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ORIGINAL ARTICLE

Subgroup analysis for the risk of cardiovascular disease with calcium supplements

Loretta T Radford, Mark J Bolland, Greg D Gamble, Andrew Grey and Ian R Reid

Bone and Joint Research Group, Department of Medicine, University of Auckland, Auckland, New Zealand.

Calcium supplements have been reported to increase the risk of myocardial infarction (MI). We wished to determine whether the effects of calcium supplements on cardiovascular risk vary across different population groups. We modeled the effect of calcium (with or without vitamin D) on the time to incident cardiovascular events in pre-specified subgroups based on age, dietary calcium intake, body mass index, smoking history, history of hypertension, diabetes and prevalent cardiovascular disease, using interaction terms in Cox proportional hazards models in two randomized controlled trial data sets—our re-analysis of the Women's Health Initiative Calcium and Vitamin D study (WHI CaD), and our pooled patient-level meta-analysis of trials of calcium supplements with or without vitamin D. For women in WHI CaD not taking calcium supplements at randomization ($n = 16\,718$), we found no significant interactions between treatment allocation, the risk of MI, stroke or coronary revascularization, or any of the baseline variables. In the pooled patient-level data set of six trials of calcium with or without vitamin D ($n = 24\,869$), there were also no significant interactions between treatment allocation, risk of MI or stroke, and any of the baseline variables. We found no evidence that the increased cardiovascular risk from calcium supplements differs across varying patient subpopulations. These findings suggest that targeted prescription of calcium supplements to specific population subgroups, such as younger people and those with low dietary calcium intake, should not be endorsed.

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Introduction

Calcium supplements have been widely used for the treatment and prevention of osteoporotic fractures, but recently their cardiovascular safety has been questioned. A secondary analysis of the Auckland Calcium Study showed a 43% increase in the rate of cardiovascular events in women randomized to 1 g daily calcium (as citrate).[1] In a subsequent meta-analysis of 11 randomized, placebo-controlled trials of calcium supplements with nearly 12 000 participants, calcium increased the risk of myocardial infarction (MI) by 27–31%.[2] In the Women's Health Initiative Calcium and Vitamin D study (WHI CaD), calcium co-administered with vitamin D (CaD) increased the risk of MI by 22% in women who were not taking personal, non-protocol calcium supplements at randomization.[3] **Figure 1** shows that the results from the meta-analysis of calcium monotherapy and the re-analysis of WHI CaD were similar, including the longer latency for the development of the effect on stroke. Because of this similarity in outcomes, we pooled the data sets to produce a meta-analysis of trials of calcium supplements with or without vitamin D. Thirteen trials were included, involving nearly 30 000 participants. Calcium increased the risk of MI by 25% and stroke by 15–20%.[3]

An important question is whether the increased cardiovascular risk from calcium supplements is consistent across the population, or whether some patient groups are at greater risk. There is already some evidence suggesting this. For example, in the meta-analysis of trials of calcium monotherapy, there was an interaction between dietary calcium intake and the risk of MI with calcium supplements.[2,4] In the group with dietary calcium intake above the median (805 mg day^{-1}), there was an increased risk of MI with calcium supplements, but there was no dose–response relationship in an analysis based on quintiles of dietary calcium intake. In the primary analysis of WHI CaD, there was an interaction between body mass index (BMI) and the risk of MI or death from coronary heart disease (CHD), with an elevated risk of this composite end point with CaD only in women with BMI $< 30\,kg\,m^{-2}$.[5] In a 5-year randomized controlled trial of calcium supplements, Lewis *et al.*[6] reported that calcium supplements reduced the risk of atherosclerotic vascular disease in women with known atherosclerotic vascular disease at baseline.

To explore these contrasting findings, we investigated whether the effects of calcium supplements on the risk of MI and stroke vary across different subgroups in our re-analysis of WHI

Correspondence: Dr MJ Bolland, Bone and Joint Research Group, Department of Medicine, University of Auckland, Private Bag 92 019, Auckland 1142, New Zealand.
E-mail: m.bolland@auckland.ac.nz

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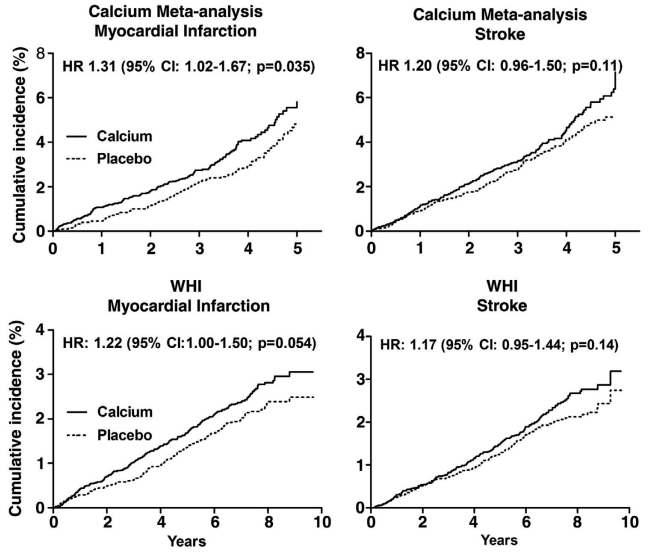

Figure 1 Kaplan–Meier survival curves for time to incident myocardial infarction or stroke by treatment allocation in a meta-analysis of patient-level data from five trials of calcium supplements used as monotherapy ($n = 8151$) and in women in the Women's Health Initiative (WHI) calcium and vitamin D trial not using personal calcium supplements at randomization ($n = 16\,718$). (Note the different scales on the y and x axes). CI, confidence interval; HR, hazard ratio.

CaD, or in the pooled patient-level data set of trials of calcium supplements with or without vitamin D. Detailed subgroup analyses have not previously been carried out in these data sets. WHI CaD had a broader range of baseline data than the pooled data set, allowing for a greater variety of subgroups to be assessed.

Results

Table 1 depicts selected baseline characteristics of women in WHI CaD who were not using calcium supplements at randomization. There were no significant differences between the groups. **Figures 2–4** show the interactions between WHI CaD allocation and baseline characteristics for the risk of MI, stroke and coronary revascularization. For each of these end points, we found no evidence of significant interactions between treatment allocation and any of the baseline variables.

In the complete WHI CaD data set,[5] there was a significant interaction between allocation to CaD, BMI and the composite end point of MI or CHD death. In our analysis of women not taking calcium supplements at randomization, we found no statistically significant interactions between allocation to CaD, BMI, and either MI, stroke or coronary revascularization (**Figures 2–4**). As our findings differed from those of the primary WHI CaD analysis, we repeated our analyses in women using personal calcium supplements at randomization and found a significant interaction between BMI and allocation to CaD for the risk of MI ($P = 0.049$), with the risk of MI from CaD inversely related to BMI (**Table 2**). To explore whether these findings were related to difference in baseline characteristics between the subgroups, we adjusted for previous stroke, previous MI, smoking history, diabetes history, age at randomization, baseline systolic blood pressure and baseline dietary calcium intake, but the hazard ratios did not substantially change.

Table 1 Selected baseline characteristics of women in the Women's Health Initiative calcium and vitamin D study who were not taking calcium supplements at baseline

Characteristic	*CaD* (n = *8429)*	*Placebo* (n = *8289)*	P-*value*
Age (years)			
Mean (s.d.)	62.9 (7.0)	62.9 (7.0)	0.91
<60	39	38	
60–70	43	44	
>70	18	18	
Body mass index (kg m^{-2})			
Mean (s.d.)	29.4 (5.9)	29.4 (6.0)	0.80
<25	24	25	
25–30	36	34	
⩾30	40	41	
Dietary calcium (mg day^{-1}):			
Mean (s.d.)	804 (489)	798 (475)	0.42
<500	28	29	
500–700	21	21	
700–900	17	18	
900–1100	12	12	
⩾1100	21	20	
History of MI	2.3	2.0	0.26
History of stroke	1.0	1.2	0.35
Smoking history			0.64
Never	51	52	
Previous	39	38	
Current	9	9	

Abbreviations: CaD, calcium and vitamin D; MI, myocardial infarction. Data are mean (s.d.) or %.

In the pooled patient-level meta-analysis data set, the overall hazard ratio for time to incident MI for calcium with or without vitamin D was 1.25 (95% CI: 1.06–1.46; $P = 0.0065$) and for time to incident stroke was 1.19 (95% CI: 1.02–1.39; $P = 0.026$). There were no significant interactions between treatment allocation and age, gender, dietary calcium intake, smoking history, history of cardiovascular disease, diabetes mellitus or hypertension either for the risk of MI (**Table 3**) or for the risk of stroke (**Table 4**).

Discussion

In women in WHI CaD who were not taking calcium supplements at baseline and in the pooled patient-level meta-analysis of trials of calcium with or without vitamin D, we found no evidence for interactions between calcium supplements and age, gender, BMI, baseline dietary calcium intake, smoking status, previous history of cardiovascular disease, diabetes mellitus or history of hypertension for the risk of MI, stroke or coronary revascularization.

Previously, in a meta-analysis of five studies of calcium monotherapy, we reported a significant interaction between dietary calcium intake and the risk of MI with calcium supplements.[2] The group with intake greater than the median of 805 mg day^{-1} had an increased risk of MI with calcium, whereas those with intake below the median had no alteration of risk. However, when the cohort was divided by quintile of dietary calcium intake, there was no evidence of a dose–response relationship. There was also no interaction between dietary calcium intake and the risk of stroke, or the composite cardiovascular end point with calcium. Therefore, we concluded

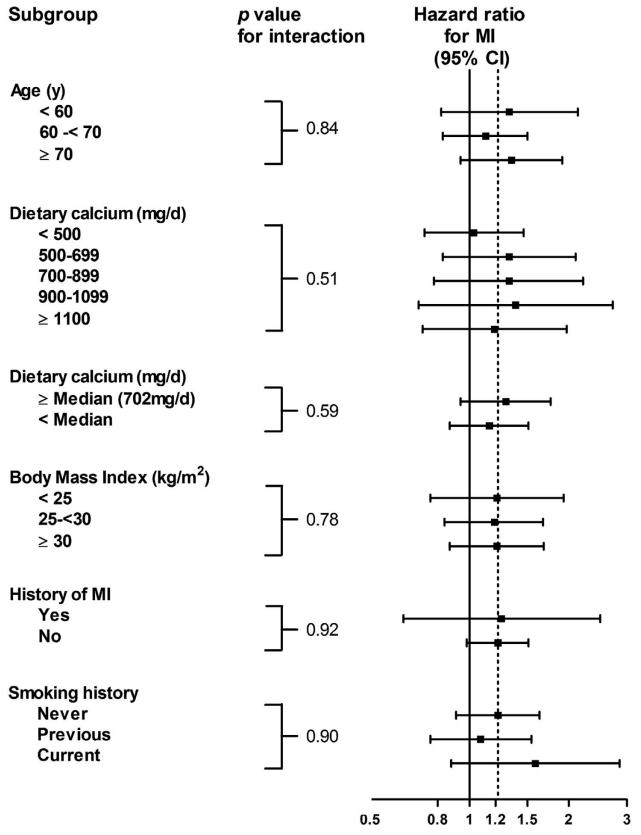

Figure 2 Risk of myocardial infarction (MI) in women in the Women's Health Initiative calcium and vitamin D trial not using personal calcium supplements at randomization by treatment allocation in subgroups defined by various baseline characteristics. Results are reported as hazard ratios with 95% confidence intervals (CI) (horizontal bar). The dotted vertical line represents the hazard ratio in the entire cohort (hazard ratio 1.22, 95% CI: 1.00–1.50, $P = 0.05$).

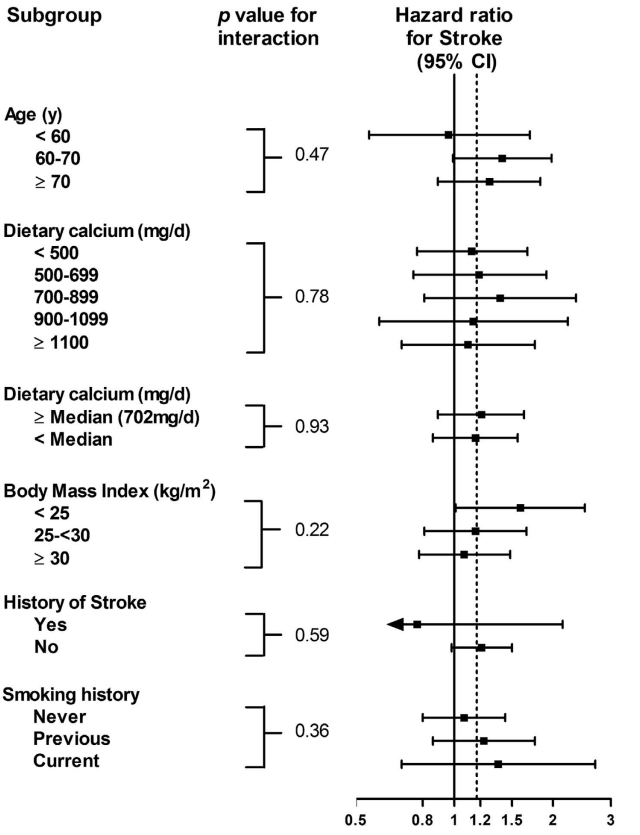

Figure 3 Risk of stroke in women in the Women's Health Initiative (WHI) calcium and vitamin D trial not using personal calcium supplements at randomization by treatment allocation in subgroups defined by various baseline characteristics. Results are reported as hazard ratios with 95% confidence intervals (CI) (horizontal bar). The dotted vertical line represents the hazard ratio for the entire cohort (hazard ratio 1.17, 95% CI: 0.95–1.44, $P = 0.14$).

that the evidence for a relationship between dietary calcium intake, calcium supplement use and cardiovascular risk was weak. The current study supports this conclusion: there was no significant interaction between dietary calcium intake (when assessed either by median intake or by quintiles of intake) and allocation to calcium with or without vitamin D for the risk of MI, stroke or coronary revascularization. Some, however, interpreted the previous findings as suggesting that the increased cardiovascular risk was related to the total calcium intake—the use of calcium supplements on the background of a high dietary calcium intake—and therefore that calcium supplements were safe for individuals with low calcium intake. The current study does not support this interpretation, as the hazard ratios for MI, stroke and coronary revascularization were similar across all quintiles of dietary calcium intake.

In the primary analysis of WHI CaD, Hsia *et al.*[5] reported a significant interaction between BMI and the use of CaD for the risk of the composite end point of MI or CHD death, with an increased risk with CaD observed in women with BMI $< 30\,kg\,m^{-2}$. In contrast, we observed no interaction between CaD and BMI for the risk of MI in women in WHI CaD who did not use calcium supplements at randomization. However, in those women using non-protocol calcium supplements at randomization, there was a significant interaction between BMI, CaD and the risk of MI, with an inverse relationship between BMI and the risk of MI from CaD. In women with normal BMI ($< 25\,kg\,m^{-2}$), the hazard ratio was 1.19, similar to the risk observed in women not taking personal calcium supplements at randomization, whereas overweight and obese women had no alteration of risk (hazard ratio 0.99) and a reduced risk (hazard ratio 0.76), respectively. This inverse relationship persisted after adjustment for traditional cardiovascular risk factors. It seems most likely that this finding is either due to chance or due to confounding by other unmeasured variables, rather than there being a true relationship between BMI and the risk of MI from CaD.

Lewis *et al*.[6] reported that calcium supplements reduced the risk of an atherosclerotic vascular event during 5 years of follow-up in women who had a history of atherosclerotic vascular disease.[6] This result should be treated with caution for several reasons. The composite outcome contained end points that may result from a wide number of pathogenetic processes unrelated to atherosclerosis, such as atrial fibrillation and congestive heart failure. All patient events were obtained from unadjudicated hospital discharge codes, and only the primary code for each admission was utilized, which is likely to have resulted in missed events. For example, there were 28 MIs identified from coding in 1460 women of mean age 75 years

followed for 5 years. Compared to other studies in our meta-analysis of calcium monotherapy,[2] this event rate was approximately half to one-third the rate in women of similar age in two studies,[7,8] and similar to the rate in women who were on average 12–16 years younger in two other studies.[5,9] The study lacked adequate power, either in the primary analysis or in subgroup analyses, to detect differences in event rates between the treatment groups of the magnitude observed in our meta-analyses. Finally, the authors did not follow recommendations for the reporting of subgroups,[10,11] in that they have reported hazard ratios and *P* values for single subgroups. The recommended approach is to report the results of interaction tests between subgroups (that is, the subgroups with or without atherosclerotic vascular disease at baseline) and only consider individual subgroup results if the interaction test is statistically significant. We did not confirm interactions between history of MI or stroke and the risk of cardiovascular events with calcium in WHI CaD.

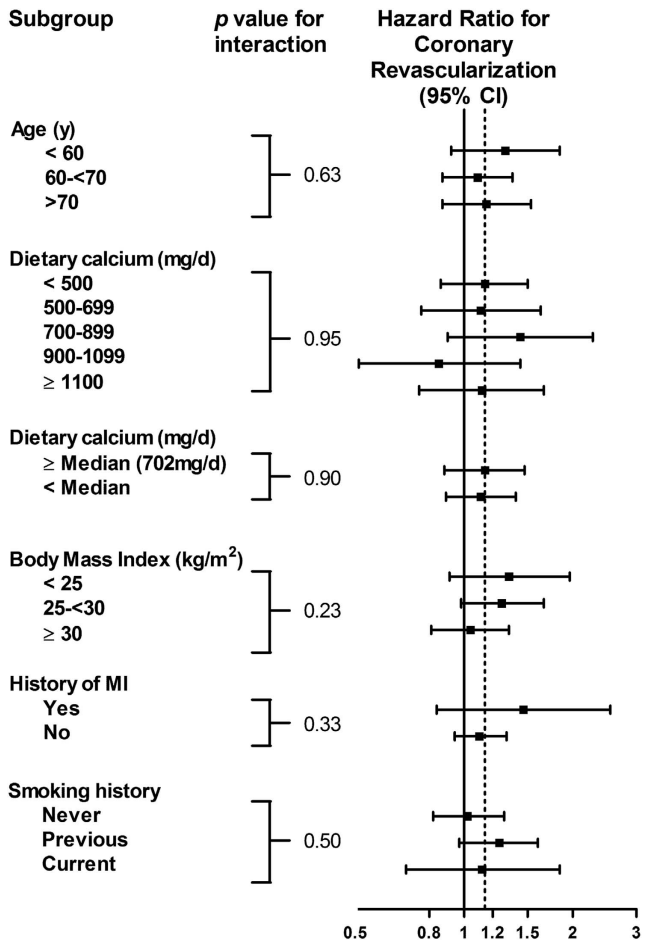

Figure 4 Risk of coronary revascularization in women in the Women's Health Initiative (WHI) calcium and vitamin D trial not using personal calcium supplements at randomization by treatment in subgroups defined by various baseline characteristics. Results are reported as hazard ratios with 95% confidence intervals (CI) (horizontal bar). The dotted vertical line represents the hazard ratio for the entire cohort (hazard ratio 1.15, 95% CI: 0.98–1.34, $P = 0.09$).

Our study has some limitations. As we used the WHI limited-access clinical trials data set for our analysis, we are limited to the information available in this data set. Subgroup analyses increase the likelihood of detection of false-positive results and therefore significant results require cautious interpretation. However, we have not identified significant interactions in the current analysis. Lack of power is also potentially an issue when performing subgroup analyses, because the decrease in the number of relevant events in each group analyzed may result in a Type 2 error. The large number of events in the data set suggests that if such an error occurred, it is not likely to be clinically relevant.

In conclusion, calcium supplements with or without vitamin D are associated with an increased risk for MI and stroke, and this risk appears to apply across subgroups defined by important baseline characteristics. These findings suggest that targeted prescription of calcium supplements to specific population subgroups, such as younger people and those with low dietary calcium intake, should not be endorsed.

Materials and Methods

In brief, WHI CaD was a randomized, double-blind, placebo-controlled study of 1 g calcium/400 IU vitamin D_3 daily in 36 282 post-menopausal women followed for an average duration of 7 years.[5,12] Medical records related to self-reported medical events for MI, stroke and coronary revascularization were adjudicated centrally by physician adjudicators using

Table 2 Effect of BMI on the risk of MI and stroke with CaD in the WHI CaD Study, grouped by personal use of calcium supplements at randomization

	No personal use of calcium				*Any personal use of calcium*			
	CaD, n (%)	*Placebo,* n (%)	*HR (95% CI)*	P-*value for interaction*	*CaD,* n (%)	*Placebo,* n (%)	*HR (95% CI)*	P-*value for interaction*
MI				0.78				0.049
BMI < 25	39 (1.9)	34 (1.6)	1.21 (0.76–1.93)		48 (1.6)	42 (1.3)	1.19 (0.79–1.82)	
BMI 25–30	75 (2.5)	61 (2.1)	1.19 (0.84–1.67)		72 (2.1)	71 (2.0)	0.99 (0.71–1.39)	
BMI ⩾30	95 (2.8)	73 (2.2)	1.21 (0.87–1.68)		60 (1.8)	83 (2.6)	0.76 (0.53–1.07)	
Stroke				0.22				0.73
BMI < 25	48 (2.4)	33 (1.6)	1.59 (1.01–2.49)		47 (1.5)	58 (1.8)	0.83 (0.56–1.23)	
BMI 25–30	68 (2.3)	56 (2.0)	1.16 (0.81–1.66)		62 (1.8)	73 (2.1)	0.88 (0.62–1.24)	
BMI ⩾30	80 (2.4)	74 (2.2)	1.07 (0.78–1.48)		47 (1.4)	58 (1.8)	0.78 (0.52–1.15)	

Abbreviations: BMI, body mass index; CaD, calcium and vitamin D; CI, confidence interval; HR, hazard ratio. BMI in $kg\,m^{-2}$.

Table 3 Risk of myocardial infarction by treatment allocation in subgroups in the patient-level meta-analysis data set

	Calcium/ CaD, n *(%)*	*Placebo,* n *(%)*	*HR (95% CI)*	P-*value for interaction*
Age (years)				0.62
<60	45 (1.2)	32 (0.9)	1.28 (0.81–2.02)	
60–70	108 (2.7)	95 (2.4)	1.10 (0.83–1.46)	
⩾70	199 (4.1)	152 (3.1)	1.37 (1.10–1.70)	
Gender				0.73
Male	38 (4.0)	32 (3.8)	1.22 (0.73–2.06)	
Female	314 (2.7)	247 (2.2)	1.28 (1.08–1.52)	
Dietary calcium (mg day^{-1})				0.39
<400	63 (3.1)	59 (3.1)	1.19 (0.81–1.74)	
400–600	80 (3.1)	74 (2.8)	1.05 (0.76–1.46)	
600–800	63 (2.6)	45 (1.9)	1.52 (1.01–2.28)	
800–1100	81 (2.8)	52 (1.9)	1.24 (0.85–1.80)	
⩾1100	65 (2.5)	49 (1.9)	1.32 (0.89–1.94)	
Dietary calcium (mg day^{-1})				0.10
⩾Median (737 mg day^{-1})	164 (2.6)	117 (1.9)	1.31 (1.02–1.67)	
<Median	188 (3.0)	162 (2.6)	1.23 (0.99–1.53)	
History of CVD				0.32
Yes	50 (4.7)	49 (4.6)	1.03 (0.69–1.53)	
No	133 (2.1)	100 (1.6)	1.31 (1.01–1.70)	
Smoking history				0.89
Never	126 (2.5)	103 (2.1)	1.20 (0.92–1.57)	
Previous	93 (2.4)	74 (2.0)	1.14 (0.83–1.57)	
Current	49 (4.0)	37 (3.2)	1.39 (0.88–2.18)	
Diabetes mellitus				0.18
Yes	66 (7.8)	40 (4.9)	1.74 (1.15–2.65)	
No	285 (2.4)	239 (2.1)	1.19 (1.00–1.42)	
History of hypertension				0.17
Yes	132 (4.1)	102 (3.1)	1.40 (1.07–1.82)	
No	128 (1.9)	102 (1.6)	1.06 (0.81–1.38)	

Abbreviations: CaD, calcium and vitamin D; CI, confidence interval; HR, hazard ratio.

Table 4 Risk of stroke by treatment allocation in various subgroups in the patient-level meta-analysis data set

	Calcium/ CaD, n *(%)*	*Placebo,* n *(%)*	*HR (95% CI)*	P-*value for interaction*
Age (years)				0.57
<60	25 (0.7)	24 (0.7)	1.01 (0.58–1.77)	
60–70	102 (2.5)	87 (2.2)	1.19 (0.89–1.58)	
⩾70	236 (4.8)	195 (4.0)	1.22 (1.01–1.48)	
Gender				0.47
Male	31 (3.2)	31 (3.7)	1.00 (0.61–1.65)	
Female	332 (2.9)	275 (2.4)	1.22 (1.04–1.43)	
Dietary calcium (mg day^{-1})				0.67
<400	55 (2.7)	47 (2.4)	1.12 (0.76–1.66)	
400–600	72 (2.8)	70 (2.6)	1.06 (0.76–1.47)	
600–800	69 (2.9)	44 (1.8)	1.59 (1.09–2.33)	
800–1100	91 (3.1)	86 (3.1)	1.05 (0.78–1.41)	
⩾1100	76 (2.9)	59 (2.3)	1.31 (0.94–1.85)	
Dietary calcium (mg day^{-1})				0.90
⩾Median (737 mg day^{-1})	189 (3.0)	160 (2.6)	1.21 (0.98–1.49)	
<Median	174 (2.8)	146 (2.3)	1.18 (0.95–1.47)	
Smoking history				0.34
Never	123 (2.4)	112 (2.2)	1.13 (0.87–1.45)	
Previous	88 (2.3)	66 (1.8)	1.28 (0.93–1.76)	
Current	46 (3.8)	33 (2.9)	1.49 (0.78–2.86)	
Diabetes mellitus				0.070
Yes	39 (4.6)	44 (5.3)	0.82 (0.53–1.27)	
No	324 (2.8)	262 (2.3)	1.26 (1.07–1.48)	
History of hypertension				0.41
Yes	121 (3.8)	107 (3.3)	1.16 (0.89–1.50)	
No	123 (1.9)	89 (1.4)	1.37 (1.04–1.80)	

Abbreviations: CaD, calcium and vitamin D; CI, confidence interval; HR, hazard ratio.

standardized definitions, and all deaths were also centrally adjudicated. The primary analysis reported no effect of CaD on cardiovascular events, but 54% of participants were taking personal (non-protocol) calcium supplements at randomization. We obtained the WHI limited-access clinical trials data set from the National Heart Lung and Blood Institute. In a re-analysis of this data set, we found interactions between personal calcium supplement use and CaD for cardiovascular events.[3] In women not using personal calcium supplements at randomization, CaD increased cardiovascular risk, whereas there was no alteration of risk in women already taking calcium supplements at randomization. We have therefore restricted our current analyses to women not taking personal calcium supplements at randomization.

For the meta-analysis of calcium with or without vitamin D, we searched Medline, Embase and the Cochrane Central Register of Controlled Trials for randomized placebo-controlled trials of calcium supplements used as monotherapy in March 2010.[2] Eligible studies were randomized, placebo-controlled trials of calcium supplements (⩾500 mg day^{-1}), with 100 or more participants of mean age more than 40 years, and a study duration of more than 1 year. Fifteen trials were eligible, six supplied trial-level data only and five supplied patient-level data. In these five trials, cardiovascular events were from unadjudicated self-reports (one study); adjudicated self-reports and death certificates (one study); verified events from hospital discharge data and adjudicated death certificates (one study); self-reports, hospital admissions and death certificates that were independently adjudicated by a cardiologist or neurologist (two studies). A systematic review identified two randomized, placebo-controlled trials of CaD with cardiovascular outcomes—WHI CaD and another small study.[13] We updated the patient-level data set for trials of calcium monotherapy with our re-analysis of WHI CaD, restricting the data set to women not using personal calcium supplements at randomization. Thus, the complete data set comprised 24 869 people in six trials, with an average participant age of 66 years, 93% female and average duration of follow-up of 5.9 years. This is the same

database that was used in our previous meta-analysis of calcium with or without vitamin D.[3]

For the current analyses of the WHI CaD data set, we attempted to replicate the approach of the WHI investigators where possible. The baseline characteristics at the time of randomization to CaD are reported, whereas the WHI investigators reported these characteristics at entry to the WHI program.[5] For BMI, dietary and supplemental calcium intake, we used the latest value recorded between screening and 1 month following CaD randomization. For variables related to medical history, we used the status at entry to the WHI program. We modeled the effect of CaD on the time to incident MI, stroke and the composite end point of coronary revascularization (either percutaneous coronary angiography or coronary artery bypass grafting) in pre-specified subgroups for baseline age ($<$60, 60–70, $>$70 years), dietary calcium intake ($<$500, 500–700, 700–900, 900–1100, $\geqslant$1100 mg day^{-1}, as well as above and below the median value of 702 mg day^{-1}), BMI ($<$25, 25–30, $\geqslant$30 kg m^{-2}), smoking history, and previous MI or stroke using interaction terms in Cox proportional hazards models stratified by age, prevalent cardiovascular disease at baseline, and randomization status in the WHI hormone and dietary modification trials, following the approach of the WHI investigators.[5,12]The dietary calcium thresholds represented the quintile of intake rounded to the nearest 100 mg day^{-1}.

In the meta-analysis data set, we repeated these analyses modeling the effect of treatment allocation (calcium with or without vitamin D) on the time to incident MI and stroke in the following pre-specified subgroups for baseline age ($<$60, 60–70, $\geqslant$70 years), dietary calcium intake ($<$500, 500–700, 700–900, 900–1100, $\geqslant$1100 mg day^{-1}, as well as above and below the median value of 737 mg day^{-1}), history of cardiovascular disease, history of smoking, history of diabetes mellitus and history of hypertension using the interaction terms in the Cox proportional hazard models stratified by study. 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. All analyses were performed using SAS version 9.2. All tests were two tailed and $P<0.05$ was considered significant.

Conflict of Interest

IRR has received research funding, speaker and consultancy fees from Novartis, Merck, Procter & Gamble, and Amgen. The remaining authors declare no conflict of interest.

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Disclaimer

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