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Dietary and Supplemental Calcium Intake and Cardiovascular Disease Mortality

The National Institutes of Health–AARP Diet and Health Study

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Importance: Calcium intake has been promoted because of its proposed benefit on bone health, particularly among the older population. However, concerns have been raised about the potential adverse effect of high calcium intake on cardiovascular health.

Objective: To investigate whether intake of dietary and supplemental calcium is associated with mortality from total cardiovascular disease (CVD), heart disease, and cerebrovascular diseases.

Design and Setting: Prospective study from 1995 through 1996 in California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania and the 2 metropolitan areas of Atlanta, Georgia, and Detroit, Michigan.

Participants: A total of 388 229 men and women aged 50 to 71 years from the National Institutes of Health–AARP Diet and Health Study.

Main Outcome Measures: Dietary and supplemental calcium intake was assessed at baseline (1995-1996). Supplemental calcium intake included calcium from multivitamins and individual calcium supplements. Cardiovascular disease deaths were ascertained using the National Death Index. Multivariate Cox proportional hazards regression models adjusted for demographic, lifestyle, and dietary variables were used to estimate relative risks (RRs) and 95% CIs.

Results: During a mean of 12 years of follow-up, 7904 and 3874 CVD deaths in men and women, respectively, were identified. Supplements containing calcium were used by 51% of men and 70% of women. In men, supplemental calcium intake was associated with an elevated risk of CVD death ($RR_{>1000\ vs\ 0\ mg/d}$, 1.20; 95% CI, 1.05-1.36), more specifically with heart disease death (RR, 1.19; 95% CI, 1.03-1.37) but not significantly with cerebrovascular disease death (RR, 1.14; 95% CI, 0.81-1.61). In women, supplemental calcium intake was not associated with CVD death (RR, 1.06; 95% CI, 0.96-1.18), heart disease death (1.05; 0.93-1.18), or cerebrovascular disease death (1.08; 0.87-1.33). Dietary calcium intake was unrelated to CVD death in either men or women.

Conclusions and Relevance: Our findings suggest that high intake of supplemental calcium is associated with an excess risk of CVD death in men but not in women. Additional studies are needed to investigate the effect of supplemental calcium use beyond bone health.

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In Western countries, great emphasis has been put on calcium intake because of its proposed benefit for bone health. Calcium supplementation has become widely used, especially among the elderly population. A recent study[1] reported that more than 50% of older men and almost 70% of older women in the United States use supplemental calcium. However, beyond calcium's established role in prevention and treatment of osteoporosis, its health effect on nonskeletal outcomes, including cardiovascular health, remains largely unknown and has become increasingly contentious.[2,3]

Despite some earlier observational and interventional studies[4-6] that suggested a protective role of calcium against cardiovascular diseases (CVDs) by linking

See Invited Commentary at end of article

supplemental calcium intake with improved blood pressure or serum lipid profiles, recent analyses of several randomized controlled trials (RCTs) found an increased risk of various cardiovascular events, including myocardial infarction, stroke, and cardiovascular deaths, in the intervention arm with calcium supple-

mentation.[7-9] Likewise, the effects of dietary calcium intake on various cardiovascular outcomes also remain controversial, with most of the observational studies revealing inverse[10,11] or null associations.[12-14] The heterogeneity of the aforementioned studies and inconsistency in their results warrant further investigation into the relation between calcium intake and cardiovascular health. Therefore, in a large cohort of US men and women, we investigated whether intake of dietary and supplemental calcium is associated with mortality from total CVD, heart disease, and cerebrovascular diseases.

METHODS

STUDY POPULATION

The National Institutes of Health (NIH)–AARP Diet and Health Study recruited AARP members who were aged 50 to 71 years and resided in 1 of 6 states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) in 1995-1996. Details of the NIH-AARP study have been previously reported.[15] Of 566 399 participants who satisfactorily completed a baseline questionnaire, we excluded individuals whose questionnaire was completed by proxies (n=15 760) and those who had cancer, except nonmelanoma skin cancer (n=51 227), self-reported heart disease (n=69 025), stroke (n=6477), diabetes (n=30 990), or end-stage renal disease at baseline (n=447). In addition, we excluded individuals who reported extreme intakes (>2 times the interquartile ranges of sex-specific log-transformed intake) of total energy and dietary calcium (n=4244). The analytic cohort consisted of 219 059 men and 169 170 women. The study was approved by the National Cancer Institute Special Studies institutional review board.

MORTALITY ASCERTAINMENT

The vital status of study participants was ascertained by annual linkage to the Social Security Administration Death Master File. Cause of death information is provided by follow-up searches of the National Death Index Plus. A previous study[16] found that our ascertainment method yielded 95% accurate results. Total CVD mortality (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 390, 398, 401, 404, 410, 438, and 440-448 and *International Classification of Disease, 10th Revision* [*ICD-10*] codes I00, I09, I10, I13, I20, I51, and I60-I78) included deaths from heart diseases, cerebrovascular diseases, and other CVDs.

CALCIUM INTAKE AND RISK FACTOR ASSESSMENT

At baseline, dietary intakes were assessed with a self-administered, 124-item food frequency questionnaire, an earlier version of the Diet History Questionnaire developed at the National Cancer Institute.[17] Participants reported their usual frequency of intake and portion size during the past year. The food items, portion sizes, and nutrient database were constructed using the US Department of Agriculture's 1994-1996 Continuing Survey of Food Intakes by Individuals.[18] The questionnaire also asked participants about the frequencies (never to <1 time per week, 1-3 times per week, 4-6 times per week, or every day) and dosage of individual calcium supplements, including calcium-containing antacids (eg, Tums; GlaxoSmithKline). In addition, participants reported the frequencies and types of multivitamin intake (stress-tab type, therapeutic or Theragran type, and one-a-day type). Calcium intake was estimated from foods only (dietary calcium); from supplements only (supplemental calcium), including individual calcium supplement and calcium-containing multivitamins (therapeutic or Theragran type and one-a-day type); and from both sources (total calcium). Dietary calcium intake was adjusted for total energy intake using the residual method.[19] The food frequency questionnaire used in our study was calibrated against 2 nonconsecutive, 24-hour dietary recalls in a subgroup of participants,[20] with an energy-adjusted correlation coefficient of dietary calcium intake of 0.63 in men and 0.64 in women.

The baseline questionnaire also asked about demographic characteristics, anthropometric measurements, medical history, and other lifestyle factors. A subsequent questionnaire mailed within 6 months of baseline collected further information on diagnosis of hypertension and hypercholesterolemia and the use of medications, such as nonsteroidal anti-inflammatory drugs.

STATISTICAL ANALYSIS

Relative risks (RRs) and 2-sided 95% CIs were estimated with the Cox proportional hazards regression model using SAS statistical software (SAS Institute, Inc). Person-years of follow-up time were calculated from the baseline until the date of death or the end of follow-up (December 31, 2008), whichever came sooner. We evaluated and confirmed the proportional hazards regression model assumption for the main exposures by including interaction terms with time and using the Wald χ^2 procedure to test whether coefficients equaled zero.

A significant interaction by sex was found ($P=.001$); therefore, we conducted analysis and report results separately for men and women. Intakes of dietary and total calcium were categorized into sex-specific quintiles. Test for linear trend were performed using the median value in each quintile or category.

Multivariate models were adjusted for potential confounders, including age, race/ethnicity (non-Hispanic white, non-Hispanic black, or other), educational level (less than high school, high school graduate, some college, or college graduate/postgraduate), marital status (married or not married), self-reported health status (excellent, very good, good, fair, or poor), body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) (<18.5, 18.5-<25, 25-<30, 30-<35, or ≥35), physical activity (never/rarely, ≤3 times per month, or 1, 2, 3, 4, or ≥5 times per week), smoking status (0, 1-10, 11-20, 21-30, 31-40, 41-50, 51-60, or >60 cigarettes per day), smoking dose (0, 1-10, 11-20, 21-30, 31-40, 41-50, 51-60, or >60 cigarettes per day), years since quitting smoking (never quit, ≥10, 5-9, 1-4, or <1 year), and intakes of alcohol, fruit and vegetable, red meat, whole grain, fat, and total energy (continuous). Menopausal hormone therapy use (never, past, or current) was adjusted in women. Supplemental and dietary calcium intakes were mutually adjusted. For each covariate, missing values (generally <5%) were put in the reference group. Assigning missing values into separate groups did not change the results materially. We also examined the potentially nonlinear relationship between total calcium intake and risk of total CVD mortality using nonparametric regression analyses.[21,22] A likelihood ratio test was used to compare the model with both the linear and the cubic spline terms with the model with the linear term only.

RESULTS

During 3 549 364 person-years of follow-up, we identified 7904 CVD deaths in men and 3874 CVD deaths in

Table 1. Selected Characteristics of Study Participants by Categories of Dietary and Supplemental Calcium Intakes[a]

	Dietary Calcium				Supplemental Calcium			
	Men		Women		Men		Women	
Variable	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Nonuser	User	Nonuser	User
Age at baseline, mean, y	61.3	62.0	61.2	62.1	61.6	61.8	61.6	61.6
Dietary calcium dose, mean, mg/d	463	1336	397	1170	782	815	681	719
Supplemental calcium dose, mean, mg/d	127	163	336	423	0	289	0	554
Non-Hispanic white	90.8	95.3	87.2	94.2	93.8	93.9	89.9	92.2
College and postcollege education	40.3	49.1	25.6	35.0	44.7	48.2	26.8	33.0
Married	83.9	84.4	47.0	42.7	86.8	84.6	45.8	46.2
Self-reported health excellent	19.2	24.2	16.8	21.7	21.7	22.2	18.5	19.8
BMI, mean	27.0	27.0	26.6	26.2	27.2	26.9	27.1	26.1
Current smoker	15.9	9.4	21.2	11.4	11.7	10.0	17.8	12.9
Former smoker	54.2	51.7	35.1	37.5	52.9	55.0	34.6	38.9
Physical activity ≥5 times per week	17.5	24.2	13.1	20.0	19.7	22.5	13.9	17.7
History of hypertension	36.9	33.5	35.1	30.1	35.0	34.7	34.9	31.5
History of high cholesterol	46.4	46.9	50.1	49.6	46.9	45.7	49.8	49.3
Multivitamin use[b]	47.3	56.4	54.7	65.9	14.3	90.3	14.0	81.2
Current MHT use	NA	NA	42.5	47.1	NA	NA	36.8	49.3
Alcohol consumption, mean, g/d	36.5	9.0	11.2	3.7	40.8	17.5	6.1	6.2
Fruits and vegetable consumption, mean, servings per 1000 kcal	3.1	3.6	3.9	4.5	3.4	3.7	4.2	4.5
Red meat consumption, mean, g/1000 kcal	45	30	36	21	40	37	32	28
Whole grain consumption, mean, servings per 1000 kcal	0.47	0.74	0.52	0.74	0.62	0.68	0.63	0.70
Total fat, mean, % of energy	31	29	33	26	31	30	31	29
Total energy, mean, kcal/d	2071	2058	1569	1562	2037	2041	1572	1563
Magnesium intake, mean, mg/d	191	256	198	286	175	265	188	270

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MHT, menopausal hormonal therapy; NA, not applicable.

[a] Data are presented as percentage of patients unless otherwise specified. All within-sex group comparisons were significant ($P < .05$) using the Kruskal-Wallis (for continuous variables) and χ^2 (for categorical variables) tests.

[b] Multivitamins included the stress-tab type, therapeutic or Theragran type, and one-a-day type. Only the last 2 types contained calcium.

women. Overall, 23% of men and 56% of women took individual calcium supplements, and 56% of men and 58% of women took multivitamins containing calcium. Compared with participants in the lowest quintile of dietary calcium intake or nonusers of calcium supplement, those in the highest quintile or supplement users were more likely to be non-Hispanic white, to have a college education, to have self-rated their health as being excellent, to be physically active, to use multivitamins, and to have higher intakes of fruits and vegetables and whole grains, but they were less likely to smoke or have a history of hypertension and had lower consumption of alcohol, red meat, and total fat. Compared with women who were nonusers, women who used calcium supplement had a lower BMI and were more likely to use menopausal hormone therapy (**Table 1**).

In both men and women, dietary calcium intakes were inversely associated with both total CVD and heart disease mortality in age-adjusted models (**Table 2**). However, after adjusting for potential CVD risk factors, the associations were substantially attenuated and became null in women. Among factors controlled in the multivariate model, variables related to smoking were the strongest confounders. Restricting analyses to supplemental calcium nonusers did not change the associations between dietary calcium intake and CVD mortality (data not shown).

Supplemental calcium intake was related to a significantly elevated risk of total CVD and heart disease mortality among men (**Figure 1**). Compared with nonusers, men with an intake of supplemental calcium of more than 1000 mg/d had a significantly higher risk of total CVD death (multivariate $RR_{>1000 \text{ vs } 0 \text{ mg/d}}$, 1.20; 95% CI, 1.05-1.36) and heart disease death (multivariate $RR_{>1000 \text{ vs } 0 \text{ mg/d}}$, 1.19; 95% CI, 1.03-1.37). Supplemental calcium intake was also related to an increased risk of cerebrovascular disease death in men (P for trend = .04), but the RR for more than 1000 mg/d was not statistically significant, with a wide 95% CI, probably because of the small number of

Table 2. Relative Risks (95% CIs) for CVD Deaths for Quintiles of Dietary Calcium Intake in Men and Women

Variable	Dietary Calcium Intake					*P* Value for Trend
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	
Men						
Median intake, mg/d	478	616	739	898	1247	
No. of person-years	527 379	516 858	502 994	489 449	467 990	
All CVD deaths						
No. of cases	1879	1550	1519	1400	1556	
Age adjusted	Reference	0.81 (0.76-0.86)	0.79 (0.74-0.85)	0.75 (0.70-0.80)	0.86 (0.80-0.92)	.004
Multivariate[a]	Reference	0.91 (0.85-0.98)	0.96 (0.89-1.03)	0.92 (0.85-0.99)	1.04 (0.97-1.12)	.08
Heart disease deaths						
No. of cases	1496	1204	1223	1110	1249	
Age adjusted	Reference	0.79 (0.73-0.85)	0.81 (0.75-0.87)	0.75 (0.69-0.81)	0.87 (0.81-0.94)	.01
Multivariate[a]	Reference	0.89 (0.82-0.96)	0.97 (0.90-1.05)	0.92 (0.85-1.00)	1.06 (0.97-1.14)	.04
Cerebrovascular disease deaths						
No. of cases	268	229	214	205	230	
Age adjusted	Reference	0.83 (0.69-0.99)	0.77 (0.64-0.92)	0.75 (0.63-0.90)	0.87 (0.73-1.03)	.21
Multivariate[a]	Reference	0.92 (0.77-1.10)	0.90 (0.74-1.08)	0.89 (0.73-1.07)	1.02 (0.85-1.23)	.63
Women						
Median intake, mg/d	408	532	648	798	1101	
No. of person-years	397 388	397 012	394 567	392 622	386 100	
All CVD deaths						
No. of cases	918	785	700	708	763	
Age adjusted	Reference	0.83 (0.75-0.91)	0.73 (0.66-0.80)	0.72 (0.66-0.80)	0.76 (0.69-0.84)	<.001
Multivariate[b]	Reference	0.99 (0.90-1.09)	0.94 (0.85-1.04)	0.99 (0.89-1.10)	1.04 (0.94-1.15)	.37
Heart disease deaths						
No. of cases	692	557	497	495	536	
Age adjusted	Reference	0.78 (0.70-0.87)	0.69 (0.61-0.77)	0.67 (0.60-0.76)	0.71 (0.64-0.80)	<.001
Multivariate [b]	Reference	0.94 (0.84-1.05)	0.90 (0.80-1.01)	0.94 (0.83-1.06)	0.99 (0.87-1.12)	.93
Cerebrovascular disease deaths						
No. of cases	170	189	149	174	178	
Age adjusted	Reference	1.07 (0.87-1.32)	0.84 (0.67-1.04)	0.96 (0.78-1.19)	0.96 (0.78-1.18)	.54
Multivariate[b]	Reference	1.23 (1.00-1.52)	1.01 (0.81-1.27)	1.21 (0.97-1.51)	1.20 (0.95-1.51)	.22

Abbreviation: CVD, cardiovascular disease.

[a] Adjusted for age at baseline (continuous); race/ethnicity (non-Hispanic white, non-Hispanic black, or other); educational level (less than high school, high school graduate, some college, or college graduate/postgraduate); marital status (married or not married); health status (excellent, very good, good, fair, or poor); body mass index (<18.5, 18.5-<25, 25-<30, 30-<35, or ≥35), smoking status (never, former, or current); smoking dose (0, 1-10, 11-20, 21-30, 31-40, 41-50, 51-60, or >60 cigarettes per day); time since quitting (never quit, ≥10, 5-9, 1-4, or <1 year); vigorous physical activity (never/rarely; <3 times per month; or 1, 2, 3, 4, or ≥5 times per week); alcohol (0-<5; 5-<15; 15-<30; or ≥30 g/d); supplemental calcium intake (0, >0-<400, 400-<1000, or ≥1000 mg/d); fruit and vegetable intake (continuous); red meat intake (continuous); whole grain intake (continuous); total fat intake (continuous); and total caloric intake (continuous).

[b] Adjusted for variables listed above and use of menopausal hormone therapy (never, past, or current).

deaths (n = 36). No association between supplemental calcium intake and CVD mortality was observed among women. To minimize the effect of other nutrients in multivitamins, we assessed the effect of individual calcium supplement use in those who did not take calcium-containing multivitamins. The highest category of supplemental calcium intake was associated with an increased risk of total CVD death (multivariate $RR_{>1000 \text{ vs } 0 \text{ mg/d}}$, 1.24; 95% CI, 0.97-1.57), mainly driven by heart disease death (multivariate $RR_{>1000 \text{ vs } 0 \text{ mg/d}}$, 1.37; 95% CI, 1.06-1.77) (eTable 1; http://www.jamainternalmed.com). Consistently, null associations were observed in women. Excluding deaths that occurred during the first 2 years of follow-up also did not change the results (data not shown).

We further investigated the relationship between supplemental calcium and total CVD mortality by age, smoking status, BMI, hypertension, hypercholesterolemia (**Table 3**), total magnesium intake, and alcohol consumption (eTable 2). The number of deaths and person-years for each subgroup are given in eTable 3. In men, the positive association persisted in most of the subgroups. Smoking status appeared to have a statistically significant interaction with supplemental calcium intake in men, with stronger associations observed in current smokers. In women, the association was null for most subgroups, with the noticeable exceptions of former smokers, women with no history of hypertension, and women who had hypercholesterolemia, among whom supplemental calcium was associated with increased total CVD deaths.

Total calcium intake had a U-shaped association with total CVD mortality in men (*P* for nonlinearity = .006; **Figure 2**A), with increased total CVD mortality observed at calcium intakes of 1500 mg/d and higher. When we examined the association by quintiles of total calcium intake, compared with the lowest, the highest quintile was significantly associated with elevated total CVD mortality (multivariate $RR_{\text{Quintile 5 vs 1}}$, 1.12; 95% CI, 1.04-1.20) and heart disease mortality (multivariate $RR_{\text{Quintile 5 vs 1}}$, 1.12; 95% CI, 1.04-1.21) (eTable 4). A similar positive association was observed between total calcium intake

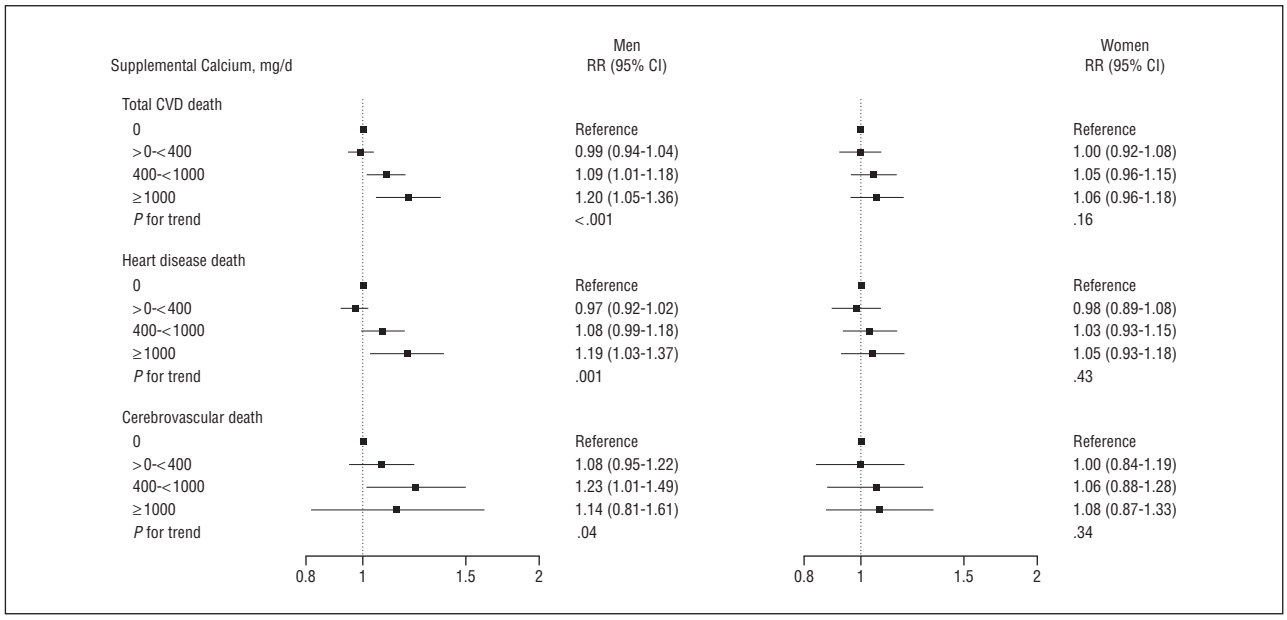

Figure 1. Adjusted multivariate relative risks (RRs) and 95% CIs (error bars) for total cardiovascular disease (CVD), heart disease, and cerebrovascular disease mortality for categories of supplemental calcium intake. To convert milligrams per deciliter of calcium to millimoles per liter, multiply by 0.25.

and cerebrovascular mortality but was not statistically significant. In women, total calcium intake was not associated with deaths from total CVD, heart disease, or cerebrovascular diseases (Figure 2B and eTable 4).

COMMENT

In this large, prospective study we found that supplemental but not dietary calcium intake was associated with an increased CVD mortality in men but not in women. The lack of association between dietary calcium and CVD mortality is generally consistent with previous observational studies. A recent meta-analysis[23] found no effect of dietary calcium on either coronary artery disease or stroke when comparing the highest intake category to the lowest. However, the analysis did not examine the dose-response relation of dietary calcium intake to coronary artery disease or stroke. Only a few studies specifically focused on cardiovascular mortality. Dietary calcium was not associated with CVD death in Dutch civil servants,[12] the US Health Professionals Follow-up Study,[13] the Japan Collaborative Cohort Study,[14] and the European Prospective Investigation into Cancer and Nutrition study.[24] However, a study of postmenopausal women in Iowa found a 37% decrease in ischemic heart disease mortality with high dietary calcium intake among those who did not take supplements,[10] a finding that we did not observe even after similar restriction was applied. A study[25] of Swedish men also reported with borderline significance that CVD mortality was 23% (RR, 0.77; 95% CI, 0.58-1.01) lower in the highest tertile of dietary calcium intake (≥1599 mg/d) vs the lowest tertile (<1230 mg/d). The dietary calcium intake in the Swedish cohort was substantially higher than that in the male participants of our study or other studies. It remains to be determined whether very high intake of dietary calcium may offer a protective effect.

Several studies examined the role of supplemental calcium on cardiovascular mortality. The Iowa Women's Health Study found reduced CVD mortality among users of calcium supplements.[10-26] The Health Professionals Follow-up Study also reported a trend toward decreased fatal ischemic heart disease risk in men with high intakes of supplemental calcium, although the sample sizes were small.[13] The recent Heidelberg cohort study observed an increased risk of myocardial infarction among calcium supplement users but lacked statistical power to examine CVD mortality.[24] To our knowledge, no RCT has tested the effect of calcium supplementation with CVD as a prespecified primary end point. Some RCTs considered CVD events as secondary outcomes, and most of the earlier studies found no effect of calcium supplementation on CVD.[27,28] However, recent secondary analyses of several RCTs have yielded provoking results. Most notably, a reanalysis of the Women's Health Initiative study observed a modestly increased risk of a variety of cardiovascular end points, especially myocardial infarction, in the intervention arm.[9] The same authors also conducted a meta-analysis of RCTs and found that elevated risk was associated with calcium supplementation.[9] However, the results of the Women's Health Initiative study were heavily weighted in the meta-analysis.

We found a significant interaction by sex. Elevated CVD mortality with increasing supplemental calcium intake was observed only in men; however, we cannot rule out the possibility that supplemental calcium intake may be associated with cardiovascular mortality in women. The sex difference is intriguing. In the reanalysis of the Women's Health Initiative study, an adverse effect of calcium supplement intervention was only observed when the analysis was restricted to women who did not take personal supplement at randomization, and personal supplement use by itself was not associated with adverse outcomes regardless of intervention.[9] The authors

Table 3. Multivariate Relative Risks (95% CIs) for Total Cardiovascular Disease Deaths by Supplemental Calcium Intake, Stratified by Age, Smoking Status, Body Mass Index, and Hypertension

Variable	Supplemental Calcium Intake, mg/d				*P* Value for Trend
	0	>0-<400	>400-<1000	≥1000	
Men					
Age, y[a]					
<60	Reference	0.97 (0.87-1.09)	1.15 (0.96-1.38)	1.47 (1.09-2.00)	.01
≥60	Reference	0.99 (0.94-1.05)	1.08 (1.00-1.18)	1.15 (1.00-1.32)	.01
P value for interaction	.16				
Smoking status[b]					
Never	Reference	0.91 (0.82-1.00)	1.05 (0.90-1.23)	1.04 (0.79-1.36)	.62
Former	Reference	0.98 (0.92-1.05)	1.08 (0.97-1.20)	1.17 (0.98-1.38)	.04
Current	Reference	1.10 (0.99-1.21)	1.12 (0.93-1.34)	1.33 (0.94-1.89)	.04
P value for interaction	.01				
Body mass index[a]					
<25	Reference	0.93 (0.85-1.02)	1.08 (0.94-1.24)	1.03 (0.82-1.31)	.45
≥25 and <30	Reference	0.97 (0.90-1.04)	1.12 (1.00-1.25)	1.36 (1.14-1.63)	<.001
≥30	Reference	1.10 (1.00-1.21)	1.03 (0.87-1.22)	1.12 (0.83-1.50)	.36
P value for interaction	.19				
Hypertension[a]					
Yes	Reference	1.03 (0.94-1.13)	1.08 (0.93-1.25)	1.44 (1.16-1.80)	.002
No	Reference	1.02 (0.93-1.12)	1.15 (0.98-1.34)	1.18 (0.91-1.52)	.06
P value for interaction	.80				
Hypercholesterolemia[a]					
Yes	Reference	1.04 (0.95-1.15)	1.22 (1.05-1.41)	1.19 (0.93-1.51)	.01
No	Reference	0.99 (0.89-1.10)	1.05 (0.89-1.24)	1.39 (1.08-1.78)	.02
P value for interaction	.94				
Women					
Age[a]					
<60	Reference	0.99 (0.82-1.21)	1.04 (0.83-1.31)	0.92 (0.70-1.22)	.68
≥60	Reference	1.00 (0.92-1.09)	1.05 (0.96-1.16)	1.09 (0.97-1.21)	.09
P value for interaction	.04				
Smoking status[b]					
Never	Reference	0.94 (0.82-1.09)	0.99 (0.85-1.16)	1.06 (0.89-1.27)	.37
Former	Reference	1.10 (0.96-1.27)	1.19 (1.02-1.38)	1.18 (1.00-1.40)	.05
Current	Reference	0.98 (0.82-1.17)	1.13 (0.95-1.35)	1.18 (0.98-1.42)	.91
P value for interaction	.06				
Body mass index[a]					
<25	Reference	1.05 (0.92-1.20)	1.15 (1.00-1.32)	1.13 (0.97-1.32)	.08
≥25 and <30	Reference	0.92 (0.81-1.06)	0.93 (0.80-1.08)	0.94 (0.78-1.13)	.55
≥30	Reference	1.03 (0.88-1.20)	1.09 (0.91-1.30)	1.18 (0.95-1.45)	.11
P value for interaction	.89				
Hypertension[a]					
Yes	Reference	0.95 (0.83-1.09)	1.05 (0.90-1.23)	1.07 (0.90-1.27)	.25
No	Reference	1.13 (0.96-1.33)	1.05 (0.87-1.26)	1.36 (1.12-1.65)	.007
P value for interaction	.17				
Hypercholesterolemia[a]					
Yes	Reference	1.03 (0.88-1.20)	1.05 (0.88-1.24)	1.21 (1.00-1.45)	.05
No	Reference	1.05 (0.89-1.23)	1.06 (0.89-1.26)	1.19 (0.99-1.44)	.08
P value for interaction	.69				

[a] Adjusted for age at baseline (continuous); race/ethnicity (non-Hispanic white, non-Hispanic black, or other); educational level (less than high school, high school graduate, some college, or college graduate/postgraduate); marital status (married or not married); health status (excellent, very good, good, fair, or poor); body mass index (calculated as weight in kilograms divided by height in meters squared) (<18.5, 18.5- <25, 25-<30, 30-<35, or ≥35); smoking status (never, former, or current); smoking dose (0, 1-10, 11-20, 21-30, 31-40, 41-50, 51-60, or >60 cigarettes per day); time since quitting (never quit, ≥10, 5-9, 1-4, or <1 year); vigorous physical activity (never/rarely, ≤3 times per month, or 1, 2, 3, 4, or ≥5 times per week); alcohol (0-<5, 5-<15, 15-<30, or ≥30 g/d); dietary calcium intake (quintiles); fruit and vegetable intake (continuous); red meat intake (continuous); whole grain intake (continuous); total fat intake (continuous); and total caloric intake (continuous). The use of menopausal hormone therapy (never, past, or current) was adjusted in women.

[b] Adjusted for variables listed in above and smoking status.

brought up an interesting hypothesis that the abrupt change in calcium intake and subsequent change in serum calcium, instead of overall calcium load, may be responsible for the adverse effects. Dietary supplement use is more prevalent and regular in women than in men, and the difference is apparent in populations as young as 20 years.[29] Although no information on duration of supplement use was collected at baseline in our study, it may be reasonable to assume that, on average, male users started taking calcium supplements at an older age. Therefore, women were more likely to have achieved calcium balance and stable calcium levels long before the study, and the effect of calcium supplement became less profound.

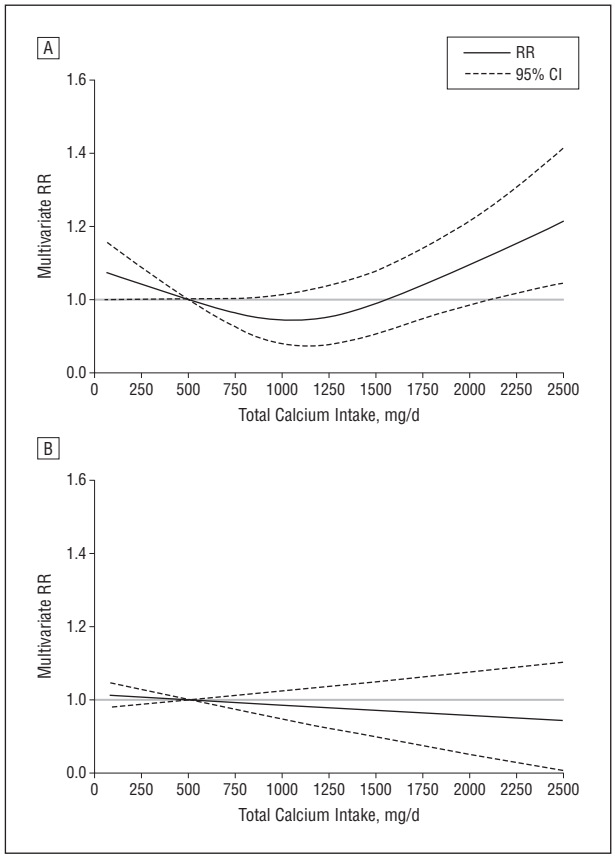

Figure 2. Nonparametric regression curve showing adjusted multivariate relative risks (RRs) and 95% CIs for the association between total calcium intake and total cardiovascular disease mortality. A, Curve for men; B, curve for women. To convert milligrams per deciliter of calcium to millimoles per liter, multiply by 0.25.

In the subgroup analyses, smoking status was a significant effect modifier, with the adverse effect of supplement calcium only observed among smokers. Smoking can cause a wide range of detrimental effects on the cardiovascular system and act synergistically with other risk factors to substantially increase the risk of CVDs.[30] Further study is needed to evaluate the interplay between calcium and smoking. Another potential effect modifier is vitamin D. Several lines of evidence have pointed to a beneficial effect of vitamin D on cardiovascular health,[31] suggesting that coadministration of calcium with vitamin D may weaken the adverse effect of calcium. Unfortunately, information on intake of individual vitamin D supplements was not collected in our study, and vitamin D in multivitamins is highly correlated with supplemental calcium intake; therefore, we were not able to assess the role of vitamin D supplement.

One plausible biological mechanism through which calcium may exert a harmful effect on cardiovascular health is vascular calcification—the deposit of calcium phosphate in cardiovascular structures. Emerging evidence has linked calcification of coronary arteries with increased atherosclerotic plaque burden,[32] risk of coronary heart disease,[33,34] and mortality.[35] Vascular calcification is an actively regulated process that not only shares key proteins and pathways but is also intricately intertwined with bone mineralization.[36] It remains unclear whether vascular calcification–like osteogenesis is also influenced by calcium supplement intake. Among patients with end-stage renal disease, daily ingestion of calcium as a phosphate-binding agent is positively correlated with coronary artery calcification.[37] A report of the Women's Health Initiative study did not find any difference in coronary artery calcification scores between the intervention and placebo groups,[38] although personal intake of supplements and poor adherence might mask the real association. In addition, increased blood coagulation and arterial stiffness have also been positively linked to serum calcium and proposed as potential mechanisms by which calcium may affect cardiovascular health.[39] However, calcium is widely involved in many aspects of human physiology, and some of its effects may be beneficial for cardiovascular health, including lower blood pressure[40,41] and improved blood lipid profile.[6] To understand the overall effects of calcium, more mechanistic studies are warranted.

Our study has some limitations. First, we did not have information on the duration of supplement use, which might be an important factor mediating the effect of calcium supplement on CVD mortality. Second, although we controlled for multiple CVD risk factors, we could not rule out the possibility that other correlated nutrients also contributed to the observed association or that the use of calcium supplements is a marker of behavior that is related to the CVD. We also lacked information on family history of CVDs that may also confound our results. Third, with self-reported intake information, we were subject to measurement error. In addition, calcium intake was only measured at baseline; therefore, we were not able to assess change in dietary or supplement intake during follow-up.

Our study has several strengths. Its large size and long follow-up allowed adequate statistical power to test the overall effect of calcium on CVD mortality and also assess the associations by age, BMI, smoking status, cardiovascular risk profile, and multivitamin intake. We were also able to examine heart disease mortality and cerebrovascular mortality separately. Moreover, we excluded people with chronic diseases at baseline whose dietary and supplement use pattern might be affected by their prevalent health conditions. We also conducted sensitivity analysis by excluding people who died within the first 2 years of follow-up, further reducing the likelihood of reverse causality.

In conclusion, our findings suggest that supplemental calcium intake is associated with elevated CVD mortality in men but not in women. Whether there is a sex difference in the cardiovascular effect of calcium supplement warrants further investigation. Given the extensive use of calcium supplement in the population, it is of great importance to assess the effect of supplemental calcium use beyond bone health.

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