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Higher Dietary Calcium Intakes Are Associated With Reduced Risks of Fractures, Cardiovascular Events, and Mortality: A Prospective Cohort Study of Older Men and Women

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ABSTRACT

The aim of this population-based, prospective cohort study was to investigate long-term associations between dietary calcium intake and fractures, non-fatal cardiovascular disease (CVD), and death from all causes. Participants were from the Melbourne Collaborative Cohort Study, which was established in 1990 to 1994. A total of 41,514 men and women (~99% aged 40 to 69 years at baseline) were followed up for a mean (SD) of 12 (1.5) years. Primary outcome measures were time to death from all causes ($n = 2855$), CVD-related deaths ($n = 557$), cerebrovascular disease-related deaths ($n = 139$), incident non-fatal CVD ($n = 1827$), incident stroke events ($n = 537$), and incident fractures ($n = 788$). A total of 12,097 participants (aged ≥50 years) were eligible for fracture analysis and 34,468 for non-fatal CVD and mortality analyses. Mortality was ascertained by record linkage to registries. Fractures and CVD were ascertained from interview ~13 years after baseline. Quartiles of baseline energy-adjusted calcium intake from food were estimated using a food-frequency questionnaire. Hazard ratios (HR) and odds ratios (OR) were calculated for quartiles of dietary calcium intake. Highest and lowest quartiles of energy-adjusted dietary calcium intakes represented unadjusted means (SD) of 1348 (316) mg/d and 473 (91) mg/d, respectively. Overall, there were 788 (10.3%) incident fractures, 1827 (9.0%) incident CVD, and 2855 people (8.6%) died. Comparing the highest with the lowest quartile of calcium intake, for all-cause mortality, the HR was 0.86 (95% confidence interval [CI] 0.76–0.98, $p_{trend} = 0.01$); for non-fatal CVD and stroke, the OR was 0.84 (95% CI 0.70–0.99, $p_{trend} = 0.04$) and 0.69 (95% CI 0.51–0.93, $p_{trend} = 0.02$), respectively; and the OR for fracture was 0.70 (95% CI 0.54–0.92, $p_{trend} = 0.004$). In summary, for older men and women, calcium intakes of up to 1348 (316) mg/d from food were associated with decreased risks for fracture, non-fatal CVD, stroke, and all-cause mortality. © 2015 American Society for Bone and Mineral Research.

KEY WORDS: DIETARY CALCIUM; FRACTURE PREVENTION; CARDIOVASCULAR DISEASES; STROKE; MORTALITY; EPIDEMIOLOGICAL STUDY

Introduction

Calcium is important for maintaining bone mass,[1–4] but its role in fracture prevention is unclear. Several observational cohort and intervention studies have reported decreases in fracture risk with higher calcium intakes,[5–8] whereas others have reported no association[9–11] or an increase in hip fracture risk with calcium supplement use.[12,13] Evidence from cohort[14–16] and interventional studies[17,18] for potential adverse cardiovascular events with calcium supplement use has generated controversy regarding its long-term safety. Some observational studies of dietary calcium intake have reported cardio-protective benefits,[19–21] whereas others have reported no association.[22–24] However, studies of dietary calcium intake and all-cause or cardiovascular disease (CVD)-related mortality are limited and lack consistency; one study showed a benefit,[25] others reported no association,[16,26] and one suggested a possible increase in mortality for postmenopausal women with dietary calcium intakes ≥1400 mg/d.[27]

Given the uncertainties regarding the role of dietary calcium in fracture prevention and cardiovascular disease, we investigated the associations between dietary calcium intake and fractures, CVD, and death from all causes using a prospective cohort study of healthy, community-dwelling people in Melbourne, Australia.

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Materials and Methods

Study population and data collection

The Melbourne Collaborative Cohort Study is a prospective study of 41,514 participants (17,045 men; 24,469 women), predominantly aged 40 to 69 years at baseline (1990 to 1994). About 25% of the participants were born in southern Europe. Details of the study have been published previously.[28] Briefly, participants were recruited by sending personal letters of invitation, using electoral registers, advertisements, and community announcements in local media. The Cancer Council Victoria and Melbourne Health Human Research Ethics Committees approved the study, and all participants gave written, informed consent.

For these analyses, we excluded participants who had no baseline food-frequency questionnaire (FFQ) ($n = 46$, $<0.01\%$), reported dietary calcium or energy intakes more than three standard deviations from their sex-specific means ($n = 478$, 1.15%), or reported a history of angina, myocardial infarction, stroke, diabetes mellitus, or cancer at baseline ($n = 6522$, 15.7%). These exclusions left 34,468 participants eligible for analyses of mortality and non-fatal CVD. Analyses of incident fractures were further restricted to the 12,097 participants aged ≥ 50 years at baseline.

Diet during the 12 months preceding baseline was assessed using a 121-item FFQ.[29] Calcium supplementation was assessed as use at least weekly. Total energy and nutrient intakes were calculated from Australian food composition tables.[30] Total calcium intake could not be calculated because data on supplement dose and frequency were not obtained.

As previously reported,[28] structured face-to-face interviews were used to obtain information on lifestyle and sociodemographic factors, including country of birth, smoking, physical activity, alcohol intake, history of hypertension and arthritis, age, and sex. Height and weight were measured, and body mass index (kg/m^2) was calculated.

Ascertainment of deaths

Deaths to December, 31, 2006, were identified from the Victorian Registry of Births, Deaths and Marriages and the National Death Index. Underlying cause of death was coded by the Australian Bureau of Statistics. For these analyses, we used deaths from all causes, any CVD (ICD-9 390–459 or ICD-10 I00–I99), myocardial infarction (410–412 or I21–I23), and cerebrovascular disease (430–438 or I60–I69).

Incident fracture and non-fatal cardiovascular disease

Data on fracture and non-fatal CVD from baseline were obtained by face-to face interviews between 2003 and 2007. For CVD, participants were asked: "Has a doctor or nurse ever told you that you had a heart attack/angina/stroke?" For fractures, participants were asked: "Have you broken or fractured a bone since you were 50 years old?" Further information on the cause of fracture was collected for hip, wrist, and shoulder fractures and categorized according to the degree of trauma (fall from a standing height or less, from a harder fall, or from a car accident/other severe trauma). Fragility fracture was defined as a fracture resulting from a fall from standing height or less.

Statistical analysis

Cox regression, with age as the time axis and stratified by sex, was used to estimate hazard ratios (HR) in relation to calcium intake for all-cause mortality and mortality from CVD, myocardial infarction, and cerebrovascular disease. Follow-up began at baseline and ended at death, date left Australia, or December, 31, 2006, whichever came first. Tests based on Schoenfeld residuals showed no evidence that the proportional hazards assumptions were violated for any covariate apart from sex. Logistic regression was used to estimate odds ratios (OR) for fractures and non-fatal CVD. Interactions between calcium intake and country of birth, sex, history of hypertension (for mortality and non-fatal cardiovascular disease), and arthritis (for fracture), smoking status, and dietary intakes of protein, fat, sodium, and phosphorus were tested for all outcomes. Statistical analyses were performed using Stata 11 (Statacorp, College Station, TX, USA).

Dietary calcium intake was adjusted for energy intake using Willett's residual method[31] separately for sex and categorized into quartiles. A pseudo-continuous variable, constructed by assigning median calcium values for each quartile, was used to test for trend; departure from linearity was assessed by comparing likelihoods of models with the linear and categorical variables. To determine whether complex dose-response relationships were missed by using the categorical intake, we also fitted restricted cubic splines for the continuous intake.

Causal diagrams were used to identify the following variables to include in statistical models: age, sex, country of birth (Australia/United Kingdom, Italy/Greece), smoking status (never, former, current), physical activity (categorized using a score combining frequency and intensity of exercise in the past 6 months), usual daily alcohol intake (none, ≤ 9, >9 to 34, >34 g/d), an area-based measure of socioeconomic status (SEIFA,[32] Socio-Economic Indices for Areas, categorized into quintiles from most disadvantaged to least disadvantaged), history of hypertension, arthritis, saturated fat, polyunsaturated fat, protein, sodium and phosphorus and fruit and vegetable intakes categorized using current Australian recommendations).[33] Nutrients were energy-adjusted and categorized into quartiles.

To assess the possibility of reverse causality owing to undiagnosed disease, we performed an analysis in which the first 2 years of follow-up were ignored. We also fitted models for women only; the results were similar with and without adjusting for hormone-replacement therapy (HRT) use, so results are presented for men and women combined.

Results

Before energy adjustment, the median (interquartile range [IQR]) dietary calcium intakes were 801 (IQR = 422) mg/d for men and 784 (IQR = 436) mg/d for women; the respective 5th and 95th percentiles of intake were 400 mg/d and 1542 mg/d and 383 mg/d and 1555 mg/d. Participants with low energy-adjusted dietary calcium intakes had higher body mass index (BMI), were more likely to have a history of smoking and higher intakes of alcohol and saturated fat, and were socioeconomically more disadvantaged than participants with the highest intakes. In contrast, participants with high dietary calcium were physically more active, had higher fruit/vegetable intakes, and were more likely to use multivitamin supplements (Table 1). About 10% of participants reported using calcium supplements at least weekly, and the prevalence of use was slightly higher for those with the highest dietary calcium intake (Table 1).

Over an average of 13.3 years of follow-up, 2855 deaths occurred, of which 557 were CVD related (including 157 from

Table 1. Baseline Characteristics According to Quartiles of Energy-Adjusted Dietary Calcium Intake

	Energy-adjusted dietary calcium intake quartiles (median)			
	Quartile 1 (641 mg/d)[a] IQR = 121 mg/d	Quartile 2 (785 mg/d) IQR = 56 mg/d	Quartile 3 (899 mg/d) IQR = 63 mg/d	Quartile 4 (1076 mg/d) IQR = 163 mg/d
No. of participants	8760	8662	8599	8447
Energy-adjusted dietary calcium intake (mg/d)	610 (113)	784 (33)	901 (37)	1122 (157)
Unadjusted dietary calcium intake (mg/d)	473 (91)	696 (55)	903 (68)	1348 (316)
Age (years)	54.6 (8.5)	54.4 (8.6)	54.5 (8.7)	54.6 (8.7)
Male sex (%)	3491 (39.9)	3449 (39.8)	3417 (39.7)	3335 (39.5)
Country of birth (%)				
Australia/NZ/UK	5946 (67.9)	6218 (71.8)	6871 (79.9)	7158 (84.7)
Italy/Greece	2814 (32.1)	2444 (28.2)	1728 (20.1)	1289 (15.3)
Body mass index (kg/m^2) (%)				
<25	2948 (33.7)	3007 (34.7)	3305 (38.4)	3613 (42.8)
≥25 to <30	3779 (43.1)	3823 (44.1)	3689 (42.9)	3498 (41.4)
≥30 to <35	1523 (17.4)	1367 (15.8)	1239 (14.4)	1034 (12.2)
≥35	510 (5.8)	465 (5.4)	366 (4.3)	302 (3.6)
Energy intake (kJ/d)	10,041 (3,342)	8389 (2,821)	8553 (2,882)	9939 (3,547)
Saturated fat intake (g/d)	37 (16)	30 (13)	31 (13)	35 (15)
Polyunsaturated fat intake (g/d)	15 (7)	12 (5)	12 (5)	12 (5)
Protein intake (g/d)	103 (36)	90 (29)	93 (29)	108 (34)
Sodium intake (mg/d)	3373 (1191)	2908 (990)	2941 (991)	3274 (1100)
Phosphorus intake (mg/d)	1624 (609)	1489 (551)	1645 (593)	2148 (825)
Daily fruit intake (%)				
0 to 2 times	1614 (18.4)	1469 (17.0)	1180 (13.7)	757 (9.0)
3 to 4 times	3010 (34.4)	3349 (38.7)	3226 (37.5)	2769 (32.8)
5 to 6 times	1987 (22.7)	2148 (24.8)	2373 (27.6)	2552 (30.2)
6+ times	2149 (24.5)	1696 (19.6)	1820 (21.2)	2369 (28.1)
Daily vegetable intake (%)				
0 to 3 times	2588 (29.5)	2684 (31.0)	2220 (25.8)	1688 (20.0)
4 to 5 times	2927 (33.4)	2905 (33.5)	2892 (33.6)	2515 (29.8)
6 to 7 times	1793 (20.5)	1824 (21.1)	2007 (23.3)	2134 (25.3)
7+ times	1452 (16.6)	1249 (14.4)	1480 (17.2)	2110 (25.0)
Calcium supplement use (%)	867 (9.9)	836 (9.7)	960 (11.2)	1074 (12.7)
Multivitamin use (%)	1189 (13.6)	1351 (15.6)	1472 (17.1)	1684 (19.9)
Smoking status (%)				
Never	4916 (56.1)	5076 (58.6)	5086 (59.2)	5218 (61.8)
Former	2531 (28.9)	2563 (29.6)	2666 (31.0)	2546 (30.1)
Current	1313 (15.0)	1023 (11.8)	846 (9.8)	683 (8.1)
Alcohol intake (%)				
None	2577 (29.4)	2694 (31.1)	2715 (31.6)	2910 (34.5)
Low (0.1 to 9 g/day)	1940 (22.2)	2386 (27.6)	2719 (31.6)	2958 (35.0)
Moderate (9.1 to 34 g/day)	2454 (28.0)	2724 (31.5)	2591 (30.1)	2223 (26.3)
High (>34 g/d)	1789 (20.4)	858 (9.9)	574 (6.7)	356 (4.2)
Physical activity score (%)				
None	2426 (27.7)	2111 (24.4)	1746 (20.3)	1417 (16.8)
Low	1907 (21.8)	1829 (21.1)	1745 (20.3)	1502 (17.8)
Medium	2936 (33.5)	2900 (33.5)	2980 (34.7)	3123 (37.0)
High	1491 (17.0)	1822 (21.0)	2128 (24.8)	2405 (28.5)
Socioeconomic disadvantage (%)				
1st quintile (most disadvantaged)	1336 (15.3)	1198 (13.9)	1172 (13.7)	1104 (13.1)
2nd quintile	1966 (22.5)	1838 (21.3)	1648 (19.2)	1553 (18.5)
3rd quintile	1687 (19.3)	1607 (18.6)	1603 (18.7)	1434 (17.1)
4th quintile	1715 (19.7)	1782 (20.6)	1842 (21.5)	1813 (21.6)

Table 1. (*Continued*)

	Energy-adjusted dietary calcium intake quartiles (median)			
	Quartile 1 (641 mg/d)[a] IQR = 121 mg/d	Quartile 2 (785 mg/d) IQR = 56 mg/d	Quartile 3 (899 mg/d) IQR = 63 mg/d	Quartile 4 (1076 mg/d) IQR = 163 mg/d
5th quintile (least disadvantaged)	2025 (23.2)	2212 (25.6)	2309 (26.9)	2507 (29.8)
Hypertension (%)	1818 (20.8)	1626 (18.8)	1542 (17.9)	1640 (19.4)

All values represent means with standard deviations (in parentheses) for continuous variables and proportions (percentage, %) for categorical variables.

[a]Median values of quartiles for energy-adjusted dietary calcium intake with interquartile range (IQR).

myocardial infarction and 139 from cerebrovascular disease). The majority of the deaths were related to cancer as the leading cause ($n = 1787$) followed by CVD-related deaths (Supplemental Table S7). Overall, 110 people left Australia, of whom 2 died when they were overseas, and were censored for analysis. The mortality rate was inversely related to calcium intake, with the HR for the highest versus lowest quartile being 0.86 (95% confidence interval [CI] 0.76–0.98) (Table 2 and Fig. 1). Similar trends were observed for mortality from CVD (HR = 0.83, 95% CI 0.62–1.12), myocardial infarction (HR = 0.75, 95% CI 0.42–1.33),

Table 2. Mortality Rates and Hazard Ratios (HR) According to Quartiles of Energy-Adjusted Dietary Calcium Intake

	Energy-adjusted dietary calcium intake quartiles (median)						
Cause of death	Quartile 1 (641 mg/d)[a] IQR = 121 mg/d	Quartile 2 (785 mg/d) IQR = 56 mg/d	Quartile 3 (899 mg/d) IQR = 63 mg/d	Quartile 4 (1,076 mg/d) IQR = 163 mg/d			
Hazard ratio (HR) for cause-specific mortality[b](95% confidence interval)					HR (per 200 mg/d)	P_{trend}	$P_{departure}$
Mean age at study entry (years)	54.6	54.4	54.5	54.6			
Mean age at study exit (years)	68.1	67.8	67.8	67.8			
Mean follow-up time (years)	13.5	13.4	13.3	13.2			
Person-years at risk	117,911	116,017	114,382	111,421			
All causes							
No.of deaths	825	730	666	634			
Rate per 1000 person-years (95%CI)	7.00 (6.54–7.49)	6.29 (5.85–6.77)	5.82 (5.40–6.28)	5.69 (5.26–6.15)			
Hazard ratio[c]	1.00	0.93 (0.84–1.04)	0.88 (0.79–0.99)	0.86 (0.76–0.98)	0.93 (0.88–0.98)	0.01	0.72
Cardiovascular disease							
No.of deaths	162	144	134	117			
Rate per 1000 person-years (95%CI)	1.37 (1.18–1.60)	1.24 (1.05–1.46)	1.17 (0.99–1.39)	1.05 (0.88–1.26)			
Hazard ratio[c]	1.00	0.92 (0.72–1.17)	0.91 (0.71–1.19)	0.83 (0.62–1.12)	0.93 (0.82–1.06)	0.28	0.93
Cerebrovascular disease							
No.of deaths	46	32	31	30			
Rate per 1000 person-years (95%CI)	0.39 (0.29–0.52)	0.28 (0.20–0.39)	0.27 (0.19–0.39)	0.27 (0.19–0.39)			
Hazard ratio[c]	1.00	0.74 (0.46–1.20)	0.73 (0.44–1.23)	0.61 (0.34–1.09)	0.80 (0.62–1.04)	0.1	0.8
Myocardial infarction							
No.of deaths	50	38	40	29			
Rate per 1000 person-years (95%CI)	0.42 (0.32–0.56)	0.33 (0.24–0.45)	0.35 (0.26–0.48)	0.26 (0.18–0.37)			
Hazard ratio[c]	1.00	0.76 (0.48–1.21)	0.91 (0.56–1.48)	0.75 (0.42–1.33)	0.91 (0.70–1.18)	0.48	0.53

[a]Median values of quartiles for energy-adjusted dietary calcium intake with interquartile range (IQR).

[b]Study start date: age at baseline; study end date December 31, 2006. Stratified cox regression used for analysis.

[c]Adjusted for age, sex, country of birth, body mass index, SEIFA, vegetable and fruit intake, protein, saturated fat, polyunsaturated fat, sodium, and phosphorus intake, calcium and multivitamin use, physical activity, smoking status, alcohol intake, history of hypertension, and total energy from the diet.

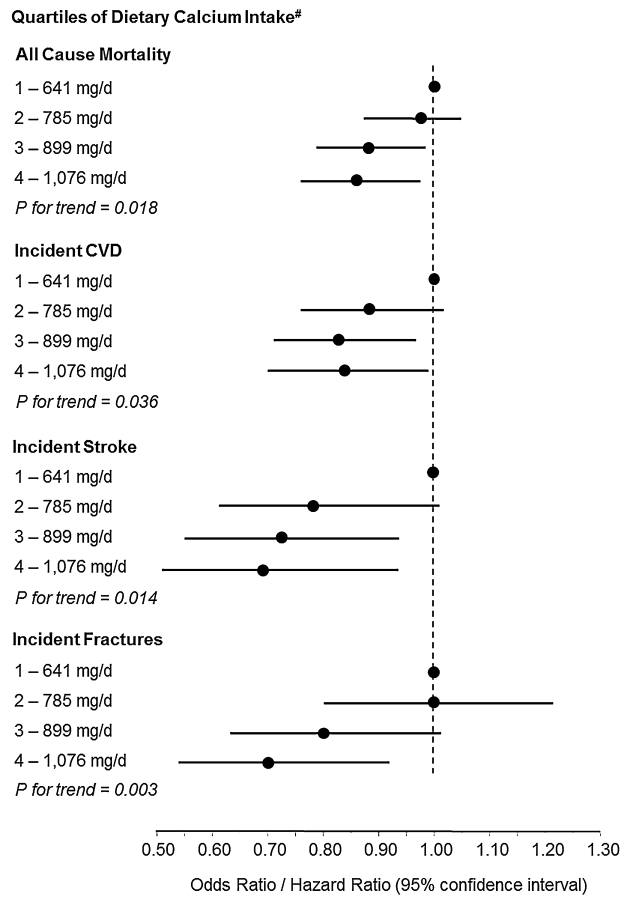

Fig. 1. Hazard ratios and odd ratios (with 95% confidence intervals) by quartiles of energy-adjusted dietary calcium intake. Multivariate models adjusted for age, sex, country of birth, SEIFA, alcohol intake, dietary energy intake, dietary protein intake, dietary saturated fat intake, dietary polyunsaturated fat intake, dietary sodium intake, dietary phosphorus intake, calcium supplements intake, multivitamin intake, physical activity, history of hypertension, history of arthritis, smoking status, daily fruit intake, daily vegetable intake, and BMI.

and cerebrovascular disease (HR = 0.61, 95% CI 0.34–1.09), but these were nonsignificant (Table 2). Cancer-related diseases were the leading cause of death in the cohort during follow-up and, therefore, dietary calcium intake was tested further for any association with cancer-related deaths specifically. The cancer-related mortality rate was not associated with dietary calcium intake when potential confounders were included in the multivariate model (Supplemental Table S4). Besides CVD and cancer, other systemic diseases caused fewer than 5% of deaths and, therefore, in view of limited number of deaths, further analysis was not conducted. No significant interactions were observed between calcium intake and country of birth, sex, history of hypertension, smoking status, dietary protein, fat, sodium, and phosphorus intakes. Results were similar when restricted to participants who did not use calcium supplements (Supplemental Table S1) and when excluding incident cases in the first two years of follow-up.

Data on incident, non-fatal CVD were available for 20,312 (58.9%) participants, including 4933 (56.3%) people in the lowest quartile of calcium intake and 5202 (61.6%) in the highest quartile ($p < 0.001$). Baseline characteristics of participants whose follow-up information on incident CVD could not be obtained were similar to those for participants whose follow-up information was available (Supplemental Table S3). Of those included in the study, 1827 (9.0%) participants reported incident CVD; 813 (3.5%) incident myocardial infarction (MI); 1385 (6.8%) incident ischemic heart disease (IHD), and 537 (2.3%) incident stroke. There was an inverse association between risk of CVD and calcium intake, with the OR for the highest versus lowest quartile being 0.84 (95% CI 0.70–0.99; Table 3). There were no associations between calcium intake and myocardial infarction or ischemic heart disease risk. Stroke risk was inversely associated with calcium intake, with the OR for the highest versus lowest quartile being 0.69 (95% CI 0.51–0.93). For participants without a history of hypertension, the OR for the highest versus the lowest quartile of calcium intake for stroke risk was 0.49 (95% CI 0.34–0.73), whereas for participants with a history of hypertension, there was no association (OR = 1.12, 95% CI 0.69–1.84; $p_{interaction} = 0.001$). No other interactions were significant (any CVD, $p = 0.06$; MI, $p = 0.70$; IHD, $p = 0.51$). Similar results were obtained after excluding participants who used calcium supplements at baseline (Supplemental Table S2).

Data on incident fractures were available for 7736 (64.0%) participants aged ≥50 years, including 1850 (61.6%) participants in the lowest and 1880 participants (64.6%) in the highest quartile of calcium intake ($p < 0.001$). Baseline characteristics of participants who were lost to follow-up were similar to participants in the analytical cohort (Supplemental Table S3). Of those included in the study, 788 (10.2%) reported a fracture and 96 (1.3%) reported a fragility fracture. Fracture risk was inversely associated with dietary calcium, with the OR for the highest versus lowest quartile being 0.70 (95% CI 0.54–0.92) (Table 3 and Fig. 1). No significant associations were found for fragility or wrist fractures, although the numbers were small and confidence intervals were wide. No significant interactions were observed between calcium intake and country of birth, sex, history of hypertension, smoking status, dietary protein, fat, sodium, and phosphorus intake.

The analysis using splines showed similar dose-response relationships as for the categorized variable for all outcomes. In addition, the results were similar after excluding participants who used calcium supplements at baseline (Supplemental Table S2).

Discussion

In this prospective cohort study, in which the median dietary calcium intake (excluding supplements) was 792 (IQR = 428) mg/d, calcium intake was inversely associated with the mortality rate from all causes and risk of incident fracture and non-fatal CVD, specifically stroke. We did not find any indication that higher dietary calcium intake could be harmful to health.

This study has a number of strengths. It assessed the long-term associations of dietary calcium in a large cohort of older men and women with substantial information on potential confounding variables, and for the mortality analyses, there was little loss to follow-up. We used energy-adjusted dietary calcium intake because energy from the diet is a potential confounder in dietary studies.[31] We used a FFQ specifically designed for our study population and which had fair to moderate agreement for food items when completed 12 months apart.[34] In addition, we excluded participants with chronic diseases at baseline whose diet might have been affected by ill health. Finally, we tested for

Table 3. Odds Ratios (OR) for Non-Fatal Cardiovascular Disease and Fractures According to Quartiles of Energy-Adjusted Dietary Calcium Intake

	Energy-adjusted dietary calcium intake quartiles (median)						
	Quartile 1 (641 mg/d)[a] IQR = 121 mg/d	Quartile 2 (785 mg/d) IQR = 56 mg/d	Quartile 3 (899 mg/d) IQR = 63 mg/d	Quartile 4 (1076 mg/d) IQR = 163 mg/d			
Odd ratios (OR) for incident non-fatal cardiovascular disease (95% confidence interval)					OR (per 200 mg/d)	P_{trend}	$P_{departure}$
All cardiovascular disease							
Number	501	438	434	454			
Odds ratio[b]	1.00	0.88 (0.76–1.02)	0.83 (0.71–0.97)	0.84 (0.70–0.99)	0.92 (0.85–1.00)	0.04	0.36
Myocardial infarction							
Number	219	188	194	212			
Odds ratio[b]	1.00	0.92 (0.75–1.15)	0.97 (0.78–1.22)	1.08 (0.84–1.37)	1.04 (0.93–1.16)	0.48	0.51
Ischemic heart disease							
Number	373	329	334	349			
Odds ratio[b]	1.00	0.91 (0.77–1.08)	0.91 (0.76–1.09)	0.94 (0.77–1.14)	0.98 (0.89–1.07)	0.59	0.55
Stroke							
Number	157	126	125	129			
Odds ratio[b]	1.00	0.78 (0.61–1.01)	0.72 (0.55–0.94)	0.69 (0.51–0.93)	0.85 (0.74–0.97)	0.02	0.44
Odd ratios (OR) for incident fractures (95% confidence interval)							
All fractures							
Number	206	231	189	162			
Odds ratio[b]	1.00	1.00 (0.80–1.23)	0.80 (0.63–1.01)	0.70 (0.54–0.92)	0.84 (0.74–0.94)	0.004	0.41
Fragility fractures[c]							
Number	27	32	18	19			
Odds ratio[b]	1.00	1.09 (0.63–1.89)	0.61 (0.31–1.21)	0.88 (0.43–1.83)	0.88 (0.63–1.23)	0.46	0.21
Fragility wrist fractures							
Number	20	28	16	15			
Odds ratio[b]	1.00	1.27 (0.69–2.35)	0.73 (0.35–1.54)	0.98 (0.43–2.23)	0.92 (0.64–1.34)	0.67	0.26

[a]Median values of quartiles for energy-adjusted dietary calcium intake.

[b]Adjusted for age, sex, country of birth, body mass index, SEIFA, vegetable and fruit intake, protein, saturated fat, polyunsaturated fat, sodium and phosphorus intake, calcium and multivitamin use, physical activity, smoking status, alcohol intake, history of hypertension (non-fatal cardiovascular disease), history of arthritis (fractures), and total energy from the diet.

[c]Two participants suffered both a wrist and a shoulder fracture during follow-up.

interactions between calcium intake and dietary nutrients known to influence calcium metabolism.

There are also limitations. Although we controlled for known risk factors for CVD, we cannot rule out residual confounding. We had no information on family history of CVD or fractures. Second, self-reported dietary calcium intake is subject to measurement error, and individual variations in diet during follow-up is likely. However, in our cohort, mean (SD) dietary calcium intake measured at baseline ($n = 41{,}468$; 864 [421] mg/d) and during follow-up ($n = 24{,}948$; 883 [324] mg/d) was similar. Calcium supplement use was higher in 2003 to 2007 than at baseline (27.7% versus 10.8%) and this might have influenced the observed associations, but the proportion of participants who reported calcium supplement use at least once daily at the follow-up interview was similar in the highest and the lowest quartile of baseline dietary calcium intake (20.2% versus 21.4%; $p = 0.27$). Third, another limitation was the lack of quantitative assessment of calcium supplements use at baseline (dosage, frequency, and the type of calcium supplement). As a result, it was not possible to further analyze this variable, but asensitivity analysis that excluded participants who reported calcium supplement use at baseline did not alter the estimates for the association between dietary calcium intake and important outcomes (Supplemental Table S1). Fourth, there was a small number of deaths from cerebrovascular disease or myocardial infarction and there was a limited number of fragility fractures, thus our results are imprecise for these outcomes. Fifth, we relied on self-reported outcomes, which is subject to error, although self-reported fractures have previously been validated.[35] Finally, there was a loss to follow-up of 41% for non-fatal CVD incidence and 36% for fracture incidence, which included deaths, and this could have affected the associations, although the baseline characteristics of these participants were similar to those participants for whom follow-up data were obtained.

The relationship between dietary calcium intake (excluding supplements) and all-cause mortality in a mixed population of older men and women has not been previously investigated. In line with our results, a prospective study of 23,366 Swedish men reported a 25% decrease in all-cause mortality risk for the highest compared with the lowest tertile of calcium intake (HR = 0.75; 95% CI 0.63–0.88; $p_{trend} < 0.001$), [26] but CVD-related mortality was not significantly related to dietary calcium intake

(HR = 0.77, 95% CI 0.58–1.01; $p_{trend} = 0.064$). Another prospective cohort study of 3139 older Chinese men and women with a habitual low baseline dietary calcium intake (mean [SD], 596.1 [279.4] mg/d) reported a significantly decreased risk of all-cause mortality (HR = 0.63, 95% CI 0.49–0.81; $p_{trend} < 0.001$) but not of CVD-related mortality (HR = 0.70, 95% CI 0.41–1.21; $p_{trend} = 0.228$) for the highest compared with the lowest quartile of calcium intake.[36] This study did not report on incident CVD or incident fractures, and the number of CVD-related deaths was relatively low ($n = 114$). A recent meta-analysis of randomized controlled trials of vitamin D and calcium supplement use reported a decrease in all-cause mortality risk with calcium supplements when used with vitamin D.[37] Similarly, the Women's Health Initiative randomized trial of calcium plus vitamin D supplementation reported a nonsignificant decrease in all-cause mortality with supplement use compared with placebo.[38] In apparent contrast to a number of previous studies, the Swedish Mammography Cohort study of 61,433 women found that those with both a high calcium intake (≥1400 mg/d) or low intake (<600 mg/d) had the highest mortality risk, suggesting a U-shaped association and the lowest level of risk for women consuming 600 to 1000 mg of dietary calcium daily.[27] Although it is difficult to compare these results with our findings because of differences in calcium intake, our analysis using splines revealed no increase in risk at either high or low dietary calcium intakes.

Studies of dietary calcium intake and its association with CVD events are also inconclusive.[14,20,26,27,39,40] Although some studies have reported a decrease in CVD risk with higher dietary calcium intake,[20,26] others have reported no association[14,39,40] and one an increased risk.[27] The JPHC Study Cohort reported dietary calcium intake to be inversely associated with stroke risk but unrelated to CVD risk.[39] The National Institutes of Health-AARP Diet and Health Study, reported dietary calcium intake to be unrelated to total CVD death for either sex, but calcium supplement use (>1000 mg/d) was associated with an increased mortality risk only for men.[40] The EPIC Heidelberg cohort reported a significantly lower MI risk comparing the third quartile (820 mg/d) of total calcium intake with the lowest quartile (reference category; 513 mg/d), but reported higher dietary calcium status to be unrelated to either stroke risk or CVD-related mortality.[14]

Other studies have reported an association between dietary calcium intake and risk of stroke.[19,21,39] Consistent with these findings, we also found an inverse association between dietary calcium intake and stroke risk. An earlier study of 85,764 women in the Nurses' Health Study reported a 31% decreased risk of ischemic stroke comparing the highest and lowest quintiles of calcium intake.[21] Another study of 3150 men also reported a decrease in the risk of stroke events with higher dietary calcium intake.[19] Similarly, the JPHC Study Cohort reported the highest quintile of total calcium intake (diet plus supplements) to be associated with a 30% decrease in stroke risk compared with the lowest quintile (HR = 0.70, 95% CI 0.56–0.88; $p_{trend} = 0.02$).[39] Conversely, there are studies that have reported no association between calcium intake and stroke risk.[14,24,27,40,41] In contrast, a meta-analysis of randomized controlled trials of calcium supplement use with and without vitamin D reported a borderline increase in stroke risk (HR = 1.20, 95% CI 1.00–1.43; $p = 0.05$).[18]

Consistent with several previously published studies, we found dietary calcium intake to be inversely associated with fracture risk after 50 years of age.[5,6,8,42] For instance, Holbrook and colleagues reported a significant inverse association between dietary calcium intake and risk of hip fracture (RR = 0.6 per 198 mg/1000 kcal).[6] Similarly, Matkovic and colleagues reported higher proximal femur fracture rates in populations with low compared with high dietary calcium intake in two geographically distinct regions of Yugoslavia.[8] In a systematic review of 16 observational studies of postmenopausal women, the pooled OR for hip fracture was 0.96 (95% CI 0.93–0.99) per 300 mg/d increase in dietary calcium intake.[42] Conversely, the Swedish Mammography Cohort reported a nonlinear association between dietary calcium intake and fracture risk.[5] When compared with a mean (SD) dietary calcium intake of 966 (314) mg/d as the reference, the HR was 1.18 (95% CI 1.12–1.25) for the lowest quintile of dietary calcium intake (641 [313] mg/d). Calcium intakes above the reference category did not afford any further benefit to fracture risk reduction. In our study, we found that dietary calcium intake had a linear inverse association with fracture risk (Table 3 and Fig. 1).

High dietary calcium intake could hypothetically decrease CVD risk by modifying several risk factors, including lipid profiles,[26,27] blood pressure,[28] and even obesity.[26,27] Elderly populations have been reported to have a generally low dietary calcium intake, and calcium balance tends to shift toward the negative end of the spectrum,[43,44] which can increase the risk of secondary hyperparathyroidism. This is important because high levels of serum parathyroid hormone (PTH) have been shown to increase the risk of vascular calcification and subsequent CVD risk.[45,46] We found no evidence that a high dietary calcium intake was associated with any adverse health outcome and may actually decrease risk of non-fatal CVD, stroke, and all-cause mortality, as well as fracture for older men and women. The estimates were similar and associated with decreased mortality rates and fracture risks when associations were tested using quartiles of raw dietary calcium intake (unadjusted for dietary energy intake; Supplemental Table S5). Because milk products and dishes are the major source of calcium in the Australian diet (providing 42% of the dietary source of calcium),[47] dairy intake (serves/wk) was further analyzed to test the associations between increasing quartiles of dairy intake and mortality rates, non-fatal CVD, and fracture risk. Increasing quartiles of dairy intake (serves/wk) were unrelated to all-cause mortality and cardiovascular disease-related deaths, although compared with the reference quartile (<18 serves/wk), higher dairy intakes (quartile 4; >48 serves/wk) were associated with a 12% decreased risk of fractures after 50 years of age; OR = 0.78 (95% CI 0.62–0.99).

In our study, a dietary calcium intake approximating the current Recommended Dietary Intake (RDI) in Australia and other countries of 1300 mg/d for postmenopausal women and elderly men over 70 years of age[48–51] was associated with a decrease in the risk of clinically important outcomes, including CVD, stroke, and fracture. Hypertension is an independent risk factor for stroke, and our study revealed that history of hypertension was a significant effect modifier of the association between dietary calcium intake and stroke risk. For participants without a history of hypertension, a higher dietary calcium intake was associated with a 51% decreased risk of stroke, suggesting that higher dietary calcium intake is more likely to be beneficial in populations without preexisting hypertension, though the effect of hypertension in modifying the association between calcium intake and CVD requires further study.

In summary, this study indicates that higher intake of calcium derived from food, in the range consistent with the RDI of 1000 tot 1300 mg/d after the age of 50 years, is associated with a

decreased risk of incident fractures and a decreased risk of non-fatal CVD events. In addition, a beneficial effect of dietary calcium intake on stroke risk is more likely to be manifested in populations without preexisting hypertension. In conclusion, this study suggests that higher dietary calcium intake within the current recommendation is safe and likely to be beneficial to health and to be associated with a decreased risk of all-cause mortality.

Disclosures

All authors state that they have no conflicts of interest.

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Authors' roles: BK collected, analyzed, interpreted the data, and drafted the manuscript. PRE wrote the research proposal, obtained funding, supervised the PhD student, drafted the manuscript, supervised statistical analysis, and edited the final manuscript. DRE conceived and designed the study and oversaw statistical analysis and interpretation of the data and writing of the manuscript. CAN was involved in the conception and study design, interpretation of the data, advised reanalysis, and reviewed the manuscript. RMD was involved in analysis and interpreting the data and drafting the final manuscript. GGG conceived and designed the study and revised the final manuscript. AMH conceived and designed the study and assisted in developing the program for calculating calcium intakes from FFQ in the MCCS, interpreting the data, and drafting the final manuscript.

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