BMJ

RESEARCH

Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis

Mark J Bolland, senior research fellow,[1] Alison Avenell, clinical senior lecturer,[2] John A Baron, professor,[3] Andrew Grey, associate professor,[1] Graeme S MacLennan, senior research fellow,[2] Greg D Gamble, research fellow,[1] Ian R Reid, professor[1]

[1]Department of Medicine, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92 019, Auckland 1142, New Zealand

[2]Health Services Research Unit, University of Aberdeen

[3]Department of Medicine, and Department of Community and Family Medicine, Dartmouth Medical School, NH, USA

Correspondence to: I R Reid
i.reid@auckland.ac.nz

Cite this as: *BMJ* 2010;341:c3691
doi:10.1136/bmj.c3691

ABSTRACT

Objective To investigate whether calcium supplements increase the risk of cardiovascular events.

Design Patient level and trial level meta-analyses.

Data sources Medline, Embase, and Cochrane Central Register of Controlled Trials (1966-March 2010), reference lists of meta-analyses of calcium supplements, and two clinical trial registries. Initial searches were carried out in November 2007, with electronic database searches repeated in March 2010.

Study selection Eligible studies were randomised, placebo controlled trials of calcium supplements (≥500 mg/day), with 100 or more participants of mean age more than 40 years and study duration more than one year. The lead authors of eligible trials supplied data. Cardiovascular outcomes were obtained from self reports, hospital admissions, and death certificates.

Results 15 trials were eligible for inclusion, five with patient level data (8151 participants, median follow-up 3.6 years, interquartile range 2.7-4.3 years) and 11 with trial level data (11 921 participants, mean duration 4.0 years). In the five studies contributing patient level data, 143 people allocated to calcium had a myocardial infarction compared with 111 allocated to placebo (hazard ratio 1.31, 95% confidence interval 1.02 to 1.67, P=0.035). Non-significant increases occurred in the incidence of stroke (1.20, 0.96 to 1.50, P=0.11), the composite end point of myocardial infarction, stroke, or sudden death (1.18, 1.00 to 1.39, P=0.057), and death (1.09, 0.96 to 1.23, P=0.18). The meta-analysis of trial level data showed similar results: 296 people had a myocardial infarction (166 allocated to calcium, 130 to placebo), with an increased incidence of myocardial infarction in those allocated to calcium (pooled relative risk 1.27, 95% confidence interval 1.01 to 1.59, P=0.038).

Conclusions Calcium supplements (without coadministered vitamin D) are associated with an increased risk of myocardial infarction. As calcium supplements are widely used these modest increases in risk of cardiovascular disease might translate into a large burden of disease in the population. A reassessment of the role of calcium supplements in the management of osteoporosis is warranted.

INTRODUCTION

Osteoporosis is a major cause of morbidity and mortality in older people.[1] Calcium supplements marginally reduce the risk of fracture,[2 3] and most guidelines recommend adequate calcium intake as an integral part of the prevention or treatment of osteoporosis.[4 5] Consequently, calcium supplements are commonly used by people over the age of 50. Observational studies suggest that high calcium intake might protect against vascular disease,[6-8] and the findings are consistent with those of interventional studies of calcium supplements that show improvement in some vascular risk factors.[9-11] In contrast, calcium supplements accelerate vascular calcification and increase mortality in patients with renal failure, in both dialysis and predialysis populations.[12-14] Furthermore, a five year randomised controlled trial of calcium supplements in healthy older women, in which cardiovascular events were prespecified as secondary end points, recently reported possible increases in rates of myocardial infarction and cardiovascular events in women allocated to calcium.[15 16] We carried out a meta-analysis of cardiovascular events in randomised trials of calcium supplements.

METHODS

In November 2007 we searched Medline, Embase, and the Cochrane Central Register of Controlled Trials for randomised placebo controlled trials of calcium supplements, using the terms "calcium", "randomised controlled trial", and "placebo" as text words, and corresponding MeSH terms (full details are available from the authors). We searched for studies in the reference lists of meta-analyses published between 1990 and 2007 of the effect of calcium supplements on bone density, fracture, colorectal neoplasia, and blood pressure, and in two clinical trial registries (ClinicalTrials.gov and Australian New Zealand Clinical Trials Registry). No language restrictions were applied. In March 2010 we updated the searches of the electronic databases (Medline: January 1966-March 2010, Embase: January 1980-March 2010, Central Register of Controlled Trials: first quarter 2010).

Study selection

We included studies if they were randomised, double blind, placebo controlled trials; elemental calcium was administered at a dose of ≥500 mg/day; the participants' mean age at baseline was more than 40 years; 100 or more participants were randomised; participants of either sex were studied; and the trial duration was more than one year.

We excluded trials concerning calcium and vitamin D given together with a placebo comparator (trials were only eligible if vitamin D was given to both intervention and control groups, because vitamin D supplementation has been associated with decreased mortality[17]); trials in which calcium was administered in the form of dietary modification or a complex nutritional supplement; and trials in which most participants had a major systemic disease other than osteoporosis.

Search results

One investigator (MB) carried out the initial search and two investigators (AG and MB) independently reviewed all potentially relevant studies. Overall, 190 potentially relevant reports of studies were identified from the initial searches, but only 15 studies were eligible for analysis.[15 16 18-33] Thirteen studies compared calcium supplements with placebo,[15 16 18-27 29 31-33] one study had a 2×2 factorial design allowing comparison of calcium with placebo and calcium plus vitamin D with vitamin D,[28] and one study compared calcium plus alendronate with alendronate.[30]

Data description

We invited the lead author of each eligible study to provide patient level data on cardiovascular events that occurred during the study irrespective of whether the participant was still taking the trial drug. When such data were not available we requested summary data at trial level. We obtained patient level data on cardiovascular outcomes for five studies, and partially complete trial level data for six. No data were available for four studies because the original records were no longer available and cardiovascular events were not previously reported,[18 20] or no cardiovascular data were available.[23 26] Thus, patient level data on cardiovascular outcomes were available for 63% of participants in the 15 eligible studies, complete trial level data for 85% of participants, and at least partially complete trial level data for 93% of participants. Basic demographic and other trial related data were either supplied by the lead authors (or nominated deputies) or extracted from the original publication by an investigator (MB).

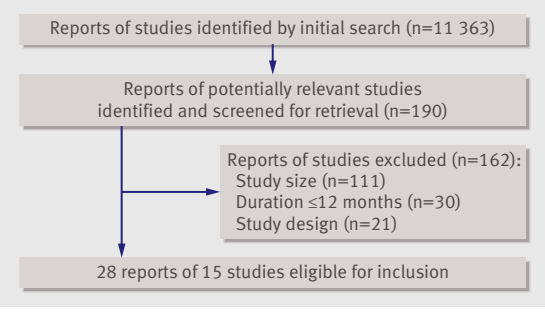


Fig 1 | Flowchart of studies. Initial search was in November 2007: 9358 reports were identified, 173 reports of potentially relevant studies retrieved, 150 reports excluded, and 23 reports of 15 individual studies identified. Search was updated in March 2010: a further 2005 reports were identified and 17 reports retrieved but no new studies identified

Ascertainment of cardiovascular events

We considered a myocardial infarction to have occurred when either of the terms "myocardial infarction" or "heart attack", or code 410 (international classification of diseases, ninth revision), was used to describe the event. A stroke was considered to have occurred when any of the terms "stroke", "cerebral infarction", "intracerebral hemorrhage", "subarachnoid hemorrhage", or "cerebrovascular accident", or any of the ICD-9 codes 430, 431, 433, 434 were used to describe the event. We considered a sudden death to have occurred when the term "sudden death" or the ICD-9 code 798 was used to describe the event.

Five studies contributed patient level data on cardiovascular events. For one study,[21 22] self reports of unadjudicated events were supplied. Another study[28] supplied self reports of hospital admissions and cause of death from death certificates. Each event was then independently adjudicated by two physicians blinded to the treatment allocation of the participants (MB, AG), and any disagreements were resolved by consensus. For another study,[25] verified events from hospital discharge data were supplied along with causes of deaths from death certificates. The causes of death were again independently adjudicated. For two studies,[15 33] data from self reports, hospital admissions, and death certificates were independently adjudicated by a cardiologist or neurologist, as previously described.[16] For six studies contributing trial level data, all data on cardiovascular events were supplied by the lead authors and were obtained from physician reported cause of death in one study[27] and a combination of self reports and hospital discharge data in five studies.[19 24 29-32]

End points

The prespecified primary end points were time to first myocardial infarction, time to first stroke, and time to first event for the composite end point of myocardial infarction, stroke, or sudden death. The secondary end point was time to death (all cause mortality).

Statistical analysis

In trials with patient level data, we analysed each end point using a Cox proportional hazards model, with a dummy coded variable representing each study in the model, and we reported the hazard ratio, with 95% confidence interval, and number needed to treat. The assumption of proportional hazards was explored by

Table 1 | Characteristics of 15 studies eligible for inclusion in meta-analysis

Studies	No in calcium group/ No in control group	Daily dose and supplement type	Trial duration (years)	Primary end point	Baseline mean age (years)	% female
Patient level data on cardiovascular outcomes:						
Reid 1993[21 22]	68/67	1 g lactogluconate-carbonate	4	Bone mineral density	58	100
Baron 1999[25]	464/466	1.2 g carbonate	4	Colorectal adenoma	61	28
Grant 2005[28]	2617/2675	1 g carbonate	4*	Low trauma fracture	77	85
Reid 2006[15 16]	732/739	1 g citrate	5	Clinical fracture	74	100
Reid 2008[33]	216/107	0.6 g or 1.2 g citrate	2	Spine bone mineral density	56	0
Subtotal/average†	4097/4054	—	4.1	—	73	78
Trial level data on cardiovascular outcomes‡:						
Dawson-Hughes 1990[19]	238/123	0.5 g carbonate or citrate	2	Spine bone mineral density	58	100
Riggs 1998[24]	119/117	1.6 g citrate	4	Bone mineral density	66	100
Bonithon-Kopp 2000[27]	204/212	2 g lactogluconate-carbonate	3	Colorectal adenoma	59	37
Prince 2006[29]	730/730	1.2 g carbonate	5	Osteoporotic fracture	75	100
Bonnick 2007[30]	282/281	1 g carbonate	2	Spine bone mineral density	66	100
Lappe 2007[31 32]	446/288	1.4 g citrate or 1.5 g carbonate	4	Fracture incidence	67	100
Subtotal/average†	2019/1751	—	3.8	—	68	93
Total/average†	6116/5805		4.0		72	83
No data on cardiovascular outcomes:						
Smith 1989[18]§	84/85	1.5 g carbonate	4	Arm bone mineral density	51	100
Elders 1991[20]	198/97	1g or 2g lactogluconate-carbonate or citrate	2	Spine bone mineral density	NA	100
Recker 1996[23]	95/102	1.2 g carbonate	4	Vertebral fracture	74	100
Peacock 2000[26]	126/135	0.75 g citrate	4	Hip bone mineral density	76	72
Subtotal/average†	503/419	—	4.0	—	69	88

NA=not available.
*All participants were followed for two years with a median follow-up of 45 months.
†Weighted by person years of follow-up.
‡Complete trial level data were available for two studies.[29 31] Partially complete data were available for four studies[19 24 27 30] (see table 2 for details).
§No original records remained but lead author recalled no heart attacks in either treatment group.

carrying out a test for proportionality of the interaction between variables included in the model and the logarithm of time. For a small number of events (<10%) the timing was unknown. We treated these events as if they had occurred on the last day of follow-up for that participant. Possible confounding by covariates was assessed by repeating these models including prespecified covariates likely to be associated with cardiovascular outcomes (age, sex, smoking status, presence of diabetes, dyslipidaemia, and hypertension at baseline, and history of coronary heart disease) where data were available for more than 80% of participants. Prespecified subgroup analyses for dietary calcium, age, sex, vitamin D status (serum 25-hydroxyvitamin D ≥50 nmol/l or <50 nmol/l), and supplement type were done using interaction terms between treatment allocation and the factor of interest.

We used Poisson regression models to assess the relation between the total number of events and treatment allocation. Because recurrent cardiovascular events in an individual are unlikely to be independent, we used Poisson regression with general estimating equations to account for the intra-individual dependence of events.

To assess statistical heterogeneity between summary data at trial level we used Cochran's Q statistic ($P<0.10$) and the I^2 statistic ($I^2>50\%$). No significant statistical heterogeneity existed between trials in any of the analyses. We used random effects models to pool summary data at trial level. Publication bias was assessed using Funnel plots and Egger's regression model.[34] Analyses were done using SAS version 9.1 or Comprehensive Meta-analysis version 2 (Biostat, Englewood, NJ). All tests were two tailed and we considered $P<0.05$ as significant.

RESULTS

Figure 1 shows the results of the literature search and table 1 the characteristics of the eligible studies. The quality of the five studies contributing patient level data has been independently assessed in previous systematic reviews.[3 35 36]

All 11 eligible trials were double blind, randomised studies. The method of randomisation was stated explicitly in seven: one used a central randomisation service and six used computer generated random numbers. Allocation concealment was explicitly described in four studies. Ten studies gave details of participants who withdrew or were lost to follow-up. Compliance was reported in all 11 studies, but the definitions for compliance differed between studies and were not always comparable. In general, studies reported compliance of more than 75% in participants who were taking tablets at study completion. Table 2 shows the baseline cardiovascular characteristics, dietary calcium intake, and vitamin D status of participants.

Table 2 | Baseline cardiovascular and other variables in trials with patient or trial level data available for cardiovascular outcomes. Values are means (standard deviations) unless stated otherwise

Studies	Dietary calcium (mg/day)	Vitamin D* (nmol/l)	Weight (kg)	Current smoker (%)	Hypertension (%)	Diabetes (%)	Ischaemic heart disease (%)	Lipid disorder (%)
Dawson-Hughes[19]	406 (84)	NA	NA	NA	NA	NA	NA	NA
Reid[21 22]	750 (290)	93 (37)	65 (9)	10	9	0	2	1
Riggs[24]	710 (290)	80 (25)	NA	NA	NA	NA	NA	NA
Baron[25]	880 (440)	73 (27)	82 (15)	19	37	10	12	32
Bonithon-Kopp[27]	980 (380)	NA	NA	NA	NA	NA	NA	NA
Grant[28]	820 (350)	45 (18)†	65 (13)	12	NA	8	NA	NA
Reid[15 16]	860 (390)	54 (18)	67 (11)	3	29	3	8	8
Prince[29]	915	NA	69 (13)	NA	NA	NA	NA	NA
Bonnick[30]	1240 (580)	NA	NA	0.4	NA	NA	NA	NA
Lappe[31 32]	1070	72 (20)	77 (15)	NA	NA	NA	NA	NA
Reid[33]	870 (450)	92 (33)	83 (12)	3	8	0.3	0.3	4

NA=not available.
*25-hydroxyvitamin D.
†25-hydroxyvitamin D measured in sample of 80 participants.

Cardiovascular events by treatment allocation are shown in table 3.

Patient level analysis

Table 4 shows the baseline characteristics of the treatment groups in the five studies contributing patient level data. The median (interquartile range) duration of follow-up in both groups was 3.6 (2.7-4.3) years.

In total, 143 people allocated to calcium had a myocardial infarction during follow-up compared with 111 allocated to placebo. The risk of incident myocardial infarction in those allocated to calcium increased by 31% (hazard ratio 1.31, 95% confidence interval 1.02 to 1.67, P=0.035. fig 2). During follow-up, 167 people allocated to calcium and 143 allocated to placebo had a stroke (1.20, 0.96 to 1.50, P=0.11), 293 people allocated to calcium and 254 allocated to placebo had any of myocardial infarction, stroke, or sudden death (1.18, 1.00 to 1.39, P=0.057), and 519 people allocated to calcium and 487 allocated to placebo died (1.09, 0.96 to 1.23, P=0.18). The number needed to treat (NNT) with calcium for five years to cause one incident event was 69 for myocardial infarction, 100 for stroke, 61 for any of myocardial infarction, stroke, or sudden death, and 77 for death. Adjusting for prespecified covariates related to cardiovascular outcomes with data available for more than 80% of participants (age, sex, smoking status, and diabetes) did not change the results of the primary analyses.

Prespecified subgroup analyses showed a significant interaction between treatment allocation and dietary calcium intake for myocardial infarction. Calcium treatment was associated with an increased risk of myocardial infarction in people with dietary calcium intake above the median of 805 mg/day (hazard ratio 1.85, 95% confidence interval 1.28 to 2.67) but no increased risk in those with dietary calcium intake below the median (0.98, 0.69 to 1.38, P for interaction 0.01). When the cohort was divided by fifths of dietary calcium intake rounded to the nearest 100 mg/day, the respective hazard ratios (95% confidence intervals) for the effect of calcium treatment on myocardial infarction were 1.18 (0.70 to 2.00) for <500 mg/day, 0.68 (0.39 to 1.18) for 500-699 mg/day, 2.28 (1.26 to 4.15) for 700-899 mg/day, 1.81 (0.97 to 3.41) for 900-1099 mg/day, and 1.41 (0.81 to 2.48) for ≥1100 mg/day; test for linear trend when hazard ratios are expressed relative to the <500 mg/d fifth, P=0.12. Interactions between treatment allocation and age, sex, vitamin D status, or supplement type for myocardial infarction were not significant, nor were they between treatment allocation and any of these variables or dietary calcium intake for stroke, the composite end point, or death.

Recurrent cardiovascular events tended to be more common in people allocated to calcium. Comparing people allocated to calcium with those allocated to placebo, 19 versus 13 had more than one myocardial infarction (P=0.38), 21 versus 13 had more than one stroke (P=0.23), and 59 versus 32 had more than one of myocardial infarction, stroke, or sudden death (P=0.006). Poisson regression models with general estimating equations were used to estimate the effect of calcium on the total number of events, including incident and recurrent events. Overall, 164 myocardial infarctions occurred in people allocated to calcium compared with 125 in those allocated to placebo (relative risk 1.32, 95% confidence interval 1.02 to 1.71, P=0.032). Stroke occurred in 190 people allocated to calcium compared with 156 allocated to placebo (1.24, 0.99 to 1.56, P=0.07). In total, 361 myocardial infarctions, strokes, or sudden deaths occurred in people allocated to calcium compared with 287 in people allocated to calcium (1.27, 1.07 to 1.51, P=0.006).

Trial level analysis

Table 3 shows summary data on cardiovascular events at trial level. Eight studies[15 16 21 22 25 28-33] were included in the main analysis. A further three trials[19 24 27] had data only available for subgroups of participants. These three trials were included in a sensitivity analysis that included data from all 11 trials. Publication bias

Table 3 | Number of people with cardiovascular events and deaths by treatment allocation

Studies	Calcium group					Placebo group				
	No of participants	Myocardial infarction	Stroke	Composite*	Death	No of participants	Myocardial infarction	Stroke	Composite*	Death
Dawson-Hughes[19]†	238	0	0	NA	NA	123	0	1	NA	NA
Reid[21 22]	68	0	2	2	0	67	0	1	1	0
Riggs[24]‡	119	0	0	0	1	117	0	0	0	0
Baron[25]	464	20	15	31	25	466	17	11	28	22
Bonithon-Kopp[27]§	204	0	1	1	8	212	0	0	1	9
Grant[28]¶	1311	45	56	97	238	1332	39	48	86	217
Grant[28]**	1306	44	60	100	220	1343	34	58	89	218
Reid[15 16]	732	31	34	60	34	739	21	25	50	29
Prince[29]††	730	21	38	56	29	730	17	40	56	38
Bonnick[30]‡‡	282	0	1	NA	2	281	0	2	NA	1
Lappe[31 32]††	446	2	5	8	NA	288	2	4	8	NA
Reid[33]	216	3	0	3	2	107	0	0	0	1
Total	6116	166	212	358	559	5805	130	190	319	535

NA=not available.
*Any of myocardial infarction, stroke, or sudden death. Seventeen events were classified as sudden deaths that occurred in eight people allocated to calcium and nine allocated to placebo.
†Unpublished trial level data provided by author. Data on stroke available only for participants who withdrew from study.
‡Unpublished trial level data provided by author. Data available only for participants who withdrew from study.
§Unpublished trial level data provided by author. Data on cause of death only.
¶Calcium versus placebo arms in Randomised Evaluation of Calcium or Vitamin D (RECORD) study.
**Calcium and vitamin D versus placebo plus vitamin D arms in Randomised Evaluation of Calcium or Vitamin D (RECORD) study.
††Unpublished trial level data provided by author.
‡‡Unpublished trial level data provided by Boyd Scott.

was not evident on inspection of Funnel plots or in Egger's regression model in any analysis (P>0.40 for all analyses). Figure 3 shows the results of the main analysis. Allocation to calcium supplements was associated with an increased risk of myocardial infarction (relative risk 1.27, 95% confidence interval 1.01 to 1.59, P=0.038) but not stroke, the composite end point, or death. Including data from the three additional studies in the sensitivity analysis did not significantly change the results for any end point.

DISCUSSION

In this pooled analysis of around 12 000 participants from 11 randomised controlled trials, calcium supplements were associated with about a 30% increase in the incidence of myocardial infarction and smaller, non-significant, increases in the risk of stroke and mortality. When recurrent events in 10-17% of participants were included in analyses, the results were similar, although the relative risks tended to be slightly larger. The findings were consistent across trials, with an increased relative risk of myocardial infarction with calcium observed in six of the seven trials in which at least one event occurred, although no individual trial reported a statistically significant effect. The risk of myocardial infarction with calcium tended to be greater in those with dietary calcium intake above the median but was independent of age, sex, and type of supplement.

Limitations of the review

Our study has some limitations. We excluded studies that compared coadministered calcium and vitamin D supplements with placebo. The results therefore may not apply to coadministered calcium and vitamin D supplements. None of the trials had cardiovascular outcomes as the primary end points, and data on cardiovascular events were not gathered in a standardised manner. In only two of the trials were the data adjudicated by blinded trial investigators. However, unless there was differential misclassification or misreporting of cardiovascular events in people treated with calcium, this is unlikely to alter the results, because the data came from blinded, placebo controlled trials. Incomplete or no data on cardiovascular outcomes were available for seven trials in our analysis, comprising about 15% of the total number of participants. However, the small size of these trials and the consistency of the findings in the other eight larger trials suggest the missing data are unlikely to have substantially changed the results.

Comparison with other studies

The current findings are consistent with trials of patients with renal failure, in which calcium supplements were associated with an increase in mortality.[13] Few comparable data are available from observational studies of calcium supplements. One study reported a 24% increase in coronary heart disease in Finnish postmenopausal women using calcium supplements (with or without vitamin D) compared with non-users.[37] Non-fatal myocardial infarction in US men using calcium supplements compared with non-users did not increase significantly, although the relative risk for each fifth of supplement intake ranged between 1.02 and 1.07.[38]

The relations between dietary calcium intake and cardiovascular events have also been examined. The inverse relation between calcium intake and

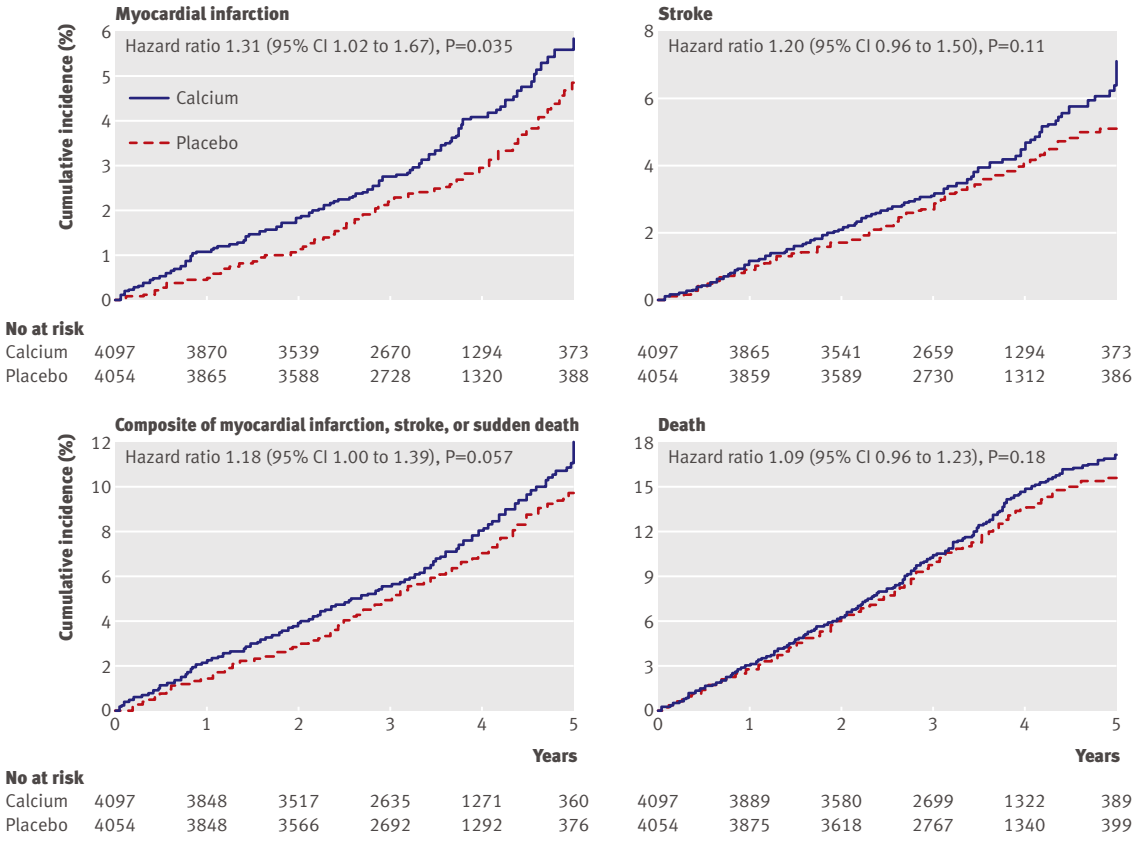


Fig 2 | Cumulative incidence of myocardial infarction, stroke, composite of myocardial infarction, stroke, or sudden death, and death by treatment allocation in five studies that contributed patient level data

standardised mortality ratios for ischaemic heart disease in the United Kingdom was strong.[6] In two US prospective observational studies, women in the highest fourth of calcium intake had 30-40% lower cardiovascular mortality than those in the lowest fourth,[7] and those in the highest fifth of calcium intake had a 30-40% lower risk of ischaemic stroke than those in the lowest fifth.[8] No relation between calcium intake and ischaemic heart disease or stroke was observed in prospective studies of US men,[38 39] or of Dutch civil servants.[40] Thus, in contrast with the observational and interventional studies of calcium supplements, these observational studies do not show increased cardiovascular risks with higher dietary calcium intake. These differences suggest that cardiovascular risks from high calcium intake might be restricted to use of calcium supplements.

A body of evidence related to the current work comes from studies comparing coadministered calcium and vitamin D supplements with placebo, which were excluded from our meta-analysis. Recently, the Women's Health Initiative reported that calcium and vitamin D had no effect on the risk of coronary heart disease or stroke.[41] The findings of that study might differ from ours for several reasons. The Women's Health Initiative used low dose vitamin D supplements, and vitamin D deficiency has been associated with increased risk of cardiovascular disease[42] and vitamin D supplementation with decreased mortality.[17] Also, the participants differed from those in our meta-analysis: on average they were younger (mean age 62 *v* 75 years), heavier (mean weight 76 *v* 68 kg; 34% in Women's Health Initiative *v* 10% of women in our meta-analysis weighed >80 kg), had higher calcium intakes (mean 1150 *v* 830 mg/day), and a higher proportion were using hormone replacement therapy (52% *v* <3% in our meta-analysis). Overall, 54% were taking non-

Table 4 | Baseline characteristics of participants in five studies included in patient level analysis by treatment allocation. Values are percentages unless stated otherwise

Characteristics	Calcium group	Placebo group
Median (interquartile range) age (years)	74.5 (70-79)	74.6 (71-79)
Women	76.5	79.2
White ethnicity	97.2	97.7
Mean (SD) weight (kg)	68.4 (14.1)	67.9 (13.7)
Mean (SD) dietary calcium (mg/day)	837 (377)	831 (370)
Mean (SD) 25-hydroxyvitamin D (nmol/l)*	66.1 (28.9)	64.3 (27.5)
Current smoker	11.0	10.2
Hypertension†	28.0	28.4
Ischaemic heart disease†	8.1	7.8
Lipid disorder†	14.8	15.4
Diabetes	7.0	6.7

Proportion of women was significantly higher in placebo group because one study that only involved men had a 2:1 ratio of allocation to calcium or placebo.[33] No other differences existed between groups. Medical conditions at baseline were self reported by participants.
*Data available from four studies for 1445 participants in calcium groups and 1355 in placebo groups.
†Data available from four studies for 1480 participants in calcium groups and 1379 in placebo groups.

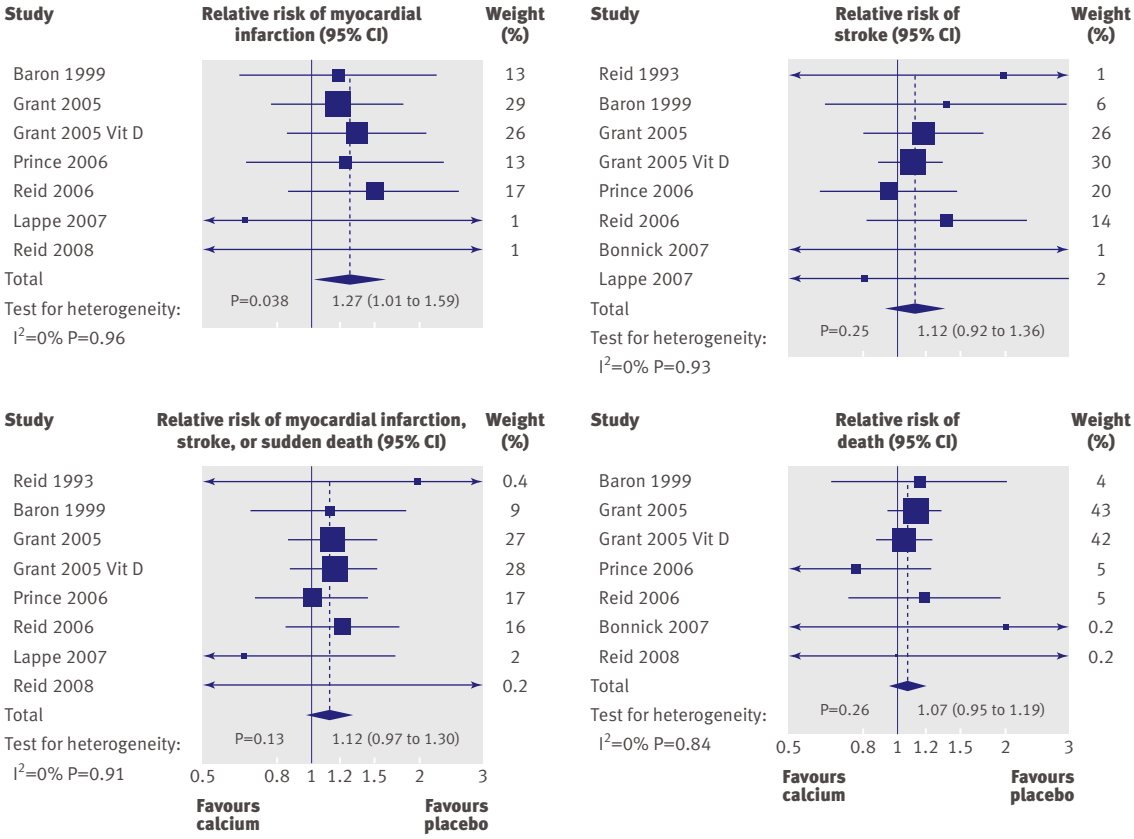


Fig 3 | Random effects models of effect of calcium supplementation on cardiovascular events and death. Full data were available from these eight trials, but some trials do not appear in the figures because no events occurred during the trial: no myocardial infarctions occurred in the study by Reid 1993[21 22] or Bonnick 2007,[30] no strokes occurred in the study by Reid 2008,[33] and no deaths occurred in the study by Reid 1993.[21 22] Data on composite end point were not available for the study by Bonnick 2007[30] or Lappe 2007.[31 32] Grant 2005 is a Randomised Evaluation of Calcium or Vitamin D (RECORD) study calcium versus placebo arms, and Grant 2005 vitamin D is a RECORD study calcium plus vitamin D versus vitamin D plus placebo arms

protocol calcium supplements at baseline (30% were taking ≥500 mg/day), increasing to 69% at the final visit,[43 44] compared with 1.2% taking non-protocol calcium supplements at baseline in our meta-analysis. In the subgroups of women in the Women's Health Initiative who most closely approximated the participants in our analyses (age 70-79 years, body mass index <30 kg/m^2, total calcium intake <800 mg/day), the confidence intervals of the hazard ratios for coronary heart disease with calcium and vitamin D included the hazard ratio for myocardial infarction we observed. It would be valuable to reanalyse the results of the Women's Health Initiative to assess the effects of calcium and vitamin D in non-obese women and in women not taking non-protocol calcium supplements. Interestingly, the only study in our analysis that reported a relative risk of less than 1.0 for myocardial infarction with calcium also had high non-protocol use of calcium supplements.[31 32 45]

The current analyses do not deal with the mechanisms by which calcium supplements might increase the risk of myocardial infarction, but we have reviewed this elsewhere.[46] Calcium supplements acutely increase serum calcium levels to a modest degree.[47] Serum calcium levels have been positively associated with an increased incidence of myocardial infarction in large observational studies.[48-50] Primary hyperparathyroidism, a condition in which serum calcium levels are raised, has also been associated with an increased risk of cardiovascular events and death.[51 52] Ingestion of equivalent doses of calcium from dairy products has a much smaller effect than calcium supplements on serum calcium levels,[53] which might account for the absence of a detrimental vascular effect of dietary calcium intake in the observational studies reviewed. Vascular calcification is an established risk factor for cardiovascular disease,[54] and the process of vascular calcification is similar to osteogenesis.[55] Because calcium supplements increase bone density it is possible that they may also increase vascular calcification and thereby cardiovascular events. In patients with renal failure (both dialysis and predialysis populations) calcium supplements accelerate vascular calcification and increase mortality.[12-14] Our graphical data are consistent with the possibility that an increased risk of myocardial infarction with calcium supplements emerges quickly, pointing to mechanisms such as increased coagulability or altered vascular flow, perhaps mediated directly through the calcium sensing receptor or indirectly through alterations in calcitropic hormones.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Calcium supplements are commonly taken by older people for skeletal health

A randomised placebo controlled trial suggested calcium supplements might increase the risk of myocardial infarction and cardiovascular events

WHAT THIS STUDY ADDS

A meta-analysis of trials totalling 12 000 participants found that calcium supplements increase the risk of myocardial infarction by about 30%

Given the modest benefits of calcium supplements on bone density and fracture prevention, a reassessment of the role of calcium supplements in the management of osteoporosis is warranted

Calcium supplements modestly increase bone density[3 15 33] and have marginal efficacy against fracture.[2 3] In a pooled analysis of studies contributing patient level data,[15 21 22 25 28 33] the hazard ratio for fracture was 0.90 (95% confidence interval 0.80 to 1.01) and NNT for five years to prevent one fracture was 39. A recent meta-analysis of the effect of calcium with or without vitamin D on fracture reported a similar NNT for five years of 48.[3] Later meta-analyses reported that combined supplementation with calcium and vitamin D reduced fractures, whereas vitamin D alone did not.[56 57] Incorporating the results from the current analysis of studies contributing patient level data, treatment of 1000 people with calcium for five years would cause an additional 14 myocardial infarctions, 10 strokes, and 13 deaths, and prevent 26 fractures.

Conclusions

In summary, randomised studies suggest that calcium supplements without coadministered vitamin D are associated with an increased incidence of myocardial infarction. The vascular effects of calcium supplements, especially without vitamin D, should be studied further. Although the magnitude of the increase in risk is modest, the widespread use of calcium supplements means that even a small increase in incidence of cardiovascular disease could translate into a large burden of disease in the population. The likely adverse effect of calcium supplements on cardiovascular events, taken together with the possible adverse effect on incidence of hip fracture[2 58] and its modest overall efficacy in reducing fracture (about 10% reduction in total fractures)[2 3] suggest that a reassessment of the role of calcium supplements in the prevention and treatment of osteoporosis is warranted.

We thank the investigators who provided unpublished data on cardiovascular events from their studies including Larry Riggs, Richard Prince, Claire Bonithon-Kopp, Joan Lappe, Boyd Scott, and Kathy Zhu, as well as Adrian M Grant, M K Campbell, Alison M McDonald and Gladys C McPherson from the Randomised Evaluation of Calcium or Vitamin D trial.
Contributors: MJB, AG, and IRR drafted the protocol. AA and JAB critically revised the protocol. MJB and AG carried out the literature search and event adjudication. All authors provided individual patient data from their studies. MJB and GDG did the analyses. MJB drafted the paper. All authors critically reviewed the paper. MJB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MJB is the guarantor.
Funding: This review was funded by the Health Research Council of New Zealand and the University of Auckland School of Medicine Foundation. AA is funded by a career scientist award of the chief scientist office of the Scottish government health directorates. The Health Services Research Unit is funded by the chief scientist office of the Scottish government health directorates. The sponsors of the study had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The authors are independent from the funders.
Competing interests: All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that: (1) no author has support from companies for the submitted work; (2) IR has received research support from and acted as a consultant for Fonterra that might have an interest in the submitted work in the previous 3 years; JB, IR, AA and GM had study drugs for clinical trials of calcium supplementation supplied by Wyeth; Mission Pharmacal; Shire Pharmaceuticals and Nycomed; and Shire Pharmaceuticals and Nycomed, respectively, might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) no author has non-financial interests that may be relevant to the submitted work.
Ethical approval: Not required.
Data sharing: No additional data available.

1 Sambrook P, Cooper C. Osteoporosis. *Lancet* 2006;367:2010-8.
2 Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, Burckhardt P, Li R, Spiegelman D, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr* 2007;86:1780-90.
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 American Association of Clinical Endocrinologists. Medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis. *Endo Pract* 2003;9:545-64.
5 National Osteoporosis Foundation. Physician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation, 2008.
6 Knox EG. Ischaemic-heart-disease mortality and dietary intake of calcium. *Lancet* 1973;1:1465-7.
7 Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. *Am J Epidemiol* 1999;149:151-61.
8 Iso H, Stampfer MJ, Manson JE, Rexrode K, Hennekens CH, Colditz GA, et al. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. *Stroke* 1999;30:1772-9.
9 Griffith LE, Guyatt GH, Cook RJ, Bucher HC, Cook DJ. The influence of dietary and nondietary calcium supplementation on blood pressure —an updated metaanalysis of randomized controlled trials. *Am J Hypertens* 1999;12:84-92.
10 Reid IR, Mason B, Horne A, Ames R, Clearwater J, Bava U, et al. Effects of calcium supplementation on serum lipid concentrations in normal older women: a randomized controlled trial. *Am J Med* 2002;112:343-7.
11 Reid IR, Horne A, Mason B, Ames R, Bava U, Gamble GD. Effects of calcium supplementation on body weight and blood pressure in normal older women: a randomized controlled trial. *J Clin Endocrinol Metab* 2005;90:3824-9.
12 Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;342:1478-83.
13 Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 2007;71:438-41.
14 Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney Int* 2007;72:1255-61.
15 Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, et al. Randomized controlled trial of calcium in healthy older women. *Am J Med* 2006;119:777-85.
16 Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ* 2008;336:262-6.
17 Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. *Arch Intern Med* 2007;167:1730-7.

18 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.
19 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.
20 Elders PJ, Netelenbos JC, Lips P, van Ginkel FC, Khoe E, Leeuwenkamp OR, 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.
21 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.
22 Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *Am J Med* 1995;98:331-5.
23 Recker RR, Hinders S, Davies KM, Heaney RP, Stegman MR, Lappe JM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *J Bone Miner Res* 1996;11:1961-6.
24 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.
25 Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 1999;340:101-7.
26 Peacock M, Liu G, Carey M, McClintock R, Ambrosius W, Hui S, 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.
27 Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. *Lancet* 2000;356:1300-6.
28 Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 2005;365:1621-8.
29 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.
30 Bonnick S, Broy S, Kaiser F, Teutsch C, Rosenberg E, DeLucca P, 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.
31 Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;85:1586-91.
32 Lappe JM, Heaney RP. Calcium supplementation: results may not be generalisable. *BMJ* 2008;336:403.
33 Reid IR, Ames R, Mason B, Reid HE, Bacon CJ, Bolland MJ, et al. Randomized controlled trial of calcium supplementation in healthy, nonosteoporotic, older men. *Arch Intern Med* 2008;168:2276-82.
34 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
35 Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, et al. Vitamin D and calcium: a systematic review of health outcomes. Evidence report No 183. Agency for Healthcare Research and Quality, 2009.
36 Weingarten MA, Zalmanovici A, Yaphe J. Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps. *Cochrane Database Syst Rev* 2008;1:CD003548.
37 Pentti K, Tuppurainen MT, Honkanen R, Sandini L, Kroger H, Alhava E, et al. Use of calcium supplements and the risk of coronary heart disease in 52-62-year-old women: the Kuopio Osteoporosis Risk Factor and Prevention Study. *Maturitas* 2009;63:73-8.
38 Al-Delaimy WK, Rimm E, Willett WC, Stampfer MJ, Hu FB. A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men. *Am J Clin Nutr* 2003;77:814-8.
39 Ascherio A, Rimm EB, Hernan MA, Giovannucci EL, Kawachi I, Stampfer MJ, et al. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. *Circulation* 1998;98:1198-204.
40 Van der Vijver LP, van der Waal MA, Weterings KG, Dekker JM, Schouten EG, Kok FJ. Calcium intake and 28-year cardiovascular and coronary heart disease mortality in Dutch civil servants. *Int J Epidemiol* 1992;21:36-9.
41 Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation* 2007;115:846-54.
42 Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008;117:503-11.
43 Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-83.
44 Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006;354:684-96.
45 Lappe JM, Davies KM, Travers-Gustafson D, Heaney RP. Vitamin D status in a rural postmenopausal female population. *J Am Coll Nutr* 2006;25:395-402.
46 Reid IR, Bolland MJ, Grey A. Does calcium supplementation increase cardiovascular risk? *Clin Endocrinol (Oxf)* 2010; published online 23 Feb.
47 Reid IR, Schooler BA, Hannan SF, Ibbertson HK. The acute biochemical effects of four proprietary calcium preparations. *Aust N Z J Med* 1986;16:193-7.
48 Lind L, Skarfors E, Berglund L, Lithell H, Ljunghall S. Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. *J Clin Epidemiol* 1997;50:967-73.
49 Jorde R, Sundsfjord J, Fitzgerald P, Bonaa KH. Serum calcium and cardiovascular risk factors and diseases: the Tromso study. *Hypertension* 1999;34:484-90.
50 Foley RN, Collins AJ, Ishani A, Kalra PA. Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 2008;156:556-63.
51 Nilsson IL, Yin L, Lundgren E, Rastad J, Ekbom A. Clinical presentation of primary hyperparathyroidism in Europe—nationwide cohort analysis on mortality from nonmalignant causes. *J Bone Miner Res* 2002;17(suppl 2):N68-74S.
52 Vestergaard P, Mollerup CL, Frokjaer VG, Christiansen P, Blichert-Toft M, Mosekilde L. Cardiovascular events before and after surgery for primary hyperparathyroidism. *World J Surg* 2003;27:216-22.
53 Green JH, Booth C, Bunning R. Postprandial metabolic responses to milk enriched with milk calcium are different from responses to milk enriched with calcium carbonate. *Asia Pac J Clin Nutr* 2003;12:109-19.
54 Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. *Arch Int Med* 2004;164:1285-92.
55 Demer LL. A skeleton in the atherosclerosis closet. *Circulation* 1995;92:2029-32.
56 Avenell A, Gillespie WJ, Gillespie LD, O'Connell D. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *Cochrane Database Syst Rev* 2009;2:CD000227.
57 DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ* 2010;340:b5463.
58 Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. *Osteoporos Int* 2008;19:1119-23.

Accepted: 21 May 2010

BMJ

RESEARCH

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

Mark J Bolland, senior research fellow,[1] Andrew Grey, associate professor,[1] Alison Avenell, clinical research fellow,[2] Greg D Gamble, research fellow,[1] Ian R Reid, professor of medicine and endocrinology[1]

[1]Department of Medicine, University of Auckland, Private Bag 92 019, Auckland 1142, New Zealand

[2]Health Services Research Unit, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, Scotland

Correspondence to: I R Reid
i.reid@auckland.ac.nz

Cite this as: *BMJ* 2011;342:d2040
doi:10.1136/bmj.d2040

ABSTRACT

Objectives To investigate the effects of personal calcium supplement use on cardiovascular risk in the Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study), using the WHI dataset, and to update the recent meta-analysis of calcium supplements and cardiovascular risk.

Design Reanalysis of WHI CaD Study limited access dataset and incorporation in meta-analysis with eight other studies.

Data source WHI CaD Study, a seven year, randomised, placebo controlled trial of calcium and vitamin D (1g calcium and 400 IU vitamin D daily) in 36 282 community dwelling postmenopausal women.

Main outcome measures Incidence of four cardiovascular events and their combinations (myocardial infarction, coronary revascularisation, death from coronary heart disease, and stroke) assessed with patient-level data and trial-level data.

Results In the WHI CaD Study there was an interaction between personal use of calcium supplements and allocated calcium and vitamin D for cardiovascular events. In the 16 718 women (46%) who were not taking personal calcium supplements at randomisation the hazard ratios for cardiovascular events with calcium and vitamin D ranged from 1.13 to 1.22 (P=0.05 for clinical myocardial infarction or stroke, P=0.04 for clinical myocardial infarction or revascularisation), whereas in the women taking personal calcium supplements cardiovascular risk did not alter with allocation to calcium and vitamin D. In meta-analyses of three placebo controlled trials, calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.21 (95% confidence interval 1.01 to 1.44), P=0.04), stroke (1.20 (1.00 to 1.43), P=0.05), and the composite of myocardial infarction or stroke (1.16 (1.02 to 1.32), P=0.02). In meta-analyses of placebo controlled trials of calcium or calcium and vitamin D, complete trial-level data were available for 28 072 participants from eight trials of calcium supplements and the WHI CaD participants not taking personal calcium supplements. In total 1384 individuals had an incident myocardial infarction or stroke. Calcium or calcium and vitamin D increased the risk of myocardial infarction (relative risk 1.24 (1.07 to 1.45), P=0.004) and the composite of myocardial infarction or stroke (1.15 (1.03 to 1.27), P=0.009).

Conclusions Calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction, a finding obscured in the WHI CaD Study by the widespread use of personal calcium supplements. A reassessment of the role of calcium supplements in osteoporosis management is warranted.

INTRODUCTION

Calcium supplements, with or without vitamin D, are widely used for the prevention and treatment of osteoporosis. Recently, we reported increases in rates of cardiovascular events in women allocated to calcium supplements in the Auckland Calcium Study, a five year randomised, placebo controlled trial in healthy older women, in which cardiovascular events were pre-specified secondary end points.[1] Subsequently, we carried out a meta-analysis of cardiovascular events in randomised, placebo controlled trials of calcium supplements (without vitamin D co-administration).[2] Calcium supplements significantly increased the risk of myocardial infarction by 31% in five trials involving 8151 participants where patient level data were available, and by 27% in 11 trials involving 11 921 participants where trial level data were available.[2] There were no statistically significant increases in the risk of stroke; the composite end point of myocardial infarction, stroke, or sudden death; or death (relative risks or hazard ratios ranged from 1.07 to 1.20), but the meta-analyses did not have sufficient power to detect effect sizes of these magnitudes.[2]

An important question that arises is whether co-administered calcium and vitamin D affects cardiovascular risk. The Women's Health Initiative reported no adverse effect of calcium and vitamin D (1 g calcium/400 IU vitamin D daily) on any cardiovascular end point in their large (n=36 282), seven year, randomised, placebo controlled trial.[3 4] However, 54% of the participants were taking personal (non-protocol)

calcium supplements at randomisation and 47% were taking personal vitamin D supplements, effectively rendering this trial a comparison of higher dose and lower dose calcium and vitamin D for most of the participants.

Allowing clinical trial participants free access to the intervention being studied is unusual and has the potential to obscure both adverse and beneficial effects. We hypothesised that the frequent personal use of calcium supplements might have obscured an adverse effect of calcium and vitamin D on cardiovascular risk. Therefore, we analysed the limited access dataset of the Women's Health Initiative Calcium/Vitamin D Supplementation Study (WHI CaD Study) to determine whether there were interactions between personal use of calcium supplements and allocation to calcium and vitamin D supplementation for cardiovascular events. Using data from women not using personal calcium supplements at randomisation in the study, we have updated our previous meta-analysis to provide the best current estimate of the effects of calcium supplements, with or without vitamin D, on the risk of cardiovascular events.

Table 1 | Characteristics of participants in the WHI CaD Study at randomisation, grouped by personal use of calcium supplements. Values are percentages (numbers) unless stated otherwise

	No personal use of calcium		Any personal use of calcium	
Characteristic	CaD (n=8429)	Placebo (n=8289)	CaD (n=9747)	Placebo (n=9817)
Age (years):				
Mean (SD)	62.9 (7.0)	62.9 (7.0)	63.9 (6.9)	63.9 (6.8)
50–60	39 (3259)	38 (3148)	31 (3030)	32 (3100)
60–70	43 (3633)	44 (3625)	49 (4741)	48 (4726)
≥70	18 (1537)	18 (1516)	20 (1976)	20 (1991)
Body mass index (kg/m^2):				
Mean (SD)	29.4 (5.9)	29.4 (6.0)	28.4 (5.7)	28.3 (5.7)
<30	59 (4974)	59 (4868)	66 (6421)	68 (6579)
Mean (SD) calcium intake (mg/day):				
Personal supplement	0	0	582 (538)	582 (520)
Dietary intake	804 (489)	798 (475)	826 (454)	828 (451)
Mean (SD) blood pressure (mm Hg):				
Systolic	126 (17)	126 (17)	125 (17)	125 (17)
Diastolic	75 (9)	75 (9)	74 (9)	74 (9)
Medical history*:				
HRT use (in trials or personal)	49 (4120)	51 (4199)	54 (5301)	55 (5401)
High serum cholesterol requiring pills	12 (898)	12 (870)	12 (1110)	12 (1094)
Cardiovascular disease	14 (1066)	15 (1074)	14 (1276)	15 (1333)
Hypertension	34 (2802)	35 (2861)	33 (3144)	32 (3100)
Stroke	1.0 (85)	1.2 (96)	0.7 (71)	1.0 (96)
Myocardial infarction	2.3 (191)	2.0 (167)	1.5 (149)	1.5 (147)
Smoking status*:				
Never smoked	52 (4298)	53 (4307)	52 (5027)	53 (5121)
Former smoker	39 (3260)	38 (3154)	41 (3995)	41 (3979)
Current smoker	9 (772)	9 (732)	7 (633)	6 (624)

CaD=allocation to calcium and vitamin D supplement. HRT=hormone replacement therapy.
*Data recorded at randomisation except for medical history and smoking status, which were recorded at entry to Women's Health Initiative clinical trials programme: 91% of participants in the CaD Study entered at their first annual visit for the WHI programme, and the remainder at their second annual visit.

METHODS

Analyses of WHI CaD Study

The design and results of the WHI CaD Study have been published in full.[3 4] Medical records related to self reported medical events for myocardial infarction, stroke, and coronary revascularisation were adjudicated centrally by physician adjudicators using standardised definitions, and all deaths were also centrally adjudicated.[4] We obtained the WHI limited access, clinical trials dataset from the National Heart Lung and Blood Institute. A statistical analysis proposal was submitted to the institute before the database was made available.

We attempted to replicate the approach of the WHI investigators where possible, carrying out pre-specified analyses looking for interactions between pre-specified subgroups based on use (no use *v* any use) and dose (0, 1–499, 500–999, ≥1000 mg/day) of personal calcium supplements at randomisation for cardiovascular events. We pre-specified assessment of four cardiovascular end points and their combinations: myocardial infarction, coronary revascularisation (coronary artery bypass grafting or percutaneous coronary intervention), death from coronary heart disease, and stroke. Serial electrocardiograms were carried out in the WHI CaD Study, allowing detection of silent myocardial infarctions. Because silent myocardial infarctions were not determined in any of the trials in our meta-analysis, we analysed data separately for clinical myocardial infarctions and total myocardial infarctions (including clinical and silent myocardial infarction). We have reported four different composite end points: total deaths from myocardial infarction or coronary heart disease (the major outcome reported in the WHI CaD Study); clinical myocardial infarction or coronary revascularisation (representing clinical coronary heart disease events); clinical myocardial infarction or stroke (the composite end point most similar to that used in our meta-analysis of calcium monotherapy trials); and total myocardial infarction, coronary revascularisation, and death from coronary heart disease (representing all coronary heart disease events).

We have reported the baseline characteristics at the time of randomisation to the WHI CaD Study, whereas the WHI investigators reported these characteristics at the time of entry to the WHI programme. For body mass index and for dietary and supplemental calcium intake, we used the latest value recorded between screening and one month after randomisation to the study.

To assess the effect of calcium and vitamin D on the time to first event for each end point, we used Cox proportional hazards models stratified by age, prevalent cardiovascular disease at baseline, and randomisation status in the WHI Postmenopausal Hormone Therapy Trials and Dietary Modification Trial, following the approach of the WHI investigators.[3 4] Comparisons between subgroups were assessed using interaction terms. The assumption of proportional hazards was tested by performing a test for

proportionality of the interaction between variables included in the model and the logarithm of time.

Meta-analysis of calcium with or without vitamin D

Two recent systematic reviews have independently reviewed the effects of calcium and vitamin D supplements on vascular events.[5 6] These reviews identified two trials of co-administered calcium and vitamin D with cardiovascular outcome data: the WHI CaD Study and a small, one year trial of 191 participants that reported 11 cardiovascular events during follow-up but did not provide specific details about these events.[7] During the process of gathering data for our meta-analysis of calcium monotherapy, we obtained previously unpublished data from two studies that compared co-administered calcium and vitamin D with placebo.[8 9] We therefore pooled data from these two studies together with the results for the WHI CaD Study participants who were not taking personal calcium supplements at randomisation in a meta-analysis of the effect of calcium and vitamin D on cardiovascular risk.

We then updated our previous meta-analysis of calcium supplements by including the results for the WHI CaD Study participants not taking personal calcium supplements at randomisation, to determine the effect of calcium with or without vitamin D on cardiovascular risk. Of note, only 1.2% of participants were taking non-protocol calcium supplements in the trials contributing patient-level data in our previous meta-analysis of calcium supplements,[2] and two of the six studies contributing trial-level data permitted non-protocol calcium supplements.[9 10] We used the same methods as for our previous meta-analysis:[2] the effect of calcium or calcium and vitamin D on the time to first event was assessed with Cox proportional hazards models stratified by study for patient-level data, and trial-level summary data were pooled using random effects models.[2] The assumption of proportional hazards was tested as described above.

All analyses were performed using SAS version 9.1 (SAS Institute, Cary NC, USA) or Comprehensive Meta-analysis version 2 (Biostat, Englewood NJ, USA). All tests were two tailed and $P<0.05$ was considered significant.

RESULTS

Reanalysis of the WHI CaD Study

Table 1 shows the characteristics of the participants at randomisation to the WHI CaD Study grouped by personal use of calcium supplements: 54% of participants were taking personal calcium supplements. The baseline characteristics of the participants allocated to calcium and vitamin D or to placebo seemed well matched for the subgroups defined by use of personal calcium supplement. However, participants using personal calcium supplements differed from those not using personal supplements in some factors associated with cardiovascular disease: age, body mass index, blood pressure, use of hormone replacement therapy, history of myocardial infarction or stroke, and smoking ($P<0.05$ for these variables) (table 1).

Table 2 shows the influence of personal use of calcium supplements on the effect of calcium and vitamin D on cardiovascular end points and mortality from all causes. There were significant interactions between allocation of calcium and vitamin D and personal use of calcium supplements for clinical myocardial infarction, stroke, and the composite end point of myocardial infarction or stroke. In women not taking personal calcium supplements, the hazard ratios with calcium and vitamin D were 1.16 ($P=0.04$) for the composite end point of clinical myocardial infarction or coronary revascularisation, 1.16 ($P=0.05$) for clinical myocardial infarction or stroke, 1.22 ($P=0.05$) for myocardial infarction, and 1.13–1.20 for the other cardiovascular end points. By contrast, in women taking personal calcium supplements, the hazard ratios for these end points with calcium and vitamin D were 0.83–1.08.

Table 2 | Effect of allocation to calcium and vitamin D supplement on cardiovascular events among participants in the WHI CaD Study, grouped by personal use of calcium supplements at randomisation. Values are numbers (incidence per 1000 patient years) of events unless stated otherwise

	No personal use of calcium				Any personal use of calcium				
			Comparison				Comparison		
Cardiovascular end point	CaD (n=8429)	Placebo (n=8289)	Hazard ratio (95% CI)	P value	CaD (n=9747)	Placebo (n=9817)	Hazard ratio (95% CI)	P value	P value of interaction*
Clinical MI	209 (3.5)	168 (2.9)	1.22 (1.00 to 1.50)	0.05	180 (2.7)	196 (2.9)	0.92 (0.75 to 1.13)	0.4	0.04
Total MI†	222 (3.7)	182 (3.1)	1.20 (0.99 to 1.47)	0.07	193 (2.9)	207 (3.1)	0.94 (0.77 to 1.14)	0.5	0.07
Revascularisation	348 (5.9)	299 (5.1)	1.15 (0.98 to 1.34)	0.09	326 (4.9)	308 (4.6)	1.08 (0.93 to 1.27)	0.3	0.5
Stroke	196 (3.3)	163 (2.8)	1.17 (0.95 to 1.44)	0.1	156 (2.3)	189 (2.8)	0.83 (0.67 to 1.02)	0.08	0.02
Total MI or CHD death	268 (4.5)	229 (3.9)	1.15 (0.97 to 1.38)	0.1	238 (3.5)	247 (3.7)	0.97 (0.81 to 1.16)	0.7	0.1
Clinical MI or revascularisation	422 (7.2)	359 (6.2)	1.16 (1.01 to 1.34)	0.04	394 (5.9)	378 (5.6)	1.06 (0.92 to 1.23)	0.4	0.3
Clinical MI or stroke	386 (6.5)	326 (5.6)	1.16 (1.00 to 1.35)	0.05	324 (4.8)	370 (5.5)	0.88 (0.76 to 1.02)	0.09	0.006
Total MI, CHD death, or revascularisation	476 (8.1)	417 (7.2)	1.13 (0.99 to 1.29)	0.07	447 (6.7)	421 (6.3)	1.08 (0.94 to 1.23)	0.3	0.5
Death from all causes	380 (6.3)	379 (6.4)	0.99 (0.86 to 1.14)	0.9	364 (5.4)	428 (6.3)	0.84 (0.73 to 0.97)	0.01	0.1

CaD=allocation to calcium and vitamin D supplement. MI=myocardial infarction. CHD=coronary heart disease.
*Interaction between CaD allocation and use or non-use of personal calcium supplements for each end point, testing the difference between subgroups.
†Includes clinically silent myocardial infarction diagnosed from changes in routine serial electrocardiograms.

When the personal calcium supplement users were divided into three groups by daily supplement intake (1–499, 500–999, and ≥1000 mg/day), there was no evidence of a relation between the dose of personal calcium supplements and the risk of cardiovascular events with randomisation to calcium and vitamin D for these end points (fig 1). There were no significant three-way interactions between calcium and vitamin D allocation, personal calcium supplement use, and dietary calcium intake (above or below median) for cardiovascular end points (P>0.4). We repeated these analyses in the subgroup of women not using personal calcium supplements and found no interactions between calcium and vitamin D allocation and dietary calcium intake (above or below the median) for any cardiovascular end point (P>0.5). Finally, we repeated all these analyses using dietary calcium intake grouped by tertile, and the results were similar. Together, these analyses suggest that the relation between calcium and vitamin D allocation and cardiovascular events is independent of dietary calcium intake.

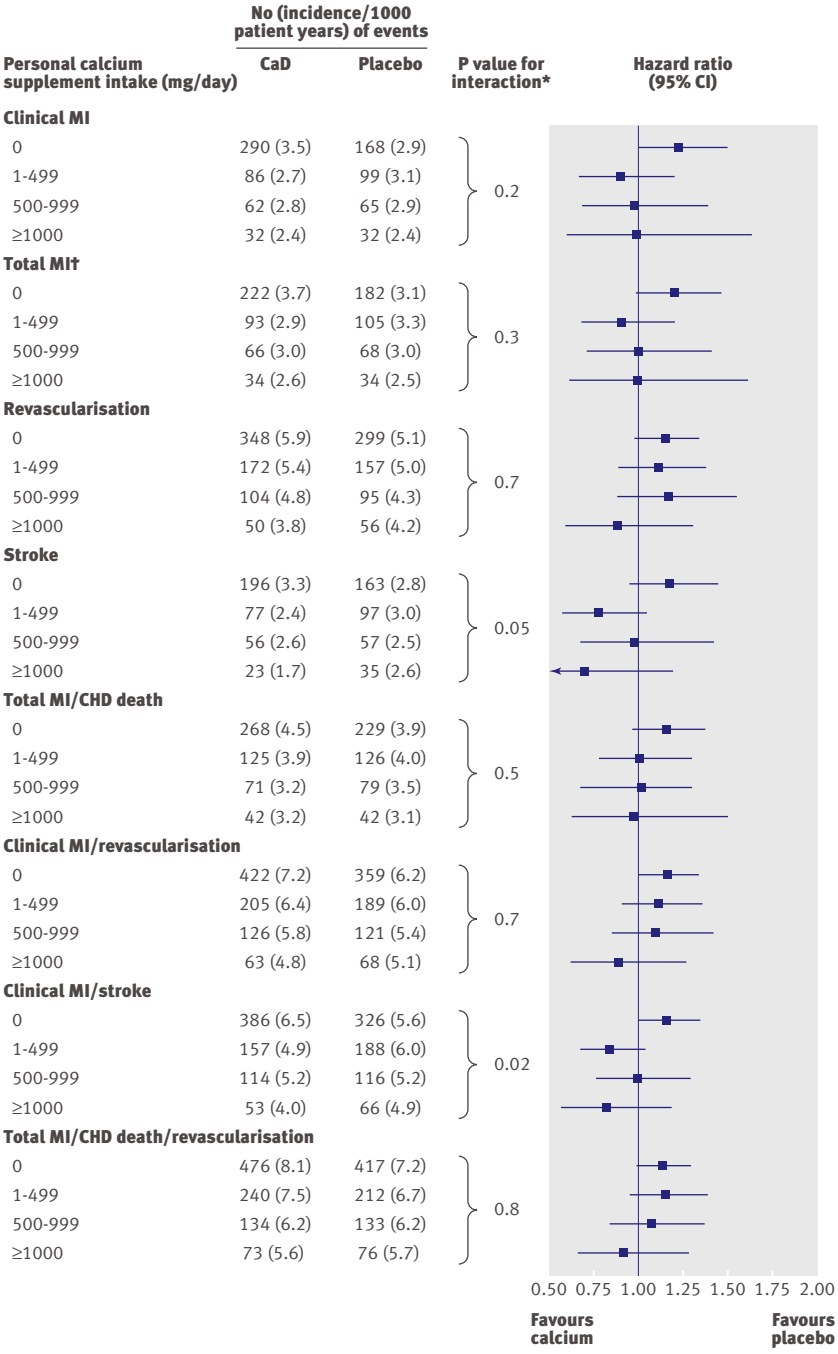
In a sensitivity analysis, we searched the WHI medication database to identify participants potentially taking calcium supplements not captured elsewhere, using WHI medication class codes for common calcium supplement preparations (791000, 791099, 781230, 783500, 783600, 483000, 489900, and 489910). We identified 930 participants listed as taking a calcium supplement before randomisation to calcium and vitamin D but recorded as having no supplemental intake of calcium at randomisation. When we repeated the analyses including these women classified as using personal calcium supplements, the results were similar (data not shown).

Personal vitamin D supplements were used in combination with personal calcium supplements by 44% of participants in the WHI database, and without personal calcium supplements by 3% of participants. When we repeated the analyses grouping participants by personal use of calcium and/or vitamin D supplements, the results were similar (data not shown).

Meta-analysis of calcium and vitamin D versus placebo

We analysed trials comparing co-administered calcium and vitamin D with placebo. Complete trial-level data for cardiovascular events were available for 20 090 participants from three trials—two trials with previously unpublished data gathered during preparation of our previous meta-analysis of calcium supplements,[8 9] and data from the WHI CaD Study participants who were not taking personal calcium supplements at randomisation. In total, 465 individuals had an incident myocardial infarction, 477 an incident stroke, and 911 an incident myocardial infarction or stroke during an average trial duration weighted by study size of 6.2 years. Figure 2 shows that calcium and vitamin D significantly increased the risk of myocardial infarction (relative risk 1.21, P=0.04), stroke (relative risk 1.20, P=0.05), and the composite of myocardial infarction or stroke (relative risk 1.16, P=0.02).

In a sensitivity analysis, we also included data from a study of calcium and vitamin D that only described cardiovascular event data in detail on trial withdrawals or deaths.[7] The relative risks with calcium and vitamin D were 1.22 (95% confidence interval 1.01 to 1.45, P=0.03) for myocardial infarction, 1.20 (1.00 to 1.43, P=0.05) for stroke, and 1.17 (1.03 to 1.32, P=0.02) for the composite end point.



CaD = allocation to calcium and vitamin D dietary supplement
MI = myocardial infarction
CHD = coronary heart disease
* Interaction between dose of personal calcium supplements and CaD allocation for each end point, testing the difference between subgroups
† includes clinically silent myocardial infarction diagnosed from changes in routine serial electrocardiograms

Fig 1 | Influence of personal calcium supplement dose at randomisation on the effect of calcium and vitamin D on cardiovascular events in the WHI CaD Study

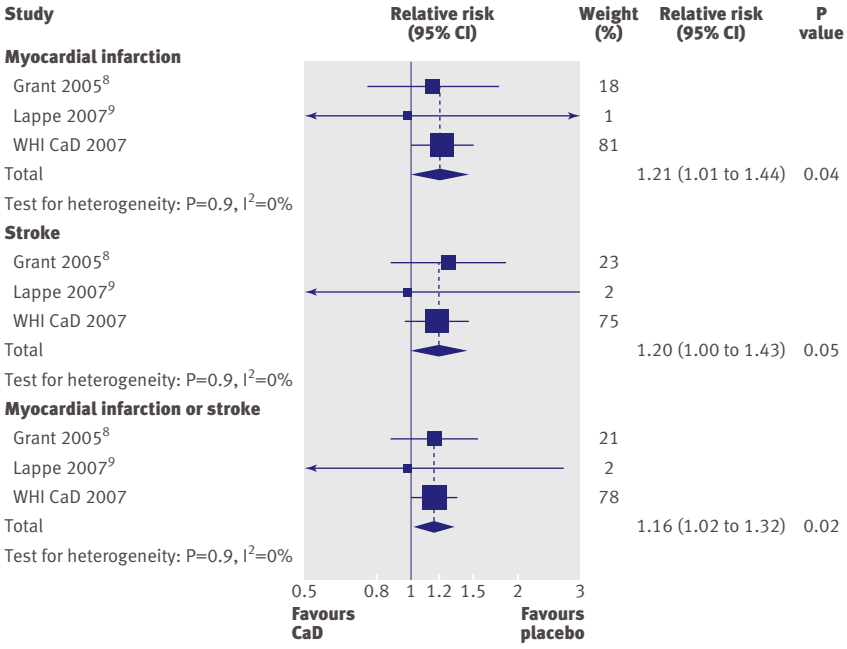


Fig 2 | Effect of calcium and vitamin D on cardiovascular events: based on trial-level data from two randomised, placebo controlled trials of calcium and vitamin D[8 9] and the WHI CaD Study participants not taking personal calcium supplements at baseline. The first two trials included calcium monotherapy and calcium and vitamin D groups: we included data only from the calcium and vitamin D group compared with the placebo group

All cause mortality was available from three studies in which cardiovascular event data were available: Brazier et al,[7] Grant et al for the RECORD trial,[8] and the WHI CaD Study. In these studies, 1200 deaths occurred during follow-up, and the relative risk for death (all causes) with calcium and vitamin D was 1.01 (0.90 to 1.12, P=0.9).

Meta-analysis of calcium with or without vitamin D versus placebo

As the magnitude of the risk of cardiovascular events with calcium and vitamin D was similar to that observed with calcium alone, we updated our previous meta-analysis by incorporating the results for the WHI CaD participants who were not taking personal calcium supplements at randomisation, and the data from the calcium and vitamin D arm of the Lappe study;[9] this arm was not included in our previous meta-analysis.

Patient-level data

Patient-level data were available for 24 869 people in six trials (WHI CaD and five randomised, placebo controlled trials of calcium supplements).[1 8 11-15] In total, 631 individuals had an incident myocardial infarction, 669 an incident stroke, 1248 an incident myocardial infarction or stroke, and 1765 died during a mean follow-up of 5.9 years. Figure 3 shows that calcium or calcium and vitamin D supplements increased the risk of myocardial infarction (hazard ratio 1.26, P=0.005), stroke (1.19, P=0.03), and the composite end point of myocardial infarction or stroke (1.17, P=0.005). The hazard ratio for death (all causes) was 1.04 (0.95 to 1.14, P=0.4).

The number needed to treat with calcium or calcium and vitamin D for five years to cause one incident event was 240 for myocardial infarction, 283 for stroke, and 178 for the composite end point. The corresponding number needed to treat to prevent one fracture was 302. Treating 1000 people with calcium or calcium and vitamin D for five years would cause an additional six myocardial infarctions or strokes and prevent three fractures.

Trial-level data

Complete trial-level data were available for 28 072 participants in nine trials (the WHI CaD study and eight randomised, placebo controlled trials of calcium supplements).[1 8 9 11-17] In total, 676 individuals had an incident myocardial infarction, 764 an incident stroke, 1384 an incident myocardial infarction or stroke, and 1835 died during an average trial duration weighted by study size of 5.7 years. Figure 4 shows that the results were similar to the patient-level analyses. Calcium or calcium and vitamin D supplements increased the risk of myocardial infarction (relative risk 1.24, P=0.004) and the composite of myocardial infarction/stroke (1.15, P=0.009). The relative risk of death (all causes) was 1.04 (0.95 to 1.13, P=0.5).

In a sensitivity analysis, we added all available data from three further randomised, placebo controlled trials of calcium supplements[10 18 19] and one trial of calcium and vitamin D supplements[7] (limited to data on deaths in trial or trial withdrawals) to the analysis of complete trial-level data. Data were available for 29 277 participants (WHI CaD Study, 11 trials of calcium supplements, and one trial of calcium and vitamin D): 679 individuals had an incident myocardial infarction, 768 an incident stroke, 1393 an incident myocardial infarction or stroke, and 1857 died during follow-up. With calcium or calcium and vitamin D supplements, the relative risks were 1.25 (1.08 to 1.45, P=0.003) for myocardial infarction, 1.15 (1.00 to 1.32, P=0.06) for stroke, 1.15 (1.04 to 1.27, P=0.008) for the composite of myocardial infarction or stroke, and 1.04 (0.95 to 1.13, P=0.4) for death.

DISCUSSION

In the Women's Health Initiative Calcium/Vitamin D Supplementation (WHI CaD) Study personal use of calcium supplement at randomisation significantly influenced the effect of randomisation to calcium and vitamin D on the risk of cardiovascular events. In the entire WHI cohort, there were significant interactions between calcium and vitamin D and personal calcium supplement use for myocardial infarction and for stroke. In the 46% of the WHI CaD participants who were not taking personal calcium supplements at randomisation, the hazard ratios for cardiovascular events with calcium and vitamin D ranged from 1.13 to 1.22. By contrast, in the participants taking personal calcium supplements at randomisation, allocation to calcium

and vitamin D did not alter cardiovascular risk. In women not taking personal calcium supplements at randomisation, the hazard ratios for clinical myocardial infarction (1.22) and stroke (1.17) were similar to those observed in our meta-analysis of trials of calcium monotherapy (1.31 and 1.20, respectively).[2]

By itself, this analysis of the WHI CaD Study data does not provide definitive evidence of an adverse effect of calcium and vitamin D on cardiovascular events. However, when these data are pooled with previously unpublished data from two other placebo controlled trials of calcium and vitamin D, there are consistent increases in the risk of myocardial infarction and stroke that are statistically significant and are of similar size to the risks observed with calcium supplements used without vitamin D. Further, when the results for calcium and vitamin D are taken together with those from trials of calcium used as monotherapy, they provide consistent evidence from 13 randomised, placebo controlled trials involving about 29 000 participants with about 1400 incident myocardial infarctions and strokes that calcium supplements with or without vitamin D increase the risk of cardiovascular events.

The size of this increase is modest, about 25%–30% for myocardial infarction and 15%–20% for stroke, but, because of the widespread use of calcium supplements either alone or with vitamin D, even small increases in cardiovascular disease incidence may translate to a substantial population burden of disease, particularly in older age groups. Furthermore, comparisons of the benefits of calcium on fracture prevention with the risk of cardiovascular events suggest that the risk to benefit profile is unfavourable: in our analysis, treating 1000 patients with calcium or calcium and vitamin D for five years would cause an additional six myocardial infarctions or strokes (number needed to harm of 178) and prevent only three fractures (number needed to treat of 302).

Limitations of study

The current analysis has some limitations. We used the publicly accessible, limited access dataset of the WHI clinical trials for these analyses, so the analysis is limited to the information available in this dataset. Several vascular end points are potentially evaluable; we prespecified those which allowed the most accurate comparisons with previous analyses. Subgroup analysis raises several issues, including false positive results and over-interpretation of findings.[20 21] To minimise these risks, we pre-specified the variable of interest (personal calcium supplement use) for this analysis before obtaining the WHI dataset, assessed its effect using interaction tests, and followed recommended approaches for subgroup analysis and interpretation.[21 22] The hypothesis that the use of personal calcium supplements might interact with the calcium and vitamin D treatment effect in the WHI CaD Study was based on plausibility from our finding in trials of calcium monotherapy, and deviation from normal clinical trial practice (allowing trial participants free access to the intervention being studied) is unusual and has the potential to mask both adverse and beneficial effects.

We followed the approach of the WHI authors in not adjusting P values for multiple subgroup analyses, and instead estimated the likelihood of false positive tests,[3] an approved approach for addressing multiplicity of

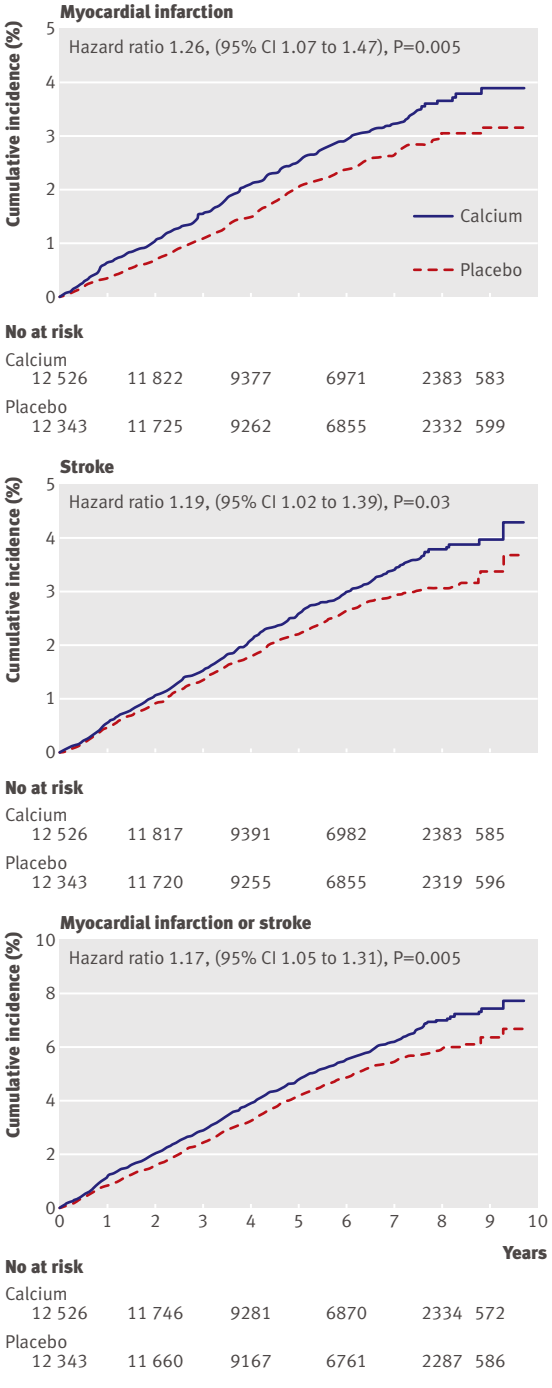


Fig 3 | Effect of calcium supplements with or without vitamin D on cardiovascular events: based on patient-level data. The panels show the time to first event for 24 869 participants in five trials of calcium supplements,[18 11-15] and the WHI CaD Study participants not taking personal calcium supplements at baseline

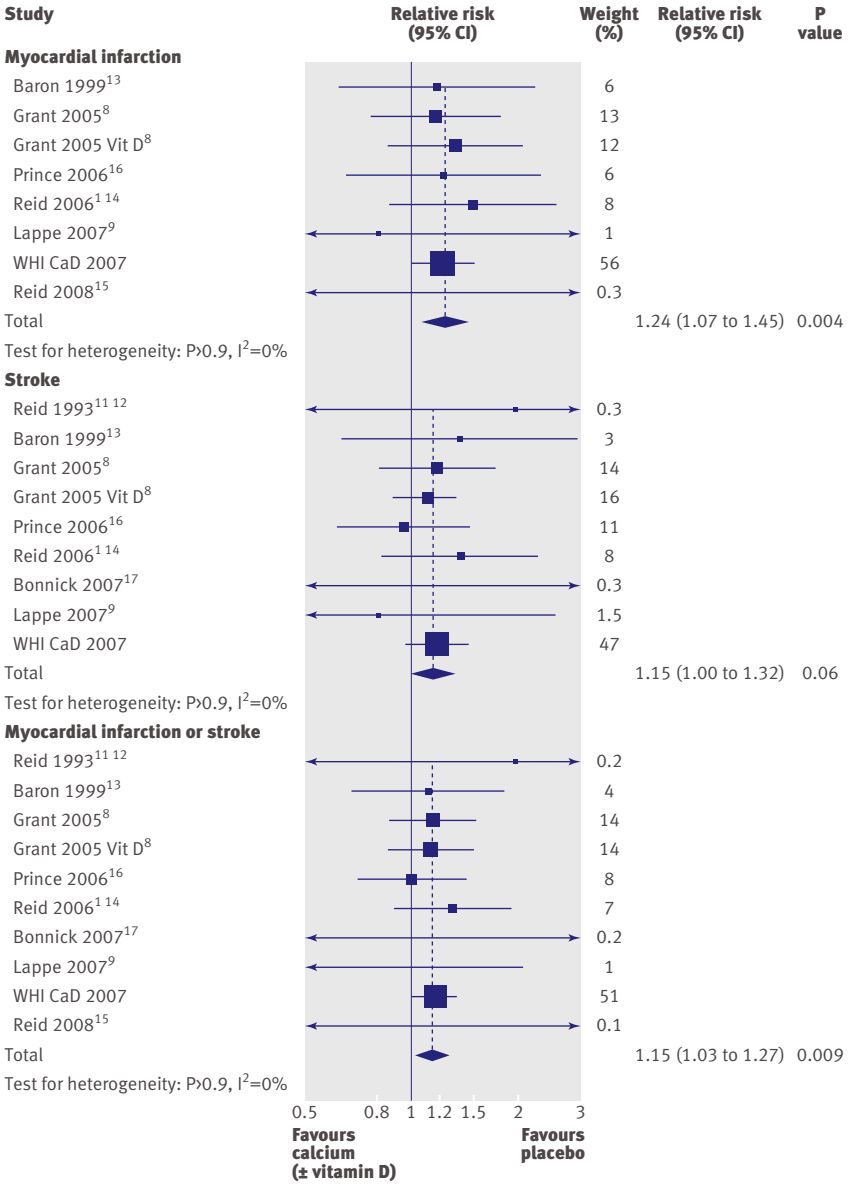


Fig 4 | Effect of calcium supplements with or without vitamin D on cardiovascular events: trial-level data. The panels show data for 28 072 participants in eight trials of calcium supplements with complete trial-level data,[1 8 9 11-17] plus data for the WHI CaD Study participants not taking personal calcium supplements at baseline. Lappe et al[9] randomised participants to calcium, calcium and vitamin D, or placebo: we pooled the outcomes from both the calcium and calcium and vitamin D arms. Grant et al[8] included calcium *v* placebo arms ("Grant 2005") and calcium plus vitamin D *v* vitamin D plus placebo arms ("Grant 2005 Vit D"). The composite outcome for Prince et al[16] was myocardial infarction, stroke, or sudden death

statistical tests.[23] Nine interaction tests were performed: if the effect of calcium and vitamin D was unrelated to personal calcium use and the end points were independent, the probability of at least one false positive interaction test is <40%.[22]

Confounding is a possible explanation of our findings as subgroup analysis may interfere with the balancing effects of randomisation on potential confounders. However, within each subgroup, the baseline characteristics of the participants allocated to calcium and vitamin D seemed well matched to those allocated to placebo. In contrast, as expected, women using personal calcium differed from women not using personal calcium in a number of factors that might influence cardiovascular outcomes. However, the WHI investigators have previously reported no significant interactions with these factors, calcium and vitamin D, and risk of death from myocardial infarction or coronary heart disease—except for body mass index, with obese women having a lower risk of death from myocardial infarction or coronary heart disease with calcium and vitamin D than non-obese women.[4] Obesity does not explain our findings since it was more common in women not using personal calcium, and would have tended to obscure an interaction effect.

In the WHI CaD participants the incidence of cardiovascular events was relatively low, reflecting the comparative youth of the cohort. Thus, despite its size and long duration, the WHI CaD Study had insufficient power to detect small effect sizes, particularly when subgroups are considered. For example, in women not taking personal calcium supplements at randomisation, the study had 80% power to detect a 33% increase in clinical myocardial infarction.

The WHI CaD Study accounts for 75%–80% of the weighting in the meta-analyses of co-administered calcium and vitamin D, and 45%–55% of the weighting in the meta-analysis of calcium with or without vitamin D. However, the results for the individual studies in all the meta-analyses are quite consistent and do not suggest an undue influence of a single outlying study or WHI CaD.

Interpretation of results

For most of its participants, the WHI CaD Study assessed the impact of adding calcium and vitamin D to personal calcium supplements, effectively comparing a higher dose of calcium with a lower dose of calcium. By restricting the analyses to women not taking personal calcium supplements, we were able to estimate the effect of calcium and vitamin D on cardiovascular events, observing increased risks of these events with calcium and vitamin D. In women taking personal calcium supplements at randomisation, the addition of calcium and vitamin D did not increase cardiovascular risk, and the risk of cardiovascular events with calcium and vitamin D was also not affected by the dose of personal calcium supplements. This suggests that there may not be a dose-response relationship between calcium supplements and the risk of cardiovascular events. Thus, even doses of <500 mg/day might be associated with an increased risk of cardiovascular events similar to doses ≥1000 mg/day. This would be consistent with the notion that the abrupt change in plasma calcium concentration after supplement ingestion causes the adverse effect, rather than it being related to the total calcium load ingested.[24 25]

In the entire WHI cohort there was no significant interaction between calcium and vitamin D, personal calcium supplement use, and mortality—and therefore no evidence of a difference in mortality risk with calcium and vitamin D in the subgroups defined by

WHAT IS ALREADY KNOWN ON THIS TOPIC

A recent meta-analysis suggested that calcium supplements taken without vitamin D increase the risk of myocardial infarction

The Women's Health Initiative reported no effect of calcium and vitamin D supplements on cardiovascular events, but most of the participants were taking personal, non-protocol calcium supplements at study entry

WHAT THIS STUDY ADDS

Re-analysis of the Women's Health Initiative data shows women allocated to calcium and vitamin D administration who were not taking personal calcium supplements were at increased risk of cardiovascular events

Meta-analyses of trials involving 29 000 people found that calcium supplements used with or without vitamin D modestly increase cardiovascular risk, suggesting their use in osteoporosis management should be reassessed

personal calcium use. In women not taking personal calcium supplements, no increase in mortality was observed with calcium and vitamin D despite the increased risk of cardiovascular events. The most likely explanation is that participants in WHI were at low risk of cardiovascular events and death. A 15% increase in myocardial infarction and stroke would lead to only a 1%–3% increase in total mortality if 10%–20% of the additional events led to death during follow-up. The subgroup analysis did not have sufficient power to detect such a difference, but the 95% confidence intervals for mortality (0.86 to 1.14) encompass an effect of this size.

If calcium supplements do increase cardiovascular risk it is important to consider the potential underlying mechanisms.[25] Calcium supplements acutely increase serum calcium concentration by a modest amount,[24] an effect that is sustained during long term treatment, as evidenced by lower levels of parathyroid hormone.[15] Serum calcium concentrations are positively associated with carotid artery plaque thickness,[26] aortic calcification,[27] incidence of myocardial infarction,[28-30] and mortality.[31] These findings are consistent with observational data suggesting increased risk of cardiovascular events and death in primary hyperparathyroidism, a condition in which serum calcium concentration is elevated.[32 33]

The process of vascular calcification is a complex, regulated process similar to osteogenesis.[34] It is possible that the increase in serum calcium concentrations from calcium supplements influences vascular calcification by altering regulators of calcification such as fetuin A, pyrophosphate, and bone morphogenic protein-7, or by directly binding to the calcium-sensing receptor that is expressed on vascular smooth muscle cells.[25] Exposing cultures of vascular smooth muscle cells to increased concentrations of calcium results in increased mineralisation of the cultures.[35] Supporting this hypothesis are studies of patients with renal impairment, in whom calcium supplements accelerate vascular calcification and increase mortality in both dialysis and pre-dialysis populations.[36-38]

It is also possible that calcium supplements adversely affect risk of arterial thrombus formation. Acute hypercalcaemia in rats increases blood coaguability,[39] potentially via an effect on platelets since calcium-sensing receptors are found on these cells.[40]

Therefore, extracellular calcium concentrations might affect the function of several cells that are implicated in the pathogenesis of vascular events. All these possibilities require further evaluation.

Conclusions

Calcium and vitamin D supplements increased the risk of cardiovascular events in the WHI CaD participants who were not taking personal calcium supplements at the time of randomisation. When these results are taken together with the results of other clinical trials of calcium supplements, with or without vitamin D, they strongly suggest that calcium supplements modestly increase the risk of cardiovascular events, particularly myocardial infarction. These data justify a reassessment of the use of calcium supplements in older people.

The Women's Health Initiative is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the WHI Study Investigators. This manuscript was prepared using a limited access dataset obtained from the NHLBI and does not necessarily reflect the opinions or views of the WHI or the NHLBI.
We thank Professor John Baron who provided patient-level data on cardiovascular events from his study, Professor Joan Lappe who provided trial-level data on her study, and Graeme MacLennan from the RECORD trial.
Contributors: MJB, AG, and IRR drafted the study protocol. All authors provided individual patient data from their studies. MJB and GDG performed the analyses. MJB drafted the paper. All authors critically reviewed the paper. MJB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MJB is the guarantor of the paper.
Funding: Funded by the Health Research Council of New Zealand, and the University of Auckland School of Medicine Foundation. AA is funded by a Career Scientist award of the Chief Scientist Office of the Scottish Government Health Directorates. The Health Services Research Unit is funded by the Chief Scientist Office of the Scottish Government Health Directorates.
The study sponsors had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, and approval of the manuscript. The authors are independent from the funders.
Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that no author has support from companies for the submitted work; IRR has received research support from and acted as a consultant for Fonterra and had study medications for clinical trials of calcium supplementation supplied by Mission Pharmacal, and AA had study medications for clinical trials of calcium supplementation supplied by Shire Pharmaceuticals and Nycomed; no other relationships or activities that could appear to have influenced the submitted work.
Ethical approval: Not required.
Data sharing: No additional data available.

1 Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, et al. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ* 2008;336:262-6.
2 Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010;341:c3691.
3 Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006;354:669-83.
4 Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation* 2007;115:846-54.

5 Chung M, Balk EM, Brendel M, Ip S, Lau J, Lee J, et al. Vitamin D and calcium: a systematic review of health outcomes. Evidence report no 183. (Prepared by the Tufts Evidence-based Practice Center under contract no HHSA 290-2007-10055-I.) AHRQ publication no 09-E015. Agency for Healthcare Research and Quality, 2009.
6 Wang L, Manson JE, Song Y, Sesso HD. Systematic review: vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 2010;152:315-23.
7 Brazier M, Grados F, Kamel S, Mathieu M, Morel A, Maamer M, et al. Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: results of a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 2005;27:1885-93.
8 Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D: RECORD): a randomised placebo-controlled trial. *Lancet* 2005;365:1621-8.
9 Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr* 2007;85:1586-91.
10 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.
11 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.
12 Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *Am J Med* 1995;98:331-5.
13 Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 1999;340:101-7.
14 Reid IR, Mason B, Horne A, Ames R, Reid HE, Bava U, et al. Randomized controlled trial of calcium in healthy older women. *Am J Med* 2006;119:777-85.
15 Reid IR, Ames R, Mason B, Reid HE, Bacon CJ, Bolland MJ, et al. Randomized controlled trial of calcium supplementation in healthy, non-osteoporotic, older men. *Arch Intern Med* 2008;168:2276-82.
16 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.
17 Bonnick S, Broy S, Kaiser F, Teutsch C, Rosenberg E, DeLucca P, 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.
18 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.
19 Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. *Lancet* 2000;356:1300-6.
20 Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 1991;266:93-8.
21 Assmann SF, Pocock SJ, Enos LE, Kasten LE. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000;355:1064-9.
22 Lagakos SW. The challenge of subgroup analyses—reporting without distorting. *N Engl J Med* 2006;354:1667-9.
23 Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine—reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007;357:2189-94.
24 Reid IR, Schooler BA, Hannan SF, Ibbertson HK. The acute biochemical effects of four proprietary calcium preparations. *Aust N Z J Med* 1986;16:193-7.
25 Reid IR, Bolland MJ, Grey A. Does calcium supplementation increase cardiovascular risk? *Clin Endocrinol (Oxf)* 2010;73:689-95.
26 Rubin MR, Rundek T, McMahon DJ, Lee HS, Sacco RL, Silverberg SJ. Carotid artery plaque thickness is associated with increased serum calcium levels: the Northern Manhattan study. *Atherosclerosis* 2007;194:426-32.
27 Bolland MJ, Wang TK, van Pelt NC, Horne AM, Mason BH, Ames RW, et al. Abdominal aortic calcification on vertebral morphometry images predicts incident myocardial infarction. *J Bone Miner Res* 2010;25:505-12.
28 Lind L, Skarfors E, Berglund L, Lithell H, Ljunghall S. Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. *J Clin Epidemiol* 1997;50:967-73.
29 Jorde R, Sundsfjord J, Fitzgerald P, Bonaa KH. Serum calcium and cardiovascular risk factors and diseases: the Tromso study. *Hypertension* 1999;34:484-90.
30 Foley RN, Collins AJ, Ishani A, Kalra PA. Calcium-phosphate levels and cardiovascular disease in community-dwelling adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J* 2008;156:556-63.
31 Leifsson BG, Ahren B. Serum calcium and survival in a large health screening program. *J Clin Endocrinol Metab* 1996;81:2149-53.
32 Nilsson IL, Yin L, Lundgren E, Rastad J, Ekbom A. Clinical presentation of primary hyperparathyroidism in Europe—nationwide cohort analysis on mortality from nonmalignant causes. *J Bone Miner Res* 2002;17(suppl 2):N68-74.
33 Vestergaard P, Mollerup CL, Frokjaer VG, Christiansen P, Blichert-Toft M, Mosekilde L. Cardiovascular events before and after surgery for primary hyperparathyroidism. *World J Surg* 2003;27:216-22.
34 Demer LL. A skeleton in the atherosclerosis closet. *Circulation* 1995;92:2029-32.
35 Alam MU, Kirton JP, Wilkinson FL, Towers E, Sinha S, Rouhi M, et al. Calcification is associated with loss of functional calcium-sensing receptor in vascular smooth muscle cells. *Cardiovasc Res* 2009;81:260-8.
36 Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 2000;342:1478-83.
37 Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int* 2007;71:438-41.
38 Russo D, Miranda I, Ruocco C, Battaglia Y, Buonanno E, Manzi S, et al. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney Int* 2007;72:1255-61.
39 Hilgard P. Experimental hypercalcaemia and whole blood clotting. *J Clin Path* 1973;28:616-9.
40 House MG, Kohlmeier L, Chattopadhyay N, Kifor O, Yamaguchi T, Leboff MS, et al. Expression of an extracellular calcium-sensing receptor in human and mouse bone marrow cells. *J Bone Miner Res* 1997;12:1959-70.

Accepted: 18 February 2011