Calcium intake and mortality from all causes, cancer, and cardiovascular disease: the Cancer Prevention Study II Nutrition Cohort[1,2]

*Baiyu Yang,[3–5] Peter T Campbell,[3] Susan M Gapstur,[3] Eric J Jacobs,[3] Roberd M Bostick,[4,6] Veronika Fedirko,[4,6] W Dana Flanders,[4,6] and Marjorie L McCullough[3]**

[3]Epidemiology Research Program, American Cancer Society, Atlanta, GA; and [4]Department of Epidemiology, Rollins School of Public Health, [5]Laney Graduate School, and [6]Winship Cancer Institute, Emory University, Atlanta, GA

ABSTRACT

Background: Calcium intake may be important for bone health, but its effects on other outcomes, including cardiovascular disease (CVD) and cancer, remain unclear. Recent reports of adverse cardiovascular effects of supplemental calcium have raised concerns.

Objective: We investigated associations of supplemental, dietary, and total calcium intakes with all-cause, CVD-specific, and cancer-specific mortality in a large, prospective cohort.

Design: A total of 132,823 participants in the Cancer Prevention Study II Nutrition Cohort, who were followed from baseline (1992 or 1993) through 2012 for mortality outcomes, were included in the analysis. Dietary and supplemental calcium information was first collected at baseline and updated in 1999 and 2003. Multivariable-adjusted Cox proportional hazards models with cumulative updating of exposures were used to calculate RRs and 95% CIs for associations between calcium intake and mortality.

Results: During a mean follow-up of 17.5 y, 43,186 deaths occurred. For men, supplemental calcium intake was overall not associated with mortality outcomes (P-trend > 0.05 for all), but men who were taking ≥1000 mg supplemental calcium/d had a higher risk of all-cause mortality (RR: 1.17; 95% CI: 1.03, 1.33), which was primarily attributed to borderline statistically significant higher risk of CVD-specific mortality (RR: 1.22; 95% CI: 0.99, 1.51). For women, supplemental calcium was inversely associated with mortality from all causes [RR (95% CI): 0.90 (0.87, 0.94), 0.84 (0.80, 0.88), and 0.93 (0.87, 0.99) for intakes of 0.1 to <500, 500 to <1000, and ≥1000 mg/d, respectively; P-trend < 0.01]. Total calcium intake was inversely associated with mortality in women (P-trend < 0.01) but not in men; dietary calcium was not associated with all-cause mortality in either sex.

Conclusions: In this cohort, associations of calcium intake and mortality varied by sex. For women, total and supplemental calcium intakes are associated with lower mortality, whereas for men, supplemental calcium intake ≥1000 mg/d may be associated with higher all-cause and CVD-specific mortality. *Am J Clin Nutr* 2016;103:886–94.

Keywords: calcium intake, cohort study, all-cause mortality, dietary supplements, cardiovascular disease mortality

INTRODUCTION

In the United States, recommendations to consume foods that are rich in calcium and vitamin D are included in dietary guidelines (1). In addition, dietary supplements that contain calcium are taken by 43% of the overall population and by 62% of individuals ≥71 y of age (2). Adequate calcium intake is important for bone health and several major physiologic functions (3). However, beyond its benefits for bone health, the effects of calcium on other health outcomes are largely unclear.

The relation between calcium and cardiovascular disease (CVD)[7] is complex and may depend on the source of calcium (4). Dietary calcium is generally weakly associated with a lower risk of incident or fatal CVD (4). In contrast, studies on supplemental calcium have reported conflicting results, whereby positive associations with CVD risk and mortality were reported in several epidemiologic studies (5–7), especially in men (6), but null or inverse associations were reported in other studies (8–13). A meta-analysis of several randomized clinical trials, primarily in older women, reported that calcium supplementation increased myocardial infarction (MI) risk by 24% and risk of a composite of MI or stroke by 15% (14). Although the trials included in the meta-analysis were not primarily designed to assess the effect of calcium supplementation on cardiovascular events, these results raised concerns about the potential harms of supplemental calcium on the cardiovascular system.

With regard to cancer, there has been generally consistent observational evidence that calcium intake is inversely associated

[1] Supported by the American Cancer Society.

[2] Supplemental Tables 1–3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

*To whom correspondence should be addressed. E-mail: marji.mccullough@cancer.org.

[7] Abbreviations used: CPS-II, Cancer Prevention Study II; CVD, cardiovascular disease; FFQ, food-frequency questionnaire; HRT, hormone replacement therapy; ICD, International Classification of Diseases; IHD, ischemic heart disease; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug.

Received June 23, 2015. Accepted for publication December 29, 2015.

First published online February 10, 2016; doi: 10.3945/ajcn.115.117994.

with colorectal cancer risk (15–17), and a major clinical trial showed statistically significantly reduced colorectal adenoma recurrence with calcium supplementation (18). In addition, some evidence has suggested that total or dietary calcium may be associated with lower risk of breast cancer (19, 20) and that total calcium or dairy intake may be positively associated with risk of prostate cancer (21), but the World Cancer Research Fund considers the level of evidence "limited" for both types of cancer (22, 23).

As reported herein, we comprehensively examined the associations of supplemental calcium intake with mortality from all causes and specifically mortality that is due to CVD and cancer, and second, we examined the associations of total and dietary calcium intake with mortality outcomes, in a large US prospective cohort study of men and women.

METHODS

Study population

The analytic cohort for this analysis consisted of men and women who were participating in the Cancer Prevention Study II (CPS-II) Nutrition Cohort, which is a prospective study of cancer incidence and mortality in US adults (24) and is a subset of the original CPS-II mortality cohort (25). At baseline enrollment (1992–1993), ~184,000 participants completed a mailed 10-page self-administered questionnaire regarding demographics, body size, medical history, diet, and other major lifestyle factors. Follow-up questionnaires were sent to participants in 1997 and biennially thereafter to update the exposure information and to learn of new cancer diagnoses (response rate was ≥89% for each follow-up questionnaire). The CPS-II Nutrition Cohort was approved by the Institutional Review Board of Emory University.

For this analysis, we excluded participants with a history of cancer at baseline (n = 21,785), a previous history of MI (n = 11,559), and a history of stroke (n = 2513) because these individuals may have changed their diets as a result of their diagnosis. We also excluded individuals with poorly completed dietary assessment instruments at baseline (n = 14,136) or uninterpretable calcium supplement intake (n = 1369). After these exclusions, 132,823 subjects remained eligible for this analysis, including 59,744 men and 73,079 women.

Dietary assessment

We first assessed calcium intake of participants at baseline (1992–1993) with the use of a 68-item modified Block food-frequency questionnaire (FFQ) (24, 26, 27), and updated this information in 1999 and 2003 with the use of a 152-item modified Willett FFQ (24, 28–30). Both FFQs included similar questions on the major food and beverage sources of calcium (**Supplemental Table 1**) (31). FFQ estimates for calcium and dairy products (a major source of dietary calcium) were in good agreement with estimates from dietary recalls or food records in validation studies (Pearson correlation coefficients ranged from 0.57 to 0.66 for calcium and from 0.52 to 0.88 for dairy products) (27–29). Dietary calcium was adjusted for energy intake with the use of the residual method (32), and total calcium was calculated as energy-adjusted dietary calcium plus raw supplemental calcium intake.

Outcome ascertainment

The vital status and cause of death were ascertained through linkage to the National Death Index up to 31 December 2012. The primary outcomes of this study were deaths from all causes, all cancers [International Classification of Diseases (ICD)-9 codes 140–208; ICD-10 codes C00–C97], and all CVDs (ICD-9 codes 390–459; ICD-10 codes I00–I99). Secondary outcomes included mortality that was specifically due to colorectal cancer (ICD-9 codes 153–154; ICD-10 codes C18–C20), lung cancer (ICD-9 codes 162; ICD-10 codes C33–C34), female breast cancer (ICD-9 codes 174–175; ICD-10 code C50), prostate cancer (ICD-9 code 185; ICD-10 code C61), ischemic heart disease (IHD; ICD-9 codes 410–414, ICD-10 codes I20–I25), and stroke (ICD-9 codes 430–438, ICD-10 codes I60–I69).

Statistical analysis

Supplemental calcium intake was categorized into 4 amounts on the basis of interpretable cutoffs for both sexes (i.e., 0, 0.1 to <500, 500 to <1000, and ≥1000 mg/d). We decided a priori to examine supplemental calcium intake ≥1000 mg/d because this dose was associated with higher CVD mortality in men from the NIH-AARP study (6). Total calcium and dietary calcium were categorized according to sex- and questionnaire-specific quintiles. To best estimate long-term calcium intake, we cumulatively updated calcium intake at 1999 and 2003 by taking the mean of all reported intakes up to that year to predict outcomes that occurred during the subsequent period. Values for missing data were carried forward from the previous questionnaire.

We used Cox proportional hazards models to estimate RRs and 95% CIs. The underlying time axis for all models was the time since baseline enrollment. The person time began on the date of baseline enrollment and ended on the date of death or the end of mortality follow-up (31 December 2012), whichever came first. We assessed the proportional hazards assumption with the use of a likelihood ratio test by comparing models with and without an interaction term between a main exposure (in categories) and time.

We chose a priori to conduct all analyses separately for men and women because of previously reported heterogeneity by sex (6) and to adjust for total energy intake (quintiles) and age at enrollment (y) in all models. We also adjusted for quintile intakes of whole grain, red and processed meats, and total folate and for cigarette smoking (never smokers; former smokers who quit ≥30, 20 to <30, or <20 y ago; and current smokers who smoked <15 or ≥15 cigarettes/d), alcohol consumption (0 drinks/d, 0.1 to <1 drink/d, and ≥1 drink/d), BMI (in kg/m^2; <18.5, 18.5–24.9, 25–29.9, and ≥30), education (less than high school, high school graduate, some college or trade school, and at least college graduate), and hormone replacement therapy (HRT) for women (none, former, or current use) because these variables either changed the RR by >10% or were established predictors of the outcome. Dietary calcium was included in supplemental calcium models and vice versa. We further adjusted for a recent colonoscopy or sigmoidoscopy in models for colorectal cancer mortality and for recent mammography in models for female breast cancer mortality. Other covariates considered included race, marital status, physical activity, use of aspirin, nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), and multivitamins, history of diabetes, high cholesterol, hypertension, and osteoporosis, and intakes of vegetables, fruit, vitamin D, and (for supplemental calcium

TABLE 1
Baseline characteristics of participants by categories of supplemental calcium: the CPS-II Nutrition Cohort (1992–2012)[1]

	Supplemental calcium intake at baseline, mg/d							
	Men				Women			
	0	0.1 to <500	500 to <1000	≥1000	0	0.1 to <500	500 to <1000	≥1000
Total, *n*	39,861	16,949	2244	690	35,277	20,918	10,387	6497
Age at enrollment, *n* (%)								
<60 y	11,450 (28.7)	4364 (25.7)	450 (20.1)	162 (23.5)	13,918 (39.5)	7797 (37.3)	3663 (35.3)	2273 (35.0)
60 to <65 y	12,041 (30.2)	5008 (29.5)	648 (28.9)	188 (27.2)	9690 (27.5)	5670 (27.1)	2881 (27.7)	1780 (27.4)
65 to <70 y	11,047 (27.7)	4789 (28.3)	638 (28.4)	193 (28.0)	7230 (20.5)	4461 (21.3)	2383 (22.9)	1422 (21.9)
≥70 y	5323 (13.4)	2788 (16.4)	508 (22.6)	147 (21.3)	4439 (12.6)	2990 (14.3)	1460 (14.1)	1022 (15.7)
Race, *n* (%)								
White/white Hispanic	38,858 (97.5)	16,539 (97.6)	2192 (97.7)	678 (98.3)	34,349 (97.4)	20,336 (97.2)	10,162 (97.8)	6402 (98.5)
Black/black Hispanic	463 (1.2)	169 (1.0)	17 (0.8)	3 (0.4)	538 (1.5)	323 (1.5)	75 (0.7)	24 (0.4)
Other/missing	540 (1.4)	241 (1.4)	35 (1.6)	9 (1.3)	390 (1.1)	259 (1.2)	150 (1.4)	71 (1.1)
Education, *n* (%)								
Less than high school	3151 (7.9)	1020 (6.0)	131 (5.8)	33 (4.8)	1765 (5.0)	923 (4.4)	345 (3.3)	151 (2.3)
High school degree	7905 (19.8)	2703 (15.9)	337 (15.0)	115 (16.7)	12,087 (34.3)	6361 (30.4)	2850 (27.4)	1634 (25.2)
Some college/ trade school	9995 (25.1)	4299 (25.4)	553 (24.6)	163 (23.6)	10,688 (30.3)	6779 (32.4)	3315 (31.9)	2210 (34.0)
College graduate	18,563 (46.6)	8831 (52.1)	1210 (53.9)	378 (54.8)	10,503 (29.8)	6717 (32.1)	3812 (36.7)	2472 (38.0)
Physical activity (MET-h/wk),[2] *n* (%)								
Quintile 1	5323 (13.4)	1701 (10.0)	207 (9.2)	70 (10.1)	3809 (10.8)	1733 (8.3)	667 (6.4)	425 (6.5)
Quintile 2	11,153 (28.0)	4378 (25.8)	536 (23.9)	184 (26.7)	11,676 (33.1)	6101 (29.2)	2877 (27.7)	1709 (26.3)
Quintile 3	5873 (14.7)	2830 (16.7)	391 (17.4)	116 (16.8)	6264 (17.8)	4380 (20.9)	2275 (21.9)	1371 (21.1)
Quintile 4	8854 (22.2)	4057 (23.9)	532 (23.7)	159 (23.0)	6797 (19.3)	4267 (20.4)	2178 (21.0)	1441 (22.2)
Quintile 5	8232 (20.7)	3827 (22.6)	560 (25.0)	156 (22.6)	6350 (18.0)	4236 (20.3)	2304 (22.2)	1509 (23.2)
BMI (kg/m^2), *n* (%)								
<18.5	124 (0.3)	82 (0.5)	12 (0.5)	8 (1.2)	509 (1.4)	336 (1.6)	219 (2.1)	209 (3.2)
18.5 to <25	13,174 (33.0)	6638 (39.2)	996 (44.4)	278 (40.3)	16,372 (46.4)	10,599 (50.7)	5967 (57.4)	3942 (60.7)
25 to <30	19,952 (50.1)	7980 (47.1)	975 (43.4)	308 (44.6)	11,475 (32.5)	6598 (31.5)	2934 (28.2)	1670 (25.7)
≥30	6017 (15.1)	1992 (11.8)	229 (10.2)	81 (11.7)	6266 (17.8)	3041 (14.5)	1145 (11.0)	595 (9.2)
History of diabetes, *n* (%)								
No	36,926 (92.6)	15,763 (93.0)	2115 (94.3)	645 (93.5)	33,352 (94.5)	19,941 (95.3)	9990 (96.2)	6279 (96.6)
Yes	2935 (7.4)	1186 (7.0)	129 (5.7)	45 (6.5)	1925 (5.5)	977 (4.7)	397 (3.8)	218 (3.4)
History of hypertension, *n* (%)								
No	25,487 (63.9)	10,888 (64.2)	1490 (66.4)	460 (66.7)	23,610 (66.9)	14,402 (68.8)	7361 (70.9)	4705 (72.4)
Yes	14,374 (36.1)	6061 (35.8)	754 (33.6)	230 (33.3)	11,667 (33.1)	6516 (31.2)	3026 (29.1)	1792 (27.6)
History of high cholesterol, *n* (%)								
No	15,744 (39.5)	7089 (41.8)	921 (41.0)	276 (40.0)	15,900 (45.1)	9801 (46.9)	4900 (47.2)	3014 (46.4)
Yes	24,117 (60.5)	9860 (58.2)	1323 (59.0)	414 (60.0)	19,377 (54.9)	11,117 (53.1)	5487 (52.8)	3483 (53.6)
Aspirin use, *n* (%)								
No	21,740 (54.5)	7749 (45.7)	992 (44.2)	350 (50.7)	22,405 (63.5)	11,977 (57.3)	5937 (57.2)	3810 (58.6)
Yes	17,228 (43.2)	8808 (52.0)	1200 (53.5)	325 (47.1)	12,106 (34.3)	8424 (40.3)	4217 (40.6)	2540 (39.1)
Nonaspirin NSAID use, *n* (%)								
No	32,005 (80.3)	12,747 (75.2)	1671 (74.5)	487 (70.6)	25,392 (72.0)	14,067 (67.2)	6904 (66.5)	4196 (64.6)
Yes	7344 (18.4)	3965 (23.5)	535 (23.9)	194 (28.1)	9114 (25.9)	6341 (30.3)	3235 (31.2)	2113 (32.5)

(Continued)

TABLE 1 (*Continued*)

	Supplemental calcium intake at baseline, mg/d							
	Men				Women			
	0	0.1 to <500	500 to <1000	≥1000	0	0.1 to <500	500 to <1000	≥1000
Smoking status, *n* (%)								
Never smoker	13,471 (33.8)	5666 (33.4)	857 (38.2)	242 (35.1)	19,383 (54.9)	11,374 (54.4)	5721 (55.1)	3517 (54.1)
Current smoker	3849 (9.7)	1407 (8.3)	109 (4.9)	34 (4.9)	3469 (9.8)	1772 (8.5)	641 (6.2)	369 (5.7)
Former smoker	22,273 (55.9)	9764 (57.6)	1262 (56.2)	413 (59.9)	12,003 (34.0)	7513 (35.9)	3909 (37.6)	2557 (39.4)
Alcohol consumption, *n* (%)								
Nondrinker	12,964 (32.5)	5536 (32.7)	810 (36.1)	283 (41.0)	16,899 (47.9)	9582 (45.8)	4466 (43.0)	2889 (44.5)
<1 drink/d	15,786 (39.6)	6773 (40.0)	865 (38.5)	224 (32.5)	13,320 (37.8)	8339 (39.9)	4343 (41.8)	2668 (41.1)
≥1 drink/d	10,366 (26.0)	4393 (25.9)	542 (24.2)	176 (25.5)	4356 (12.3)	2733 (13.1)	1461 (14.1)	883 (13.6)
Hormone replacement therapy, *n* (%)								
None	—	—	—	—	17,282 (49.0)	8612 (41.2)	3508 (33.8)	1851 (28.5)
Current user	—	—	—	—	9607 (27.2)	7028 (33.6)	4439 (42.7)	3102 (47.7)
Former user	—	—	—	—	6585 (18.7)	4156 (19.9)	1877 (18.1)	1206 (18.6)
Multivitamin use, *n* (%)								
No current use	37,924 (95.1)	754 (4.4)	619 (27.6)	242 (35.1)	33,008 (93.6)	2541 (12.1)	3494 (33.6)	2504 (38.5)
Current use	1218 (3.1)	16,177 (95.4)	1609 (71.7)	442 (64.1)	1311 (3.7)	18,290 (87.4)	6778 (65.3)	3919 (60.3)
Use of individual calcium supplements, *n* (%)								
No	39,061 (98.0)	14,143 (83.4)	57 (2.5)	0 (0)	34,265 (97.1)	12,973 (62.0)	67 (0.6)	0 (0)
Yes	0 (0)	2245 (13.2)	2183 (97.3)	690 (100.0)	0 (0)	7396 (35.4)	10,319 (99.3)	6497 (100.0)
Dietary composition								
Total energy intake, kcal/d	1828.1 ± 628.5[3]	1803.0 ± 603.3	1769.6 ± 599.5	1759.2 ± 581.5	1366.7 ± 490.1	1371.8 ± 479.0	1354.2 ± 450.8	1338.0 ± 446.8
Red/processed meat intake, servings/wk	6.1 ± 4.0	5.5 ± 3.8	5.0 ± 3.9	4.8 ± 3.9	4.6 ± 3.2	4.1 ± 3.0	3.8 ± 3.0	3.6 ± 2.9
Total folate intake, μg/d	283.3 ± 118.9	663.8 ± 219.8	685.9 ± 429.5	774.8 ± 684.6	251.3 ± 132.3	584.4 ± 249.1	555.2 ± 323.0	573.8 ± 420.7
Fruit/vegetable intake, servings/d	3.0 ± 1.6	3.3 ± 1.6	3.7 ± 1.7	3.6 ± 1.7	3.4 ± 1.6	3.6 ± 1.7	3.9 ± 1.7	4.0 ± 1.8
Whole-grain intake, g/d	60.4 ± 63.7	71.2 ± 71.2	85.4 ± 81.9	88.8 ± 90.8	52.3 ± 47.5	60.1 ± 50.5	63.9 ± 51.4	66.1 ± 55.0
Total vitamin D intake, IU/d	179.3 ± 104.5	552.2 ± 213.4	523.3 ± 425.1	565.9 ± 556.0	155.0 ± 95.0	480.1 ± 239.4	421.8 ± 304.3	431.3 ± 382.5
Dairy intake, servings/d	1.7 ± 1.3	1.8 ± 1.3	1.7 ± 1.3	1.6 ± 1.3	1.5 ± 1.2	1.7 ± 1.2	1.6 ± 1.2	1.6 ± 1.2

[1]Some percentages do not add up to 100% because of missing data or rounding. CPS-II, Cancer Prevention Study II; MET-h, metabolic equivalent hours; NSAID, nonsteroidal anti-inflammatory drug.

[2]Quintiles in men: <3.5, 3.5 to <6, 6 to <14, 14 to < 24.5, and ≥24.5; quintiles in women: <3.5, 3.5 to <4, 4 to <14, 14 to <18.5, and ≥18.5.

[3]Mean ± SD (all such values).

models only) dairy products. The Wald test was used to assess linear trends for the association between calcium and mortality by assigning the sex-specific median value for the quintile (for total and dietary calcium) or an ordinal variable for supplemental calcium category and modeling it as a continuous variable.

Several sensitivity analyses were conducted to assess the robustness of our findings as follows: *1*) with the exclusion of the first 2 y of follow-up; *2*) with the use of age as the alternative time scale; *3*) by stopping the cumulative updating of calcium if incident cancer was diagnosed or a diagnosis of CVD was reported

TABLE 2
Associations of supplemental calcium intake with mortality from all causes, cancer, and cardiovascular disease: CPS-II Nutrition Cohort (1992–2012)[1]

	Men				Women			
Supplemental calcium intake	Deaths, *n*	Person-years	RR (95% CI)	*P*-trend	Deaths, *n*	Person-years	RR (95% CI)	*P*-trend
All-cause mortality								<0.01
0 mg/d	12,103	544,192	Referent	0.18	5639	427,737	Referent	
0.1 to <500 mg/d	10,736	401,700	1.01 (0.97, 1.04)		8032	510,804	0.90 (0.87, 0.94)	
500 to <1000 mg/d	1328	49,750	1.01 (0.95, 1.08)		3857	285,534	0.84 (0.80, 0.88)	
≥1000 mg/d	246	9461	1.17 (1.03, 1.33)		1245	99,439	0.93 (0.87, 0.99)	
Cancer mortality								<0.01
0 mg/d	3723	544,192	Referent	0.19	1783	427,737	Referent	
0.1 to <500 mg/d	3175	401,700	1.05 (0.99, 1.11)		2497	510,804	0.99 (0.92, 1.06)	
500 to <1000 mg/d	380	49,750	1.05 (0.94, 1.18)		1159	285,534	0.86 (0.79, 0.94)	
≥1000 mg/d	60	9461	1.03 (0.79, 1.33)		380	99,439	0.94 (0.83, 1.06)	
Cardiovascular disease mortality								<0.01
0 mg/d	4129	544,192	Referent	0.39	1760	427,737	Referent	
0.1 to <500 mg/d	3564	401,700	0.96 (0.91, 1.02)		2413	510,804	0.83 (0.78, 0.90)	
500 to <1000 mg/d	418	49,750	0.91 (0.82, 1.01)		1184	285,534	0.81 (0.74, 0.88)	
≥1000 mg/d	93	9461	1.22 (0.99, 1.51)		355	99,439	0.84 (0.74, 0.94)	
Mortality from all other causes								0.02
0 mg/d	4251	544,192	Referent	0.06	2096	427,737	Referent	
0.1 to <500 mg/d	3997	401,700	1.01 (0.96, 1.07)		3122	510,804	0.89 (0.84, 0.95)	
500 to <1000 mg/d	530	49,750	1.09 (0.99, 1.20)		1514	285,534	0.84 (0.78, 0.91)	
≥1000 mg/d	93	9461	1.22 (0.99, 1.51)		510	99,439	0.99 (0.89, 1.10)	

[1]Supplemental calcium intake was cumulatively updated in 1999 and 2003. Models were adjusted for age at enrollment, intakes of total energy, whole grain, red and processed meats, and total folate, smoking and alcohol-drinking doses, educational level, BMI, dietary calcium intake, and hormone replacement therapy (for women). RRs (95% CIs) were calculated with the use of Cox proportional hazards models. *P*-trend values were calculated with the use of Wald test. CPS-II, Cancer Prevention Study II.

by that time point because the development of comorbidities may affect participants' subsequent calcium intakes; and *4*) with the exclusion of participants with a history of diabetes or chronic obstructive pulmonary disease at baseline.

We tested for an effect modification of supplemental calcium use and all-cause mortality by age at enrollment (<65 compared with ≥65 y), BMI (<30 compared with ≥30), physical activity (less than the median metabolic equivalent–hours per week compared with at least the median), smoking status (never compared with former compared with current), aspirin use (nonuser compared with user), other NSAID use (nonuser compared with user), and HRT use (never or former user compared with current user) with the use of likelihood ratio tests. All analyses were performed with the use of SAS version 9.3 software (SAS Institute).

RESULTS

The mean ± SD age of participants at baseline was 62.6 ± 6.3 y, and 45% of participants were men. Most subjects self-reported their race as white. Baseline characteristics of men and women by supplemental calcium intake are shown in **Table 1**. Participants with higher supplemental calcium intake were generally older, better educated, more physically active, leaner, less likely to smoke, more likely to use NSAIDs and to currently use HRT (women), and to have an overall healthier diet. Participants with supplemental calcium intake from 0.1 to <500 mg/d were more likely to take multivitamins, whereas those with intake ≥500 mg/d were more likely to take individual calcium supplements because multivitamins were counted as a source of a low amount of calcium, whereas individual calcium supplements were necessary to reach higher intakes.

In the 132,823 participants, 43,186 deaths (24,413 deaths in men; 18,773 deaths in women) occurred during a mean ± SD follow-up of 17.5 ± 4.5 y (range: 1 d to 20.2 y), including 13,157 deaths from cancer and 13,916 deaths from CVD. As shown in **Table 2**, in men, there was no linear association between supplemental calcium intake and all-cause mortality (*P*-trend = 0.18), but men who consumed ≥1000 mg supplemental calcium/d were at higher risk of all-cause mortality (RR: 1.17; 95% CI: 1.03, 1.33). A similar pattern in men was observed between supplemental calcium and CVD-specific mortality although the RR for supplemental calcium intake ≥1000 mg/d was only borderline significant (RR: 1.22; 95% CI: 0.99, 1.51). No association was observed with cancer-specific mortality at any dosage. Men with supplemental calcium intake ≥1000 mg/d were also at borderline significant higher risk of death from all other causes (RR: 1.22; 95% CI: 0.99, 1.51), particularly death from respiratory system diseases (data not shown). In women, there were inverse associations that appeared nonlinear between supplemental calcium use and mortality from all causes and CVD, which were observed at all supplemental calcium intakes, but not from cancer because 95% CIs crossed 1.0 (Table 2). None of the sensitivity analyses, such as the exclusion of the first 2 y of follow-up, changed the results materially.

The associations of supplemental calcium with the 4 leading types of cancer (lung cancer, colorectal cancer, female breast cancer, and prostate cancer) and 2 major types of ischemic heart disease (IHD) and stroke are shown in **Table 3**. Supplemental calcium was not associated with these mortality outcomes in men. In women, supplemental calcium was inversely associated with mortality from IHD and had a U-shaped association with stroke mortality; there were significant trends of inverse associations with colorectal cancer and breast cancer, but 95% CIs crossed 1.0.

TABLE 3
Associations of supplemental calcium with mortality from specific types of cancer and cardiovascular disease: CPS-II Nutrition Cohort (1992–2012)[1]

	Men					Women				
	Supplemental calcium, mg/d	Deaths, *n*	Person-years	RR (95% CI)	*P*-trend	Supplemental calcium, mg/d	Deaths, *n*	Person-years	RR (95% CI)	*P*-trend
Colorectal cancer										0.05
	0	346	544,192	Referent	0.80	0	199	427,737	Referent	
	0.1 to <500	222	401,700	0.89 (0.72, 1.11)		0.1 to <500	240	510,804	1.00 (0.80, 1.24)	
	≥500[2]	41	59,211	1.15 (0.81, 1.63)		500 to <1000	94	285,534	0.76 (0.58, 1.00)	
	—	—	—	—		≥1000	30	99,439	0.81 (0.54, 1.22)	
Prostate cancer (men)/breast cancer (women)										0.02
	0	369	544,192	Referent	0.23	0	173	427,737	Referent	
	0.1 to <500	381	401,700	1.16 (0.97, 1.38)		0.1 to <500	283	510,804	0.96 (0.77, 1.20)	
	≥500[2]	52	59,211	1.12 (0.82, 1.53)		500 to <1000	114	285,534	0.73 (0.56, 0.95)	
	—	—	—	—		≥1000	35	99,439	0.78 (0.53, 1.14)	
Lung cancer										0.62
	0	1016	544,192	Referent	0.20	0	416	427,737	Referent	
	0.1 to <500	801	401,700	1.18 (1.04, 1.33)		0.1 to <500	520	510,804	1.07 (0.92, 1.24)	
	≥500[2]	88	59,211	1.03 (0.81, 1.30)		500 to <1000	260	285,534	1.06 (0.89, 1.26)	
	—	—	—	—		≥1000	77	99,439	1.05 (0.81, 1.36)	
Ischemic heart disease										<0.01
	0	2184	544,192	Referent	0.50	0	742	427,737	Referent	
	0.1 to <500	1869	401,700	0.96 (0.89, 1.04)		0.1 to <500	988	510,804	0.86 (0.77, 0.96)	
	500 to <1000	216	49,750	0.89 (0.77, 1.03)		500 to <1000	460	285,534	0.80 (0.70, 0.91)	
	≥1000	52	9,461	1.28 (0.97, 1.70)		≥1000	129	99,439	0.76 (0.63, 0.93)	
Stroke										0.14
	0	674	544,192	Referent	0.12	0	397	427,737	Referent	
	0.1 to <500	600	401,700	0.92 (0.80, 1.05)		0.1 to <500	606	510,804	0.86 (0.74, 0.99)	
	≥500[2]	82	59,211	0.84 (0.66, 1.08)		500 to <1000	298	285,534	0.80 (0.67, 0.94)	
	—	—	—	—		≥1000	105	99,439	0.96 (0.76, 1.21)	

[1]Models were adjusted for age at enrollment, intakes of total energy, whole grain, red and processed meats, and total folate, smoking and alcohol-drinking doses, educational level, BMI, dietary calcium intake, and hormone replacement therapy (for women). We further adjusted for colonoscopy or sigmoidoscopy in colorectal cancer models and mammography in female breast cancer models. Supplemental calcium intake was cumulatively updated in 1999 and 2003. RRs (95% CIs) were calculated with the use of Cox proportional hazards models. *P*-trend values were calculated with the use of Wald test. CPS-II, Cancer Prevention Study II.

[2]Results were combined for the 500 to <1000 and the ≥1000 categories because of the small numbers of deaths.

We observed an effect modification by the use of aspirin and HRT in the association between supplemental calcium use and all-cause mortality (**Figure 1**). For men, intake of ≥1000 mg supplemental calcium/d was more strongly associated with higher all-cause mortality in aspirin nonusers than in regular users (*P*-interaction < 0.01). For women, intake of ≥1000 mg supplemental calcium/d was associated with lower all-cause mortality only in regular aspirin users or HRT never or former users (*P*-interaction = 0.01).

Total calcium intake was not associated with mortality outcomes in men but was inversely associated with all-cause, cancer-specific, and CVD-specific mortality in women. Dietary calcium was generally not associated with all-cause, cancer-specific, or CVD-specific mortality in either men or women (**Supplemental Tables 2** and **3**).

DISCUSSION

The results from this large prospective cohort study suggest that supplemental calcium intake is inversely associated with all-cause mortality in women. In men, there is no association between supplemental calcium and mortality overall; however, daily consumption of ≥1000 mg supplemental calcium/d may be associated with higher mortality (especially from noncancer causes such as CVD) in men. Total calcium intake was not associated with all-cause mortality in men but was inversely associated with all-cause mortality in women. Dietary calcium intake was not associated with mortality in both sexes. Our results provide evidence that calcium consumption (especially from supplements) may be beneficial for women; however, calcium supplements may have potential adverse CVD effects at very high intake levels in men.

We are not aware of any randomized clinical trials that were specifically designed to test the effect of calcium supplements on CVD events as the primary outcome. Meta-analyses of several trials that monitored CVD events as secondary outcomes reported higher risks of MI and a composite outcome (MI or stroke) in subjects who were randomly assigned to receive calcium compared to placebo (14, 33), although findings from 2 trials did not concur (34, 35). Several large, prospective observational studies also reported positive associations of supplemental calcium use and CVD risk or mortality: The European Prospective Investigation into Cancer and Nutrition–Heidelberg cohort showed

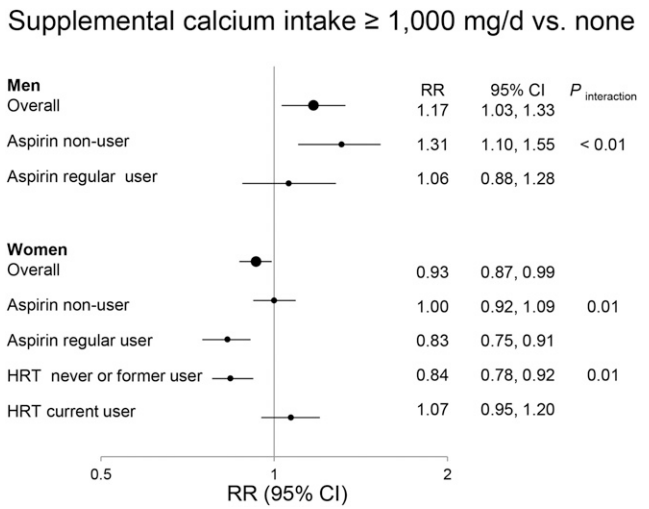

FIGURE 1 Supplemental calcium intake ≥1000 mg/d and all-cause mortality in the Cancer Prevention Study II Nutrition Cohort (1992–2012) stratified by use of aspirin (for both men and women) and HRT (for women only). RRs and 95% CIs calculated were with the use of Cox proportional hazards models. *P*-interaction values were calculated with the use of the likelihood ratio test. HRT, hormone replacement therapy.

that regular intake of supplemental calcium was associated with higher risk of incident MI in both sexes (7), a study in Finland observed 24% higher risk of incident IHD in women who took any calcium or calcium plus vitamin D supplements (5), and the NIH-AARP study reported higher risk of CVD death in men who consumed >400 mg supplemental calcium/d (especially in men who consumed ≥ 1000 mg/d) but not in women (6). Conversely, several other large observational studies reported null or inverse associations between supplemental calcium use and CVD risk or mortality (8–13). Reasons for the conflicting results in the observational studies are unclear but may have been related to the different doses examined; our study and the NIH-AARP study showed direct associations of supplemental calcium intake with cardiovascular events in men at very high doses, whereas several previous studies with null results compared lower doses of supplemental calcium intake with no intake in men or women (9, 12, 13).

One of the mechanisms that underlies the potential adverse cardiovascular effect of supplemental calcium may be vascular calcification. There has been evidence that the ingestion of calcium supplements but not of calcium-rich foods may lead to an acute increase in serum calcium (4, 36, 37). This increase may be sustained in the long term as evidenced by a persistently lower concentration of serum parathyroid hormone (which acts to restore serum calcium when the concentration is low) during 2 y of calcium supplementation in 323 healthy men (38). A high serum calcium concentration may contribute to vascular calcification (39) as shown in several studies in dialysis patients that consistently reported positive associations between arterial calcification and calcium supplement intake or a higher serum calcium concentration (40–42) although this result has not been supported by all studies (43). Vascular calcification has been linked to higher CVD risk or mortality across several ethnic groups (44–46). This adverse effect may counteract several protective effects of calcium on the cardiovascular system (e.g., the favorable regulation of cholesterol, blood pressure, and insulin sensitivity) (4).

The observed heterogeneity by sex in our cohort was consistent with results from the NIH-AARP cohort, which also primarily consists of older white participants and was initiated in the 1990s (6). Reasons for the observation of no excess mortality associated with calcium supplementation in women are unclear especially considering that, in previous calcium trials that reported elevated CVD risks, participants were primarily older women who were not concurrently taking vitamin D supplements (i.e., in many trials, the primary trial outcome was bone health) (33). One possible explanation for the observed heterogeneity by sex is that there are different patterns of bias for men and women. It is possible that, for women, calcium supplement use may be associated with better health care or health-seeking behaviors (which, in turn, may be associated with lower mortality) because of the suggested benefit of calcium in preventing or treating osteoporosis (47–49). In contrast, for men, intakes of high doses of supplemental calcium (especially ≥1000 mg/d) may be associated with medical conditions that are potentially related to higher mortality (e.g., fracture, rheumatoid, or osteoarthritis), which raises the possibility of confounding by indication. However, our study did not comprehensively collect information on these potential confounding factors throughout all questionnaires; therefore, whether the heterogeneity by sex is due to potential biases warrants investigation in future studies.

The fact that calcium supplement doses ≥1000 mg/d were associated with higher mortality risk in men, and yet, the highest quintile consumption of total calcium (diet plus supplements) was not associated with increased risk, could be partially explained by the fact that dietary intakes drive total intakes in men; the mean supplemental calcium intakes in men in the top quintile of total calcium intake were 242, 318, and 337 mg/d in 1992, 1999, and 2003, respectively.

We observed an effect modification by aspirin use in the association between supplemental calcium and all-cause mortality: despite the differences in the overall RR in men and women, both RR estimates were significantly lower in aspirin users than in nonusers. The mechanisms for such an interaction remain unclear, and we are not aware of previous reports on such interactions in relation to overall mortality. We also observed an interaction with HRT use in women such that the inverse association between supplemental calcium and all-cause mortality was only observed in HRT never or former users but not in current users. Such an interaction is theoretically plausible because there is evidence that estrogen therapy may increase calcium binding protein amounts and induce bone mineralization, both of which lead to a reduced systemic bioavailability of calcium (50). This effect may mask an inverse association between supplemental calcium and mortality in women. Overall, with consideration that we tested multiple potential effect modifiers, whether these observed interactions are true or due to chance deserve additional investigation.

The strengths of this study include its prospective design, large sample size, and detailed information on covariates. The large sample size enabled us to study very high supplemental calcium intakes (e.g., ≥1000 mg/d, which is uncommon in men) at which adverse effects on CVD risk may occur. Repeated assessments captured long-term calcium intake, which was not always available in other studies. There were also several limitations. We used different FFQs at baseline and follow-up dietary assessments; however, both FFQs were well validated and

asked similar questions concerning the major sources of calcium intake in the United States. Although we adjusted for a variety of covariates, there may still have been confounding by unmeasured confounders (e.g., access to health care). Our cohort primarily consisted of white, middle-class, well-educated participants, and our findings may have limited generalizability to other populations.

In conclusion, we showed that calcium intakes are associated with lower mortality in women even at low intakes. However, in men, high intake of supplemental calcium (≥1000 mg/d) may be associated with higher all-cause mortality risk, and such potential adverse effects warrant additional study.

We thank the central cancer registries that are supported through the Center for Disease Control and Prevention's National Program of Cancer Registries and Prevention's National Program of Cancer Registries and the cancer registries that are supported by the National Cancer Institute's Surveillance Epidemiology and End Results Program for their contributions to this study.

The authors' responsibilities were as follows—BY, PTC, SMG, EJJ, and MLM: designed and conducted the research; BY: conducted the statistical analyses; MLM: had primary responsibility for the final content of the manuscript; and all authors: interpreted the data, wrote the manuscript, and read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

REFERENCES

1. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th Edition. Washington (DC): December 2015. [cited 2016 Jan 21]. Available at http://health.gov/dietaryguidelines/2015/guidelines/.
2. Bailey RL, Dodd KW, Goldman JA, Gahche JJ, Dwyer JT, Moshfegh AJ, Sempos CT, Picciano MF. Estimation of total usual calcium and vitamin D intakes in the United States. J Nutr 2010;140:817–22.
3. Dietary reference intakes for calcium and vitamin D. Editors: Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Washington (DC): National Academies Press; 2011.
4. Wang L, Manson JE, Sesso HD. Calcium intake and risk of cardiovascular disease: a review of prospective studies and randomized clinical trials. Am J Cardiovasc Drugs 2012;12:105–16.
5. Pentti K, Tuppurainen MT, Honkanen R, Sandini L, Kroger H, Alhava E, Saarikoski S. Use of calcium supplements and the risk of coronary heart disease in 52-62-year-old women: The Kuopio Osteoporosis Risk Factor and Prevention Study. Maturitas 2009;63:73–8.
6. Xiao Q, Murphy RA, Houston DK, Harris TB, Chow W-H, Park Y. Dietary and supplemental calcium intake and cardiovascular disease mortality: the National Institutes of Health-AARP diet and health study. JAMA Intern Med 2013;173:639–46.
7. Li K, Kaaks R, Linseisen J, Rohrmann S. Associations of dietary calcium intake and calcium supplementation with myocardial infarction and stroke risk and overall cardiovascular mortality in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition study (EPIC-Heidelberg). Heart 2012;98:920–5.
8. Al-Delaimy WK, Rimm E, Willett WC, Stampfer MJ, Hu FB. A prospective study of calcium intake from diet and supplements and risk of ischemic heart disease among men. Am J Clin Nutr 2003;77:814–8.
9. Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epidemiol 1999;149:151–61.
10. Prentice RL, Pettinger MB, Jackson RD, Wactawski-Wende J, Lacroix AZ, Anderson GL, Chlebowski RT, Manson JE, Van Horn L, Vitolins MZ, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int 2013;24:567–80.
11. Van Hemelrijck M, Michaelsson K, Linseisen J, Rohrmann S. Calcium intake and serum concentration in relation to risk of cardiovascular death in NHANES III. PLoS One 2013;8:e61037.
12. Iso H, Stampfer MJ, Manson JE, Rexrode K, Hennekens CH, Colditz GA, Speizer FE, Willett WC. Prospective study of calcium, potassium, and magnesium intake and risk of stroke in women. Stroke 1999;30:1772–9.
13. Ascherio A, Rimm EB, Hernán MA, Giovannucci EL, Kawachi I, Stampfer MJ, Willett WC. Intake of potassium, magnesium, calcium, and fiber and risk of stroke among US men. Circulation 1998;98:1198–204.
14. Bolland MJ, Grey A, Avenell A, Gamble GD, Reid IR. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040.
15. Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. Nutr Cancer 2009;61:47–69.
16. Keum N, Aune D, Greenwood DC, Ju W, Giovannucci EL. Calcium intake and colorectal cancer risk: Dose-response meta-analysis of prospective observational studies. Int J Cancer 2014;135:1940–8.
17. Cho E, Smith-Warner SA, Spiegelman D, Beeson WL, van den Brandt PA, Colditz GA, Folsom AR, Fraser GE, Freudenheim JL, Giovannucci E, et al. Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. J Natl Cancer Inst 2004;96:1015–22.
18. Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, Rothstein R, Summers RW, Snover DC, Beck GJ, et al. Calcium supplements for the prevention of colorectal adenomas. N Engl J Med 1999;340:101–7.
19. Cui Y, Rohan TE. Vitamin D, calcium, and breast cancer risk: a review. Cancer Epidemiol Biomarkers Prev 2006;15:1427–37.
20. Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Res Treat 2010;121:469–77.
21. Aune D, Navarro Rosenblatt DA, Chan DS, Vieira AR, Vieira R, Greenwood DC, Vatten LJ, Norat T. Dairy products, calcium, and prostate cancer risk: a systematic review and meta-analysis of cohort studies. Am J Clin Nutr 2015;101:87–117.
22. World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report. Diet, nutrition, physical activity, and prostate cancer [Internet]. 2014 [cited 2015 Mar 13]. Available from: www.wcrf.org/sites/default/files/Prostate-Cancer-2014-Report.pdf.
23. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report. Food, nutrition, physical activity, and the prevention of breast cancer [Internet]. 2010 [cited 2015 Mar 13]. Available from: http://www.aicr.org/continuous-update-project/reports/Breast-Cancer-2010-Report.pdf.
24. Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, Feigelson HS, Thun MJ. The American Cancer Society Cancer Prevention Study II Nutrition Cohort. Cancer 2002;94:2490–501.
25. Garfinkel L. Selection, follow-up, and analysis in the American Cancer Society prospective studies. Natl Cancer Inst Monogr 1985;67:49–52.
26. Block G, Hartman AM, Naughton D. A reduced dietary questionnaire: development and validation. Epidemiology 1990;1:58–64.
27. Flagg EW, Coates RJ, Calle EE, Potischman N, Thun MJ. Validation of the American Cancer Society Cancer Prevention Study II nutrition survey cohort food frequency questionnaire. Epidemiology 2000;11:462–8.
28. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol 1992;135:1114–26.
29. Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, Willett WC. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc 1993;93:790–6.
30. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51–65.
31. Yang B, McCullough ML, Gapstur SM, Jacobs EJ, Bostick RM, Fedirko V, Flanders WD, Campbell PT. Calcium, vitamin D, dairy products, and mortality among colorectal cancer survivors: the Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol 2014;32:2335–43.
32. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
33. Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. BMJ 2010;341:c3691.

34. Baron JA, Barry EL, Mott LA, Rees JR, Sandler RS, Snover DC, Bostick RM, Ivanova A, Cole BF, Ahnen DJ, et al. A trial of calcium and vitamin d for the prevention of colorectal adenomas. N Engl J Med 2015;373:1519–30.
35. Avenell A, MacLennan GS, Jenkinson DJ, McPherson GC, McDonald AM, Pant PR, Grant AM, Campbell MK, Anderson FH, Cooper C, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). J Clin Endocrinol Metab 2012;97:614–22.
36. Reid IR, Schooler BA, Hannan SF, Ibbertson HK. The acute biochemical effects of four proprietary calcium preparations. Aust N Z J Med 1986;16:193–7.
37. Green JH, Booth C, Bunning R. Postprandial metabolic responses to milk enriched with milk calcium are different from responses to milk enriched with calcium carbonate. Asia Pac J Clin Nutr 2003;12:109–19.
38. Reid IR, Ames R, Mason B, Reid HE, Bacon CJ, Bolland MJ, Gamble GD, Grey A, Horne A. Randomized controlled trial of calcium supplementation in healthy, nonosteoporotic, older men. Arch Intern Med 2008;168:2276–82.
39. Abedin M, Tintut Y, Demer LL. Vascular calcification: mechanisms and clinical ramifications. Arterioscler Thromb Vasc Biol 2004;24:1161–70.
40. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, Wang Y, Chung J, Emerick A, Greaser L, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478–83.
41. Asmus H-G, Braun J, Krause R, Brunkhorst R, Holzer H, Schulz W, Neumayer H-H, Raggi P, Bommer J. Two year comparison of sevelamer and calcium carbonate effects on cardiovascular calcification and bone density. Nephrol Dial Transplant 2005;20:1653–61.
42. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, Raggi P. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int 2005;68:1815–24.
43. Samelson EJ, Booth SL, Fox CS, Tucker KL, Wang TJ, Hoffmann U, Cupples LA, O'Donnell CJ, Kiel DP. Calcium intake is not associated with increased coronary artery calcification: the Framingham Study. Am J Clin Nutr 2012;96:1274–80.
44. Pletcher MJ, Tice JA, Pignone M, Browner WS. Using the coronary artery calcium score to predict coronary heart disease events: a systematic review and meta-analysis. Arch Intern Med 2004;164:1285–92.
45. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 2008;358:1336–45.
46. Polonsky TS, McClelland RL, Jorgensen NW, Bild DE, Burke GL, Guerci AD, Greenland P. Coronary artery calcium score and risk classification for coronary heart disease prediction. JAMA 2010;303:1610–6.
47. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Black HR, Blanchette P, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669–83.
48. Cumming RG. Calcium intake and bone mass: a quantitative review of the evidence. Calcif Tissue Int 1990;47:194–201.
49. Nordin BE. Calcium and osteoporosis. Nutrition 1997;13:664–86.
50. Ding EL, Mehta S, Fawzi WW, Giovannucci EL. Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: reanalysis of Women's Health Initiative randomized trial. Int J Cancer 2008;122:1690–4.