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Dietary and supplemental calcium intakes in relation to mortality from cardiovascular diseases in the NIH-AARP Diet and Health Study

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Abstract

Background—Calcium intake has been promoted due to 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.

Methods—Dietary and supplemental calcium intakes were assessed at baseline (1995–96) in 388,229 men and women aged 50–71 years in the National Institutes of Health (NIH)–AARP Diet and Health Study. Supplemental calcium intake included calcium from multivitamins and individual calcium supplements. Cardiovascular disease (CVD) deaths were ascertained using the National Death Index. Multivariate Cox Proportional hazard models adjusted for demographic, lifestyle and dietary variables were used to estimate relative risks (RRs) and 95% confidence intervals (CIs).

Results—During an average 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 ($RR_{>1000 \text{ vs. } 0 \text{ mg/day}}$ =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 (RR=1.05, 95% CI: 0.93–1.18) or cerebrovascular disease death (RR=1.08, 95% CI: 0.87–1.33). Dietary calcium intake was not related to CVD death in either men or women.

Conclusion—Our finding suggests 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.

Introduction

In western countries, great emphasis has been put on calcium intake due to its proposed benefit on bone health. Calcium supplementation has become widely used, especially among the elderly. A recent study reported over 50% of older men and almost 70% of older women in the US use supplemental calcium [1]. However, beyond calcium's established role in

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prevention and treatment of osteoporosis, its health impact on nonskeletal outcomes, including cardiovascular health, remains largely unknown and has become increasingly contentious[2–3].

Despite some earlier observational and interventional studies that suggested a protective role of calcium against cardiovascular diseases (CVD) by linking supplemental calcium intake with improved blood pressure or serum lipid profiles [4–6], recent analyses of several randomized controlled trials (RCTs) showed an increased risk of various cardiovascular events, including myocardial infarction, stroke and cardiovascular deaths, in the intervention arm with calcium supplementation [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 intakes of both dietary and supplemental calcium were associated with mortality from total cardiovascular disease, heart disease and cerebrovascular diseases.

Methods

Study population

The NIH-AARP Diet and Health Study recruited AARP members who were 50 to 71 years old and resided in one of six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) in 1995–1996. Details of the NIH-AARP study were reported previously [15]. Of 566,399 participants who satisfactorily completed 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=6,477), diabetes (n=30,990), or end-stage renal disease at baseline (n=447). Additionally, 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=4,244). 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 (NDI) Plus. A previous study found that our ascertainment method yielded 95% accurate results [16]. Total CVD mortality (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 390–398, 401–404, 410–438, and 440–448 and *ICD, 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 (FFQ), 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, <1 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). 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 both 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 FFQ used in our study was calibrated against two non-consecutive 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 the baseline collected further information on diagnosis of hypertension and hypercholesterolemia as well as the use of medications such as non-steroidal anti-inflammatory drugs.

Statistical analysis

Relative risks (RR) and 2-sided 95% confidence intervals (CI) were estimated with the Cox proportional hazards model, using SAS (SAS Institute, Cary, North Carolina). 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 assumption for the main exposures by including interaction terms with time and using the Wald χ^2 procedure to test if coefficients equaled zero.

There was a significant interaction by sex (p=0.001), 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, education, marital status, self-reported health status, body mass index (BMI), physical activity, smoking status, smoking dose, years since quitting smoking, and intakes of alcohol, fruit and vegetable, red meat, whole grain, fat and total energy. Menopausal hormone therapy use 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 non-linear relationship between total calcium intake and risk of total CVD mortality using non-parametric 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 7,904 CVD deaths in men and 3,874 CVD deaths in 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 to women who were non-users, women who used calcium supplement had 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 >1000mg/d intake of supplemental calcium had significantly higher risk of total CVD death (multivariate $RR_{>1000 \text{ vs. } 0 \text{ mg/day}}$ =1.20, [95% CI, 1.05, 1.36]) and heart disease death (multivariate $RR_{>1000 \text{ vs. } 0 \text{ mg/day}}$ =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=0.04), but RR for >1000mg/day was not statistically significant with wide 95% CI, probably due to small number of deaths (n=36). No association between supplemental calcium intake and CVD mortality was observed among women. To minimize the impact 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 $RR_{>1000 \text{ vs. } 0 \text{ mg/day}}$ =1.24 [95% CI, 0.97, 1.57]), mainly driven by heart disease death (multivariate $RR_{>1000 \text{ vs. } 0 \text{ mg/day}}$ =1.37 [95% CI, 1.06, 1.77]) (supplementary table 1). 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 (supplementary table 2). The number of deaths and person-years for each subgroup are shown in supplementary table 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, 0.006, figure 2A), 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 to the lowest, the highest quintile was significantly associated with elevated total CVD mortality (multivariate $RR_{Q5 \text{ vs } Q1}$ =1.12 [95% CI, 1.04–1.20]) and heart disease mortality (multivariate $RR_{Q5 \text{ vs } Q1}$=1.12 [95% CI, 1.04–1.21]) (supplementary table 4). A similar positive association was observed between total calcium intake 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, supplementary table 4).

Discussion

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 found no effect of dietary calcium on either coronary artery disease or stroke, when comparing the highest intake category to the lowest [23]. 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], 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 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) [25]. 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 towards decreased fatal ischemic heart disease risk in men with high intakes of supplemental calcium, although the sample sizes were quite 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 endpoint. Some RCTs did consider cardiovascular disease 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 (WHI) Study observed modestly increased risk of a variety of cardiovascular endpoints, especially myocardial infarction, in the intervention arm [9]. The same authors also conducted a meta-analysis of RCTs and showed elevated risk associated with calcium supplementation[9]. However, the results of the WHI 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 WHI study, 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 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 old [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.

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 for cardiovascular diseases [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 co-administration of calcium with vitamin D may weaken the adverse impact 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 harmful impact 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 phosphate-binding agent is positively correlated with coronary artery calcification [37]. A report of the WHI 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 compliance might mask the real association. In addition, increased blood coagulation and arterial stiffness have also been positively linked with serum calcium and proposed as potential mechanisms by which calcium may affect cardiovascular health[39]. However, it is worth mentioning that 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 of information on family history of cardiovascular diseases that may also confound our results. Third, with self-reported intake information, we were subject to measurement error. Also, calcium intake was only measured at baseline and, 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 with, 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 two 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 impact of supplemental calcium use beyond bone health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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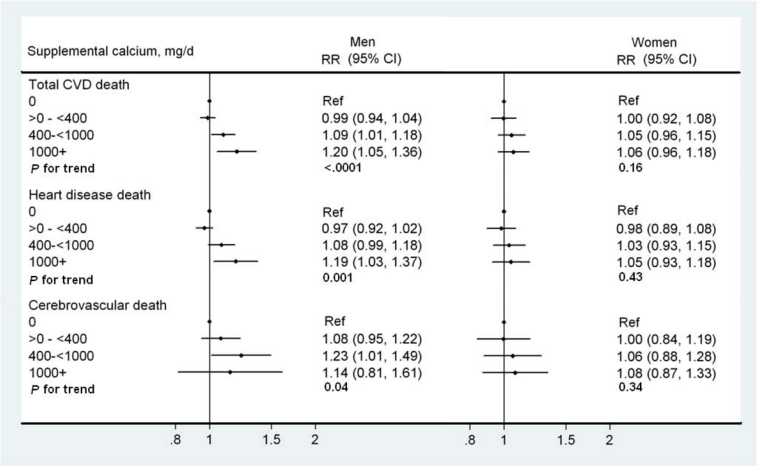

Figure 1.

Multivariate relative risks (RRs) and 95% confidence intervals (CIs) for total cardiovascular disease (CVD), heart disease and cerebrovascular disease mortality for categories of supplemental calcium intake. The multivariate RRs were adjusted for age at baseline (continuous); race/ethnicity (non-Hispanic white; non-Hispanic, black; and others); education (less than high school, high school graduate, some college and college graduate/ postgraduate); marital status (married, not married), health status (excellent, very good, good, fair, and poor); BMI (<18.5, 18.5–<25, 25–<30, 30–<35, ≥35 kg^2/m) smoking status (never, former, and current), smoking dose (0, 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and >60 cigarettes per day); time since quitting (never quit, ≥10, 5–9, 1–4, <1 years), vigorous physical activity (never/rarely; ≤3 times/mo; 1–2, 3–4, and ≥5 times/wk), alcohol (0, <5, 5–<15, 15–<30, and ≥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 and current) was adjusted in women. Dots indicate the RRs and horizontal lines indicate 95% CIs. The numbers of deaths in category 0 through ≥1000 mg/d were 3947, 2910, 794, and 253 for total CVD deaths, 3171, 2284, 627, and 200 for heart disease death, and 542, 440, 128 and 36 for cerebrovascular disease deaths in men; 1264, 1171, 893, and 576 for total CVD deaths, 931, 839, 607, and 400 for heart disease deaths, and 264, 255, 201, and 140 for cerebrovascular disease deaths in women. Person-years in each category were 1,237,051, 960,869, 234,209 and 725,40 for men, and 581,849, 604,732, 453,105, and 328,002 for women.

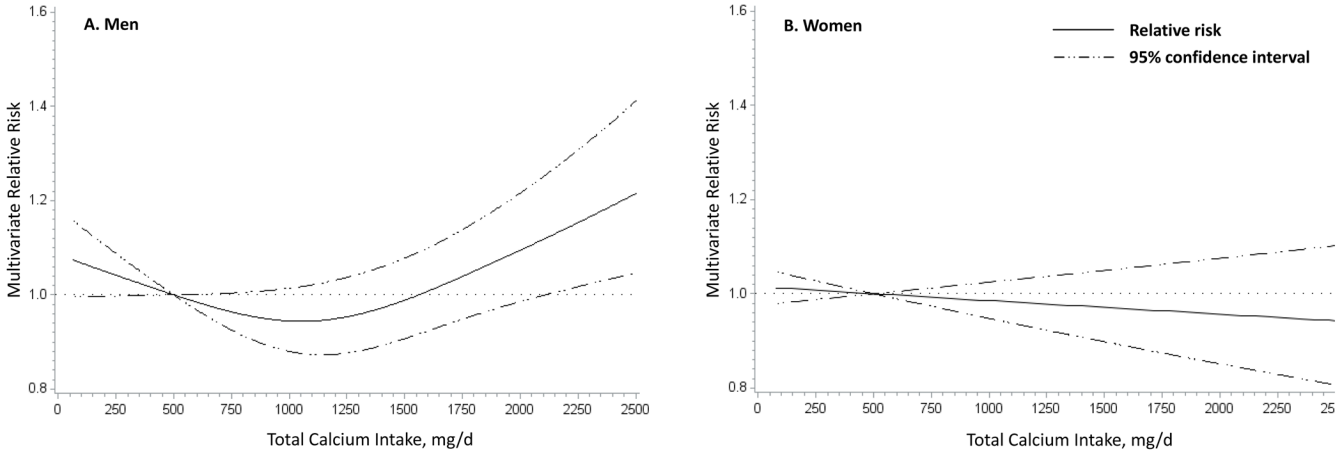

Figure 2.

Nonparametric regression curve for the association between total calcium intake and total cardiovascular disease (CVD) mortality for men (A) and women (B). Both models were adjusted for age at baseline (continuous); race/ethnicity (non-Hispanic white; non-Hispanic, black; and others); education (less than high school, high school graduate, some college and college graduate/postgraduate); marital status (married, not married), health status (excellent, very good, good, fair, and poor); BMI (<18.5, 18.5–<25, 25–<30, 30–<35, ≥35 kg^2/m) smoking status (never, former, and current), smoking dose (0, 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and >60 cigarettes per day); time since quitting (never quit, ≥10, 5–9, 1–4, <1 years), vigorous physical activity (never/rarely; ≤3 times/mo; 1–2, 3–4, and ≥5 times/wk), alcohol (0, <5, 5–<15, 15–<30, and ≥30 g/d), 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 and current) was adjusted in women.

Table 1

Selected Characteristics of Study Participants by Categories of Dietary and Supplemental Calcium Intakes *

	Dietary Calcium				Supplemental Calcium			
	Men		Women		Men		Women	
Variable [a]	Q1	Q5	Q1	Q5	Non-user	User	Non-user	User
Age at baseline	61.3	62.0	61.2	62.1	61.6	61.8	61.6	61.6
Dietary calcium, mg/d	463	1336	397	1170	782	815	681	719
Supplemental calcium, mg/d	127	163	336	423	0	289	0	554
White, non-Hispanic, %	90	94	86	93	93	93	88	91
College and postcollege, %	40	49	26	35	45	48	27	33
Married, %	83	84	46	42	86	84	45	45
Self-reported health, excellent, %	19	24	17	22	22	22	19	20
BMI, kg^2/m	27.0	27.0	26.6	26.2	27.2	26.9	27.1	26.1
Current smoker, %	16	9	21	11	12	10	18	13
Former smoker, %	54	52	35	37	53	55	35	36
Physical activity >= 5 times/wk, %	17	24	13	20	20	23	14	18
History of hypertension, %	37	33	35	30	35	35	35	32
History of high cholesterol, %	46	47	50	50	47	46	50	49
Multivitamin use, % [b]	47	56	55	66	17	90	14	81
Current MHT use, %	NA	NA	42	47	NA	NA	37	49
alcohol consumption, g/d	36.5	9.0	11.2	3.7	40.8	17.5	6.1	6.2
Fruits and vegetables, servings/1000 kcal	3.1	3.6	3.9	4.5	3.4	3.7	4.2	4.5
Red meat, g/1000 kcal	45	30	36	21	40	37	32	28
whole grains, servings/1000 kcal	0.47	0.74	0.52	0.74	0.62	0.68	0.63	0.70
total fat, % of energy	31	29	33	26	31	30	31	29
total energy, kcal/d	2071	2058	1569	1562	2037	2041	1572	1563
magnesium intake, mg/d	191	256	198	286	175	265	188	270

Abbreviations: BMI, body mass index; MHT, menopausal hormonal therapy; NA, not applicable.

All within-sex group comparisons were significant (p<.05) using the Kruskal Wallis (for continuous variables) and Chi-sq (for categorical variables) test

[a] Mean values otherwise specified

[b] Multivitamins included the "stress-tab type", "therapeutic or theragran type", and "one-a-day type". Only the latter two contained calcium

Table 2

Relative Risks and 95% Confidence Intervals for Cardiovascular Disease (CVD) Deaths for Quintiles of Dietary Calcium Intake in Men and Women

	Dietary calcium intake, Quintile					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	***P* Value for Trend**
			MEN			
Median intake, mg/d	478	616	739	898	1247	
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	Ref	0.81 (0.76, 0.86)	0.79 (0.74, 0.85)	0.75 (0.70, 0.80)	0.86 (0.80, 0.92)	0.004
Multivariate [a]	Ref	0.91 (0.85, 0.98)	0.96 (0.89, 1.03)	0.92 (0.85, 0.99)	1.04 (0.97, 1.12)	0.08
Heart disease deaths						
No. of cases	1496	1204	1223	1110	1249	
Age adjusted	Ref	0.79 (0.73, 0.85)	0.81 (0.75, 0.87)	0.75 (0.69, 0.81)	0.87 (0.81, 0.94)	0.01
Multivariate [a]	Ref	0.89 (0.82, 0.96)	0.97 (0.90, 1.05)	0.92 (0.85, 1.00)	1.06 (0.97, 1.14)	0.04
Cerebrovascular disease deaths						
No. of cases	268	229	214	205	230	
Age adjusted	Ref	0.83 (0.69, 0.99)	0.77 (0.64, 0.92)	0.75 (0.63, 0.90)	0.87 (0.73, 1.03)	0.21
Multivariate [a]	Ref	0.92 (0.77, 1.10)	0.90 (0.74, 1.08)	0.89 (0.73, 1.07)	1.02 (0.85, 1.23)	0.63
			WOMEN			
Median intake, mg/d	408	532	648	798	1101	
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	Ref	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]	Ref	0.99 (0.90, 1.09)	0.94 (0.85, 1.04)	0.99 (0.89, 1.10)	1.04 (0.94, 1.15)	0.37
Heart disease deaths						
No. of cases	692	557	497	495	536	
Age adjusted	Ref	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]	Ref	0.94 (0.84, 1.05)	0.90 (0.80, 1.01)	0.94 (0.83, 1.06)	0.99 (0.87, 1.12)	0.93

	Dietary calcium intake, Quintile					
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	***P* Value for Trend**
Cerebrovascular disease deaths						
No. of cases	170	189	149	174	178	
Age adjusted	Ref	1.07 (0.87, 1.32)	0.84 (0.67, 1.04)	0.96 (0.78, 1.19)	0.96 (0.78, 1.18)	0.54
Multivariate [b]	Ref	1.23 (1.00, 1.52)	1.01 (0.81, 1.27)	1.21 (0.97, 1.51)	1.20 (0.95, 1.51)	0.22

[a] adjusted for age at baseline (continuous); race/ethnicity (non-Hispanic white; non-Hispanic, black; and others); education (less than high school, high school graduate, some college and college graduate/ postgraduate); marital status (married, not married), health status (excellent, very good, good, fair, and poor); BMI (<18.5, 18.5–<25, 25–<30, 30–<35, ≥35 kg^2/m) smoking status (never, former, and current), smoking dose (0, 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and >60 cigarettes per day); time since quitting (never quit, ≥10, 5–9, 1–4, <1 years), vigorous physical activity (never/rarely; ≤3 times/mo; 1–2, 3–4, and ≥5 times/wk), alcohol (0, <5, 5–<15, 15–<30, and ≥30 g/d), supplemental calcium intake (0, <400, 400–<1000, ≥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 in [a] and use of menopausal hormone therapy (never, past and current).

Table 3

Multivariate Relative Risks and 95% Confidence Intervals for Total Cardiovascular Disease Deaths for Categories of Supplemental Calcium Intake, Stratified by Age, Smoking Status, Body Mass Index and Hypertension

	Supplemental Calcium Intake, mg/d				
	0	**0–400**	**400–1000**	**>1000**	**P Value for Trend**
MEN					
Age [a]					
<60	Ref	0.97 (0.87, 1.09)	1.15 (0.96, 1.38)	1.47 (1.09, 2.00)	0.01
>=60	Ref	0.99 (0.94, 1.05)	1.08 (1.00, 1.18)	1.15 (1.00, 1.32)	0.01
p value for interaction	0.16				
Smoking status [b]					
Never	Ref	0.91 (0.82, 1.00)	1.05 (0.90, 1.23)	1.04 (0.79, 1.36)	0.62
Former	Ref	0.98 (0.92, 1.05)	1.08 (0.97, 1.20)	1.17 (0.98, 1.38)	0.04
Current	Ref	1.10 (0.99, 1.21)	1.12 (0.93, 1.34)	1.33 (0.94, 1.89)	0.04
p value for interaction	0.01				
Body mass index [a]					
< 25	Ref	0.93 (0.85, 1.02)	1.08 (0.94, 1.24)	1.03 (0.82, 1.31)	0.45
>=25 and <30	Ref	0.97 (0.90, 1.04)	1.12 (1.00, 1.25)	1.36 (1.14, 1.63)	<0.001
>= 30	Ref	1.10 (1.00, 1.21)	1.03 (0.87, 1.22)	1.12 (0.83, 1.50)	0.36
p value for interaction	0.19				
Hypertension [a]					
Yes	Ref	1.03 (0.94, 1.13)	1.08 (0.93, 1.25)	1.44 (1.16, 1.80)	0.002
No	Ref	1.02 (0.93, 1.12)	1.15 (0.98, 1.34)	1.18 (0.91, 1.52)	0.06
p value for interaction	0.80				
Hypercholesterolemia [a]					
Yes	Ref	1.04 (0.95, 1.15)	1.22 (1.05, 1.41)	1.19 (0.93, 1.51)	0.01
No	Ref	0.99 (0.89, 1.10)	1.05 (0.89, 1.24)	1.39 (1.08, 1.78)	0.02
p value for interaction	0.94				
WOMEN					
Age [a]					

	Supplemental Calcium Intake, mg/d				
	0	**0–400**	**400–1000**	**>1000**	**P Value for Trend**
<60	Ref	0.99 (0.82, 1.21)	1.04 (0.83, 1.31)	0.92 (0.70, 1.22)	0.68
>=60	Ref	1.00 (0.92, 1.09)	1.05 (0.96, 1.16)	1.09 (0.97, 1.21)	0.09
p value for interaction	0.04				
Smoking status [b]					
Never	Ref	0.94 (0.82, 1.09)	0.99 (0.85, 1.16)	1.06 (0.89, 1.27)	0.37
Former	Ref	1.10 (0.96, 1.27)	1.19 (1.02, 1.38)	1.18 (1.00, 1.40)	0.05
Current	Ref	0.98 (0.82, 1.17)	1.13 (0.95, 1.35)	1.18 (0.98, 1.42)	0.91
p value for interaction	0.06				
Body mass index [a]					
< 25	Ref	1.05 (0.92, 1.20)	1.15 (1.00, 1.32)	1.13 (0.97, 1.32)	0.08
>=25 and <30	Ref	0.92 (0.81, 1.06)	0.93 (0.80, 1.08)	0.94 (0.78, 1.13)	0.55
>= 30	Ref	1.03 (0.88, 1.20)	1.09 (0.91, 1.30)	1.18 (0.95, 1.45)	0.11
p value for interaction	0.89				
Hypertension [a]					
Yes	Ref	0.95 (0.83, 1.09)	1.05 (0.90, 1.23)	1.07 (0.90, 1.27)	0.25
No	Ref	1.13 (0.96, 1.33)	1.05 (0.87, 1.26)	1.36 (1.12, 1.65)	0.007
p value for interaction	0.17				
Hypercholesterolemia [a]					
Yes	Ref	1.03 (0.88, 1.20)	1.05 (0.88, 1.24)	1.21 (1.00, 1.45)	0.05
No	Ref	1.05 (0.89, 1.23)	1.06 (0.89, 1.26)	1.19 (0.99, 1.44)	0.08
p value for interaction	0.69				

[a]adjusted for age at baseline (continuous); race/ethnicity (non-Hispanic white; non-Hispanic, black; and others); education (less than high school, high school graduate, some college and college graduate/ postgraduate); marital status (married, not married), health status (excellent, very good, good, fair, and poor); BMI (<18.5, 18.5–<25, 25–<30, 30–<35, ≥35 kg^2/m) smoking status (never, former, and current), smoking dose (0, 1–10, 11–20, 21–30, 31–40, 41–50, 51–60, and >60 cigarettes per day); time since quitting (never quit, ≥10, 5–9, 1–4, <1 years), vigorous physical activity (never/rarely; ≤3 times/mo; 1–2, 3–4, and ≥5 times/wk), alcohol (0, <5, 5–<15, 15–<30, and ≥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 and current) was adjusted in women.

[b]Adjusted for variables listed in [a] but smoking status.