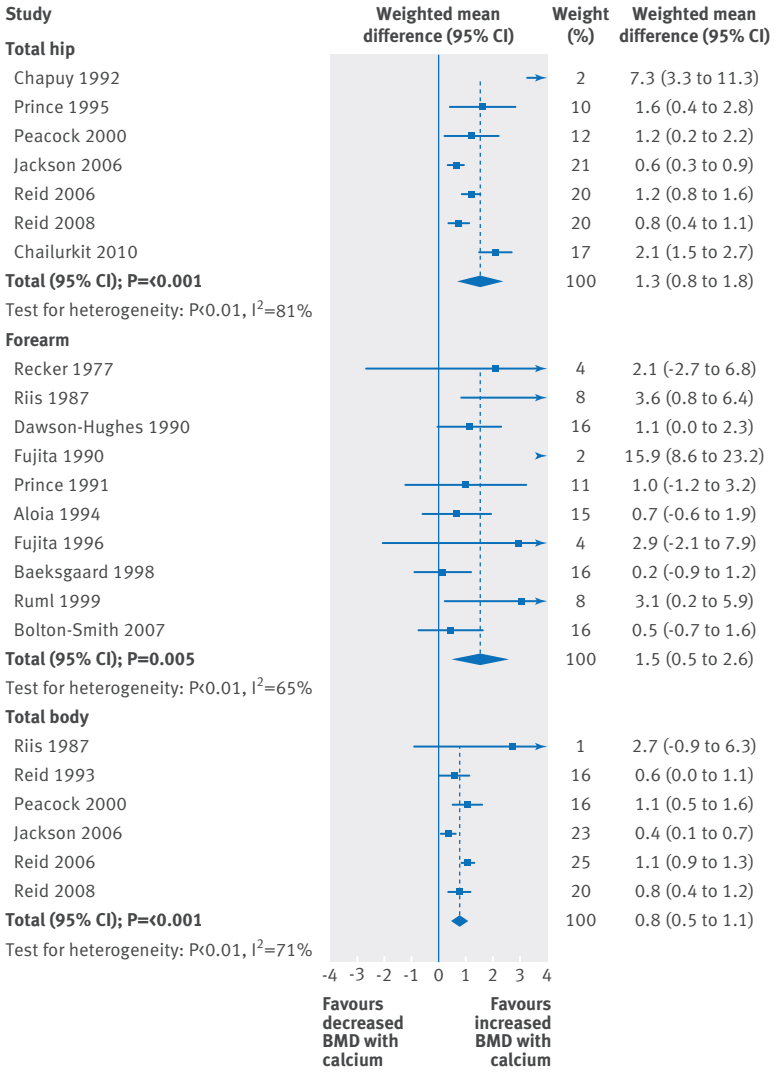

Fig 6 | **Random effects meta-analysis of effect of calcium supplements on percentage change in bone mineral density (BMD) for total hip, forearm, and total body from baseline at two years**

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.

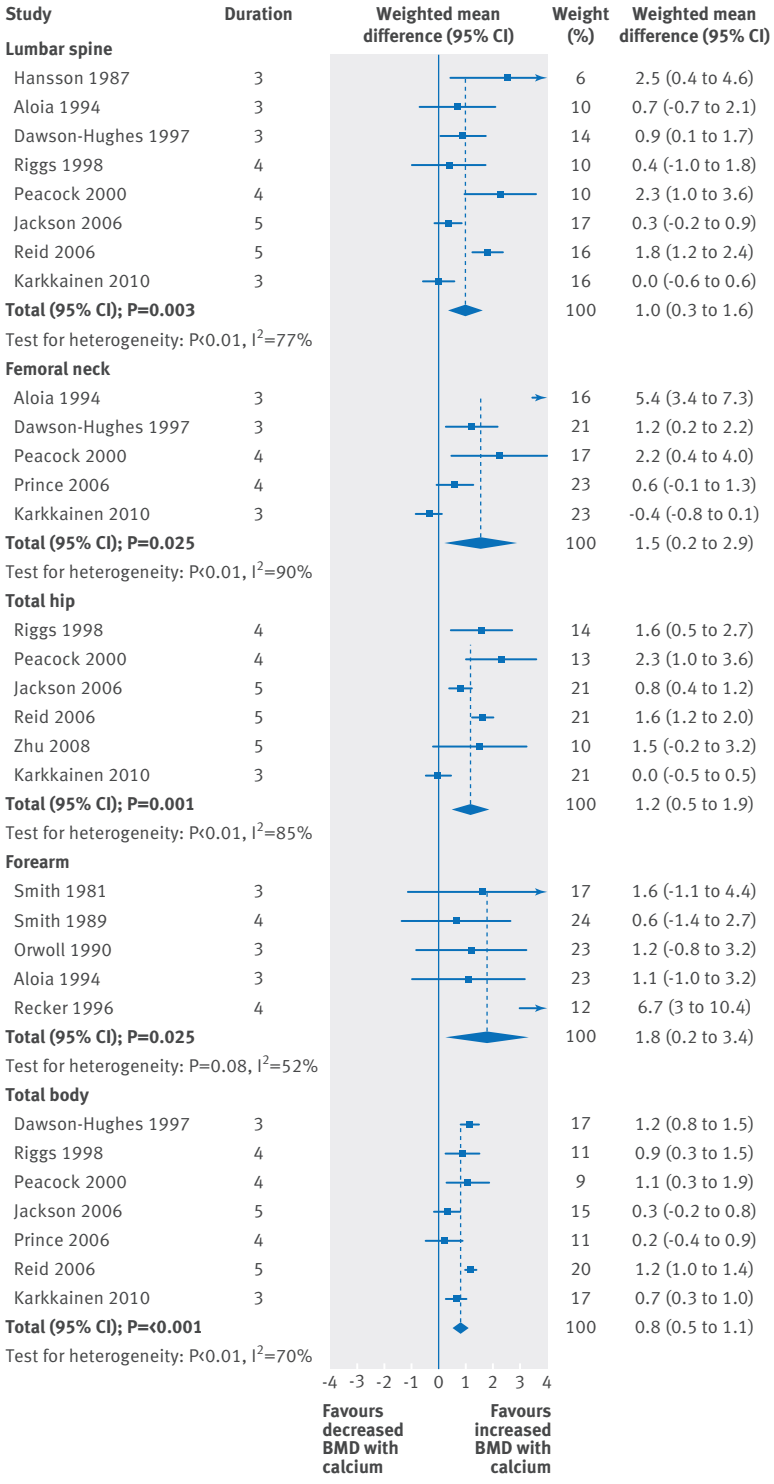

Fig 7 | Random effects meta-analysis of effect of calcium supplements on percentage change in bone mineral density (BMD) from baseline in studies that lasted more than two and a half years

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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Competing interests: All authors have completed the ICMJE uniform disclosure form athttp://www.icmje.org/coi_disclosure.pdf and declare: MJB is the recipient of a Sir Charles Hercus health research fellowship; IRR has received research grants and honorariums from Merck, Amgen, Lilly, and Novartis.

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.

1 Consensus conference: Osteoporosis. *JAMA* 1984;252:799-802.
2 IOM (Institute of Medicine). Dietary reference intakes for calcium and vitamin D. National Academies Press, 2011.
3 Tang BMP, Eslick GD, Nowson C, Smith C, Bensoussan A. 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. *Lancet* 2007;370:657-66.
4 Bolland MJ, Barber PA, Doughty RN, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ* 2008;336:262-6.
5 Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691.
6 Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ* 2011;342:d2040.
7 Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-83.
8 Lewis JR, Zhu K, Prince RL. Adverse events from calcium supplementation: relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. *J Bone Miner Res* 2012;27:719-22.
9 Bauer DC. Clinical practice. Calcium supplements and fracture prevention. *N Engl J Med* 2013;369:1537-43.
10 Bolland MJ, Leung W, Tai V, et al. Calcium intake and risk of fracture: systematic review. *BMJ* 2015;351:h4580.
11 Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. Cochrane Collaboration, 2011. www.cochrane-handbook.org.
12 Hansson T, Roos B. The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. *Calcif Tissue Int* 1987;40:315-7.
13 Peacock M, Liu G, Carey M, et al. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *J Clin Endocrinol Metab* 2000;85:3011-9.
14 Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: the Nottingham Neck of Femur (NONOF) Study. *Age Ageing* 2004;33:45-51.
15 Hitz MF, Jensen JE, Eskildsen PC. Bone mineral density and bone markers in patients with a recent low-energy fracture: effect of 1 y of treatment with calcium and vitamin D. *Am J Clin Nutr* 2007;86:251-9.
16 Recker RR, Heaney RP. The effect of milk supplements on calcium metabolism, bone metabolism and calcium balance. *Am J Clin Nutr* 1985;41:254-63.
17 Polley KJ, Nordin BE, Baghurst PA, Walker CJ, Chatterton BE. Effect of calcium supplementation on forearm bone mineral content in postmenopausal women: a prospective, sequential controlled trial. *J Nutr* 1987;117:1929-35.
18 Nelson ME, Fisher EC, Dilmanian FA, Dallal GE, Evans WJ. A 1-y walking program and increased dietary calcium in postmenopausal women: effects on bone. *Am J Clin Nutr* 1991;53:1304-11.
19 Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporos Int* 1994;4:245-52.
20 Prince R, Devine A, Dick I, et al. The effects of calcium supplementation (milk powder or tablets) and exercise on bone density in postmenopausal women. *J Bone Miner Res* 1995;10:1068-75.
21 Storm D, Eslin R, Porter ES, et al. Calcium supplementation prevents seasonal bone loss and changes in biochemical markers of bone turnover in elderly New England women: a randomized placebo-controlled trial. *J Clin Endocrinol Metab* 1998;83:3817-25.
22 Castelo-Branco C, Pons F, Vicente JJ, Sanjuan A, Vanrell JA. Preventing postmenopausal bone loss with ossein-hydroxyapatite compounds. Results of a two-year, prospective trial. *J Reprod Med* 1999;44:601-5.
23 Cleghorn DB, O'Loughlin PD, Schroeder BJ, Nordin BE. An open, crossover trial of calcium-fortified milk in prevention of early postmenopausal bone loss. *Med J Aust* 2001;175:242-5.
24 Lau EM, Woo J, Lam V, Hong A. Milk supplementation of the diet of postmenopausal Chinese women on a low calcium intake retards bone loss. *J Bone Miner Res* 2001;16:1704-9.
25 Chee WS, Suriah AR, Chan SP, Zaitun Y, Chan YM. The effect of milk supplementation on bone mineral density in postmenopausal Chinese women in Malaysia. *Osteoporos Int* 2003;14:828-34.
26 Albertazzi P, Steel SA, Howarth EM, Purdie DW. Comparison of the effects of two different types of calcium supplementation on markers of bone metabolism in a postmenopausal osteopenic population with low calcium intake: a double-blind placebo-controlled trial. *Climacteric* 2004;7:33-40.
27 Daly RM, Brown M, Bass S, Kukuljan S, Nowson C. Calcium- and vitamin D3-fortified milk reduces bone loss at clinically relevant skeletal sites in older men: a 2-year randomized controlled trial. *J Bone Miner Res* 2006;21:397-405.
28 Manios Y, Moschonis G, Trovas G, Lyritis GP. Changes in biochemical indexes of bone metabolism and bone mineral density after a 12-mo dietary intervention program: the Postmenopausal Health Study. *Am J Clin Nutr* 2007;86:781-9.
29 Kukuljan S, Nowson CA, Bass SL, et al. Effects of a multi-component exercise program and calcium-vitamin-D3-fortified milk on bone mineral density in older men: a randomised controlled trial. *Osteoporos Int* 2009;20:1241-51.
30 Gui JC, Brasic JR, Liu XD, et al. Bone mineral density in postmenopausal Chinese women treated with calcium fortification in soymilk and cow's milk. *Osteoporos Int* 2012;23:1563-70.
31 Recker RR, Saville PD, Heaney RP. Effect of estrogens and calcium carbonate on bone loss in postmenopausal women. *Ann Intern Med* 1977;87:649-55.
32 Lamke B, Sjoberg HE, Sylven M. Bone mineral content in women with Colles' fracture: effect of calcium supplementation. *Acta Orthop Scand* 1978;49:143-6.
33 Smith EL Jr, Reddan W, Smith PE. Physical activity and calcium modalities for bone mineral increase in aged women. *Med Sci Sports Exerc* 1981;13:60-4.
34 Riis B, Thomsen K, Christiansen C. Does calcium supplementation prevent postmenopausal bone loss? A double-blind, controlled clinical study. *N Engl J Med* 1987;316:173-7.
35 Smith EL, Gilligan C, Smith PE, Sempos CT. Calcium supplementation and bone loss in middle-aged women. *Am J Clin Nutr* 1989;50:833-42.
36 Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women. *N Engl J Med* 1990;323:878-83.
37 Fujita T, Fukase M, Miyamoto H, Matsumoto T, Ohue T. Increase of bone mineral density by calcium supplement with oyster shell electrolysate. *Bone Miner* 1990;11:85-91.
38 Orwoll ES, Oviatt SK, McClung MR, Deftos LJ, Sexton G. The rate of bone mineral loss in normal men and the effects of calcium and cholecalciferol supplementation. *Ann Intern Med* 1990;112:29-34.
39 Elders PJ, Netelenbos JC, Lips P, et al. Calcium supplementation reduces vertebral bone loss in perimenopausal women: a controlled trial in 248 women between 46 and 55 years of age. *J Clin Endocrinol Metab* 1991;73:533-40.
40 Prince RL, Smith M, Dick IM, et al. Prevention of postmenopausal osteoporosis. A comparative study of exercise, calcium supplementation, and hormone-replacement therapy. *N Engl J Med* 1991;325:1189-95.
41 Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med* 1992;327:1637-42.
42 Lau EM, Woo J, Leung PC, Swaminathan R, Leung D. The effects of calcium supplementation and exercise on bone density in elderly Chinese women. *Osteoporos Int* 1992;2:168-73.
43 Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Effect of calcium supplementation on bone loss in postmenopausal women. *N Engl J Med* 1993;328:460-4.
44 Aloia JF, Vaswani A, Yeh JK, Ross PL, Flaster E, Dilmanian FA. Calcium supplementation with and without hormone replacement therapy to prevent postmenopausal bone loss. *Ann Intern Med* 1994;120:97-103.
45 Strause L, Saltman P, Smith KT, Bracker M, Andon MB. Spinal bone loss in postmenopausal women supplemented with calcium and trace minerals. *J Nutr* 1994;124:1060-4.
46 Fujita T, Ohue T, Fujii Y, Miyauchi A, Takagi Y. Heated oyster shell-seaweed calcium (AAA Ca) on osteoporosis. *Calcif Tissue Int* 1996;58:226-30.
47 Perez-Jaraiz MD, Revilla M, Alvarez de los Heros JI, Villa LF, Rico H. Prophylaxis of osteoporosis with calcium, estrogens and/or eelcatonin: comparative longitudinal study of bone mass. *Maturitas* 1996;23:327-32.
48 Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res* 1996;11:1961-6.
49 Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med* 1997;337:670-6.
50 Baeksgaard L, Andersen KP, Hyldstrup L. Calcium and vitamin D supplementation increases spinal BMD in healthy, postmenopausal women. *Osteoporos Int* 1998;8:255-60.
51 Ricci TA, Chowdhury HA, Heymsfield SB, Stahl T, Pierson RN Jr, Shapses SA. Calcium supplementation suppresses bone turnover during weight reduction in postmenopausal women. *J Bone Miner Res* 1998;13:1045-50.

52 Riggs BL, O'Fallon WM, Muhs J, O'Connor MK, Kumar R, Melton LJ 3rd. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. *J Bone Miner Res* 1998;13:168-74.
53 Ruml LA, Sakhaee K, Peterson R, Adams-Huet B, Pak CY. The effect of calcium citrate on bone density in the early and mid-postmenopausal period: a randomized placebo-controlled study. *Am J Ther* 1999;6:303-11.
54 Fujita T, Fujii Y, Goto B, Miyauchi A, Takagi Y. Peripheral computed tomography (pQCT) detected short-term effect of AAACa (heated oyster shell with heated algal ingredient HAI): a double-blind comparison with CaCO3 and placebo. *J Bone Miner Metab* 2000;18:212-15.
55 Son SM, Chun YN. Effect of oral therapy with alphacalcidol or calcium in Korean elderly women with osteopenia and low dietary calcium. *Nutr Res* 2001;21:1347-55.
56 Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. *Osteoporos Int* 2002;13:257-64.
57 Grados F, Brazier M, Kamel S, et al. Effects on bone mineral density of calcium and vitamin D supplementation in elderly women with vitamin D deficiency. *Joint Bone Spine* 2003;70:203-8.
58 Doetsch AM, Faber J, Lynnerup N, Watjen I, Bliddal H, Danneskiold-Samsoe B. The effect of calcium and vitamin D3 supplementation on the healing of the proximal humerus fracture: a randomized placebo-controlled study. *Calcif Tissue Int* 2004;75:183-8.
59 Meier C, Woitge HW, Witte K, Lemmer B, Seibel MJ. Supplementation with oral vitamin D3 and calcium during winter prevents seasonal bone loss: a randomized controlled open-label prospective trial. *J Bone Miner Res* 2004;19:1221-30.
60 Riedt CS, Cifuentes M, Stahl T, Chowdhury HA, Schlussel Y, Shapses SA. Overweight postmenopausal women lose bone with moderate weight reduction and 1 g/day calcium intake. *J Bone Miner Res* 2005;20:455-63.
61 Prince RL, Devine A, Dhaliwal SS, Dick IM. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Arch Intern Med* 2006;166:869-75.
62 Reid IR, Mason B, Horne A, et al. Randomized controlled trial of calcium in healthy older women. *Am J Med* 2006;119:777-85.
63 Bolton-Smith C, McMurdo ME, Paterson CR, et al. Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. *J Bone Miner Res* 2007;22:509-19.
64 Bonnick S, Broy S, Kaiser F, et al. Treatment with alendronate plus calcium, alendronate alone, or calcium alone for postmenopausal low bone mineral density. *Curr Med Res Opin* 2007;23:1341-9.
65 Reid IR, Ames R, Mason B, et al. Randomized controlled trial of calcium supplementation in healthy, nonosteoporotic, older men. *Arch Intern Med* 2008;168:2276-82.
66 Zhu K, Devine A, Dick IM, Wilson SG, Prince RL. Effects of calcium and vitamin D supplementation on hip bone mineral density and calcium-related analytes in elderly ambulatory Australian women: a five-year randomized controlled trial. *J Clin Endocrinol Metab* 2008;93:743-9.
67 Chailurkit LO, Saetung S, Thakkinstian A, Ongphiphadhanakul B, Rajatanavin R. Discrepant influence of vitamin D status on parathyroid hormone and bone mass after two years of calcium supplementation. *Clin Endocrinol (Oxf)* 2010;73:167-72.
68 Rajatanavin R, Chailurkit L, Saetung S, Thakkinstian A, Nimitphong H. The efficacy of calcium supplementation alone in elderly Thai women over a 2-year period: a randomized controlled trial. *Osteoporos Int* 2013;24:2871-7.
69 Karkkainen MK, Tuppurainen M, Salovaara K, et al. Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS). *Maturitas* 2010;65:359-65.
70 Nakamura K, Saito T, Kobayashi R, et al. Effect of low-dose calcium supplements on bone loss in perimenopausal and postmenopausal Asian women: a randomized controlled trial. *J Bone Miner Res* 2012;27:2264-70.
71 Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. *Lancet* 2014;383:146-55.
72 Shea B, Wells G, Cranney A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocr Rev* 2002;23:552-9.
73 Bristow SM, Gamble GD, Stewart A, et al. Acute and 3-month effects of microcrystalline hydroxyapatite, calcium citrate and calcium carbonate on serum calcium and markers of bone turnover: a randomised controlled trial in postmenopausal women. *Br J Nutr* 2014;112:1611-20.
74 Bonjour JP, Brandolini-Bunlon M, Boirie Y, et al. Inhibition of bone turnover by milk intake in postmenopausal women. *Br J Nutr* 2008;100:866-74.
75 Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. *Osteoporos Int* 2005;16:581-9.
76 Cranney A, Guyatt G, Krolicki N, et al. A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis. *Osteoporos Int* 2001;12:140-51.
77 Cranney A, Tugwell P, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. IV. Meta-analysis of raloxifene for the prevention and treatment of postmenopausal osteoporosis. *Endocr Rev* 2002;23:524-8.
78 Freemantle N, Cooper C, Diez-Perez A, et al. Results of indirect and mixed treatment comparison of fracture efficacy for osteoporosis treatments: a meta-analysis. *Osteoporos Int* 2013;24:209-17.
79 Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *N Engl J Med* 1995;333:1437-43.
80 Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. *JAMA* 1998;280:2077-82.
81 Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007;356:1809-22.
82 Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med* 2009;361:756-65.
83 Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
84 Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701-12.
85 McCloskey EV, Beneton M, Charlesworth D, et al. Clodronate reduces the incidence of fractures in community-dwelling elderly women unselected for osteoporosis: results of a double-blind, placebo-controlled randomized study. *J Bone Miner Res* 2007;22:135-41.
86 Hosking D, Chilvers CE, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. *N Engl J Med* 1998;338:485-92.
87 Grey A, Bolland MJ, Wattie D, Horne A, Gamble G, Reid IR. The antiresorptive effects of a single dose of zoledronate persist for two years: a randomized, placebo-controlled trial in osteopenic postmenopausal women. *J Clin Endocrinol Metab* 2009;94:538-44.
88 Grey A, Bolland M, Wong S, Horne A, Gamble G, Reid IR. Low-dose zoledronate in osteopenic postmenopausal women: a randomized controlled trial. *J Clin Endocrinol Metab* 2012;97:286-92.

Appendix 1: Literature searches

Appendix 2: Supplementary tables A-F and figure A