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Relation of Calcium, Vitamin D, and Dairy Food Intake to Ischemic Heart Disease Mortality among Postmenopausal Women

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To investigate whether greater intakes of calcium, vitamin D, or milk products may protect against ischemic heart disease mortality, the authors analyzed data from a prospective cohort study of 34,486 postmenopausal Iowa women 55–69 years old and without a history of ischemic heart disease who completed a dietary questionnaire in 1986. Through 1994, 387 deaths due to ischemic heart disease were documented (*International Classification of Diseases*, Ninth Revision, codes 410–414, 429.2). The multivariate-adjusted relative risks for the highest versus the lowest quartiles of total calcium, vitamin D, and milk product intakes were as follows: 0.67 (95% confidence interval (CI) 0.47–0.94; *p* for trend = 0.09) for calcium, 1.41 (95% CI 0.93–2.15; *p* for trend = 0.12) for vitamin D, and 0.94 (95% CI 0.66–1.35; *p* for trend = 0.68) for milk products. The relative risk was 0.63 (95% CI 0.40–0.98) for high dietary calcium but no supplemental calcium intake and 0.66 (95% CI 0.36–1.23) for high supplemental calcium but low dietary calcium intake. These results suggest that a higher intake of calcium, but not of vitamin D or milk products, is associated with reduced ischemic heart disease mortality in postmenopausal women, and reduced risk may be achievable whether the higher intake of calcium is attained by diet, supplements, or both. *Am J Epidemiol* 1999;149:151–61.

calcium, dietary; dairy products; myocardial ischemia; prospective studies; vitamin D

Ischemic heart disease is the leading cause of death in the United States; however, much of the variability as to what causes it and how it could be prevented remains unexplained (1). Calcium, if consumed in amounts greater than that required for absorption from the gut to maintain body calcium levels, binds bile acids in the gut and increases their excretion (2–7). Bile acid-binding resins, such as cholestyramine, lower blood levels of cholesterol by just such a mechanism (8), and their use has been found to reduce the risk of ischemic heart disease (9). On the other hand, calcium is present in atherosclerotic lesions, thus raising the possibility that increased calcium consumption may increase the risk of cardiovascular disease (10). With increasing numbers of women taking calcium supplements to avoid osteoporosis (11), if calcium consumption affects the risk of cardiovascular disease, then such calcium consumption could have a substantial public health impact.

Animal experiments (3–6, 12–14) and, more recently, three randomized placebo-controlled clinical trials in humans (15–17) found that a higher consumption of calcium lowers blood cholesterol levels. Furthermore, animal experiments also found that a higher consumption of calcium reduces aortic and cardiac cholesterol levels as well as aortic atherosclerosis (5, 12, 14). Further, there is inconsistent but generally favorable evidence to suggest that higher intakes of calcium may slightly reduce blood pressure and, more importantly, reduce the risk of developing hypertension (18–20). Thus, taken altogether, we hypothesized that, in humans, higher intakes of calcium are associated with a reduced risk of death due to ischemic heart disease. Furthermore, because vitamin D is intimately associated with calcium metabolism (21), and because milk products are major sources of calcium and vitamin D (but also of atherogenic saturated fats) in the American diet, we reasoned that if calcium is associated with risk of ischemic heart disease, then associations or lack of associations of ischemic heart disease with vitamin D or milk product intake could suggest possible mechanisms of action for calcium.

Although there are considerable data on the relation of calcium to blood pressure (18–20) and cholesterol

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Abbreviation: CI, confidence interval; ICD-9, *International Classification of Diseases*, Ninth Revision; SE, standard error.

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(3–7, 12–17, 22–30), there are very few data, most (31–34) but not all (35–37) of which are from ecologic studies, on the association of calcium, vitamin D, and milk products with ischemic heart disease. Herein, we report an analysis from the Iowa Women's Health Study, a large prospective study among women, to investigate whether the intakes of calcium, vitamin D, or milk products are associated with ischemic heart disease mortality in postmenopausal women.

MATERIALS AND METHODS

The Iowa Women's Health Study cohort

The methodology of the Iowa Women's Health Study has been described previously (38, 39). Briefly, in 1986, 41,837 women 55–69 years of age who had a valid Iowa driver's license in 1985 returned a mailed questionnaire with self-reported data on known and suspected risk factors for cardiovascular disease.

Data collection

The mailed questionnaire included a semiquantitative food frequency questionnaire virtually identical to that used in the 1984 survey of the Nurses' Health Study (40). The 127-item food frequency questionnaire covered usual food intake and vitamin and mineral supplement use. The duration of vitamin and mineral use was not assessed. The rationale for use of a food frequency questionnaire to assess dietary habits and nutrient intake in a large-scale cohort study has been described elsewhere (41–43). The reliability and accuracy of this questionnaire among members of this cohort (44) are comparable to those observed in the Nurses' Health Study (41). For example, for total calcium and vitamin D, the reliability coefficients on three different determinations ranged from 0.57 to 0.82, and the validity coefficients (vs. five 24-hour dietary recalls) were 0.67 and 0.51, respectively.

The level of physical activity was determined using two questions that assessed a respondent's usual frequency of moderate and vigorous free time physical activity. Moderate activity was defined as activities such as bowling, golf, light sports or physical exercise, gardening, or taking long walks; vigorous activity was defined as activities such as jogging, racket sports, swimming, aerobics, or strenuous sports.

Data on body measurements were self-reported using a validated protocol (45). Body mass index, defined as weight (kg) divided by the square of the height (m^2), was used as a measure of relative weight. A paper tape measure and written instructions were enclosed with the questionnaire so that a friend of the respondent could measure the circumference of her waist 1 inch (2.54 cm) above the umbilicus and hips (maximal protrusion). From these measures a waist:hip ratio was calculated for each respondent.

Identification of deaths due to ischemic heart disease

Women were followed annually through the State Health Registry of Iowa, which collects information on deaths that occurred in Iowa. Deaths were also reported from follow-up questionnaires mailed in 1987, 1989, and 1992 and by linkage of nonresponders to the National Death Index. Women were considered to have died from ischemic heart disease if the cause of death was coded as *International Classification of Diseases*, Ninth Revision (ICD-9), codes 410 through 414 or 429.2. Although we did not validate cause-of-death coding, other studies have indicated that the validity of ischemic heart disease on death certificates is relatively high (46, 47).

Population analysis

Before beginning hypothesis testing, we excluded women who reported a history of ischemic heart disease at baseline (n = 4,115), those who were premenopausal (n = 569), those who left 30 or more food items blank on the food frequency questionnaire (n = 2,782), and those who measured having implausibly high or low total daily energy intake (<600 or >5,000 kcal/day) (n = 538). A total of 654 women had two or more of these exclusions. Thus, the resulting baseline population at risk was 34,486.

Statistical analyses

Age-adjusted mean baseline characteristics were computed for cases and noncases and compared using analysis of covariance. Women were categorized according to quartiles of intake of various foods, nutrients, and other characteristics as computed from the 1986 questionnaire. For nutritional supplement items, categories of intake were established on the basis of distribution of use. All categories were determined prior to hypothesis testing.

For cases, the length of follow-up was calculated for each individual as the number of days elapsed since completion of the baseline questionnaire until the date of death due to ischemic heart disease. For noncases, different termination dates were used according to the following prioritization scheme: 1) the date of death for deaths occurring in Iowa; 2) the date on which the person moved out of Iowa if the date of the move was known; 3) the midpoint between the date of the last

contact in Iowa and the first known date out of Iowa or the end of the follow-up period if the person moved from Iowa at an unknown date; or 4) the midpoint between the date of the last contact in Iowa and the date of death for non-Iowa deaths. Noncases for whom these criteria did not apply contributed follow-up time through December 31, 1994.

Person-time for each exposure was accumulated, and an incidence rate was calculated by dividing the number of first events by the person-years of follow-up. The relative risk, defined as the incidence rate in a particular category of exposure divided by the corresponding rate in the comparison category, was used as a measure of strength of association. Age-adjusted rates were calculated using 5-year categories. The Mantel extension test (48) was used to evaluate trends across categories of variables stratified according to age. Analyses to control for simultaneous effects of multiple variables were conducted using proportional hazards methods (49, 50). The multivariate-adjusted relative risk for a given category of an exposure variable was determined by exponentiating its regression coefficient. The test for trend after multivariate adjustment for covariates was determined across the vector of indicator variables for the exposure of interest, with each level of exposure weighted by its median value. For all relative risks, 95 percent confidence intervals were calculated (51).

Proportional hazards regression models were constructed by adding and/or deleting hypothesized ischemic heart disease risk factors, their interactions, and hypothesized confounding variables one at a time. Decisions on which covariates to include in the final reported models were based on 1) biologic plausibility, 2) whether the covariate entered the model at the 0.10 level of significance, and 3) whether the covariate acted as a confounder of the primary association of interest (confounding was considered to be present if the regression coefficient of the primary independent variable changed ≥10 percent after adding the potential confounding variable to the model).

RESULTS

Descriptive analyses

During 297,877 person-years of follow-up over an 8-year period, 387 deaths due to ischemic heart disease were reported. Of the 387 deaths, 57 percent were reported as due to acute myocardial infarction (ICD-9 code 410.0), 30 percent to chronic ischemic heart disease (ICD-9 code 414), and 13 percent to arteriosclerotic cardiovascular disease (ICD-9 code 429.2). As reported previously (52, 53), women were at increased risk of coronary heart disease death if they reported on the baseline questionnaire that they had hypertension or diabetes mellitus or were current smokers. Women were at decreased risk if they reported estrogen replacement use, greater physical activity, or dietary vitamin E intake. Greater body mass index and waist:hip ratio were also associated with increased risk of coronary heart disease death.

Participants who died of ischemic heart disease were, on average, slightly older (mean, 63.6 (standard error (SE), 0.2) years vs. 61.5 (SE, 0.02) years; $p = 0.0001$) than those who did not die of ischemic heart disease. Cases and noncases did not differ at $p \leq 0.05$ in mean total energy intake, total or dietary intake of calcium, vitamin D intake (total, dietary, or supplemental), dietary fiber, or total fat. The mean supplemental intake of calcium was lower in those who died of ischemic heart disease (240 (SE, 20) mg/day vs. 283 (SE, 2) mg/day; $p = 0.04$). The intake of milk products that contained fat was, on average, higher in those who died of ischemic heart disease (9.5 (SE, 0.4) servings/week vs. 8.6 (SE, 0.04) servings/week; $p = 0.03$).

Selected age-adjusted mean baseline characteristics of participants according to levels of total daily calcium intake are presented in table 1. Participants with the highest intakes of total calcium tended, on average, to be more educated; to consume more calories, total vitamin D, total and saturated fat, and total dairy foods; to be less likely to smoke; and to be more likely to use postmenopausal estrogens and to engage in vigorous exercise. Participants with the highest intakes of total calcium did not, on average, differ substantially from those with other levels of total calcium intake by age, dietary vitamin E, body mass index, waist:hip ratio, or history of diabetes mellitus.

Selected age-adjusted mean baseline characteristics of participants according to use of vitamin or mineral supplements are presented in table 2. Participants who took any vitamin or mineral supplement, a calcium supplement, or a vitamin D supplement tended, on average, to be more likely to use postmenopausal estrogens, to engage in vigorous physical activity, to be slightly more educated, to consume slightly less calories and saturated fat, and to be slightly less likely to have diabetes mellitus or to smoke. Participants who took any vitamin or mineral supplement, a calcium supplement, or a vitamin D supplement did not, on average, differ substantially from those who did not take such supplements by age, dietary vitamin E, body mass index, or the waist:hip ratio.

Age-adjusted associations

Age-adjusted relative risks for ischemic heart disease death according to categories of intake of various

TABLE 1. Selected age–adjusted* baseline characteristics of participants in the Iowa Women's Health Study in 1986 according to levels of total daily calcium intake

Quartiles† of total‡ daily calcium intake	Mean age (years)	Mean total energy intake (kcal/day)	Mean total‡ vitamin D intake (IU/day)	Mean total fat intake (g/day)	Mean saturated fat intake (g/day)	Mean dietary vitamin E intake (IU/day)	Mean total dairy intake§ (servings/week)
Quartile 1 (<696 mg)	61.6	1,441	220	57	20	6	18
Quartile 2 (696—1,051 mg)	61.6	1,772	341	69	24	8	21
Quartile 3 (1,052—1,425 mg)	61.5	1,904	460	72	26	8	22
Quartile 4 (>1,425 mg)	61.4	2,096	627	78	29	9	24

Quartiles† of total‡ daily calcium intake	Mean fat-containing dairy intake¶ (servings/week)	Mean body mass index (kg/m²)	Mean waist:hip ratio	Diabetes mellitus (%)	Currently smoke (%)	Use post-menopausal estrogens (%)	≥ College graduate (%)	Physical activity vigorous (%)
Quartile 1 (<696 mg)	16	27	0.84	6	19	33	8	18
Quartile 2 (696—1,051 mg)	17	27	0.84	5	16	36	12	24
Quartile 3 (1,052—1,425 mg)	17	27	0.84	6	14	39	15	26
Quartile 4 (>1,425 mg)	18	26	0.83	5	12	44	18	32

* Dietary variables except for total energy intake also adjusted for total energy intake.
† Quartile 1 (n = 8,622); quartile 2 (n = 8,620); quartile 3 (n = 8,622); quartile 4 (n = 8,622).
‡ Total intake = dietary sources plus supplements.
§ Milk products excluding butter.
¶ Milk products (other than butter) containing fat minus skim milk.

dietary components are presented in table 3. There were statistically significant inverse trends for ischemic heart disease death with increasing total calcium (p = 0.02) and supplemental calcium (p = 0.01). Furthermore, risks for those in the highest categories of intake of both total and supplemental calcium were approximately two-thirds lower than those in the lowest categories of intake. There were no material associations of ischemic heart disease mortality with intake of dietary calcium and with intakes of total, dietary, and supplemental vitamin D. The patterns of association for total milk product (i.e., all milk products combined except butter) intake also appeared null, but there was a statistically insignificant increased risk with higher intakes of milk products that contain fat (i.e., total milk products minus skim milk).

Multivariate-adjusted associations

In multivariate models, we included the nutrient or food group of interest plus age, total energy intake, body mass index, waist:hip ratio, history of diabetes mellitus, cigarette smoking status, postmenopausal estrogen use, alcohol intake, education, physical activity, dietary vitamin E intake, and saturated fat intake (as residuals of total energy intake on saturated fat intake). A history of hypertension was not included in the final models because hypertension was considered a possible intermediate mechanism in the calcium and vitamin D association with ischemic heart disease; furthermore, inclusion of the hypertension variable in the model had negligible impact on the estimated relative risks. Also, a variable to indicate non-calcium-containing nutritional supplement-taking behavior had negligible impact on the estimated relative risks and thus was not included in final models. Simultaneous inclusion of vitamin D, calcium, and one of the milk product variables in models yielded no substantive differences in risk estimates. Examples of other omitted covariates that did not confound associations or did not fit the final models at the 0.10 level of significance include interactions of total calcium intake with total fat, saturated fat, dietary fiber, or vitamin D.

After multivariate adjustment, previous patterns for supplemental calcium and vitamin D held, but they were attenuated and not statistically significant at $p \leq 0.05$ (table 4). However, findings for total calcium were

TABLE 2. Selected age-adjusted* baseline characteristics of participants (n = 34,486) in the Iowa Women's Health Study in 1986 according to use or nonuse of vitamin or mineral supplements

Vitamin/mineral supplement	Mean age (years)	Mean total energy intake (kcal/day)	Mean saturated fat intake (g/day)	Mean body mass index (kg/m²)	Mean waist:hip ratio	Mean dietary vitamin E intake (IU/day)
Any vitamin/mineral supplement						
Users (n = 21,844)	61.6	1,788	24	27	0.83	8
Nonusers (n = 12,642)	61.5	1,830	26	27	0.84	8
Calcium supplement						
Users (n = 16,600)	61.5	1,770	24	27	0.83	8
Nonusers (n = 17,826)	61.5	1,835	26	27	0.84	8
Vitamin D supplement						
Users (n = 12,477)	61.6	1,790	24	27	0.83	8
Nonusers (n = 22,009)	61.5	1,811	25	27	0.84	8

	Diabetes mellitus (%)	Currently smoke (%)	Use post-menopausal estrogens (%)	≥ College graduate (%)	Physical activity vigorous (%)
Any vitamin/mineral supplement					
Users (n = 21,844)	5	14	42	14	28
Nonusers (n = 12,642)	7	17	31	11	20
Calcium supplement					
Users (n = 16,600)	5	13	44	15	29
Nonusers (n = 17,826)	7	17	33	12	21
Vitamin D supplement					
Users (n = 12,477)	5	14	43	15	30
Nonusers (n = 22,009)	6	16	35	12	23

* Dietary variables except for total energy intake also adjusted for total energy intake.

essentially unchanged with risk statistically significantly reduced for those in the second and fourth quartiles of calcium intake. The risk for those in the highest quartile of intake of total calcium was two-thirds that of those in the lowest quartile of intake (relative risk = 0.67; 95 percent confidence interval (CI) 0.47–0.94). Relative risks for ischemic heart disease mortality for those in the upper quantiles of intake of dietary and supplemental calcium were 0.76 and 0.88, respectively, and were not statistically significant. None of the findings for vitamin D was statistically significant. None of the findings for milk products was statistically significant, all of the relative risks were close to 1.0, and all were similar to those from the simple age-adjusted models.

It was postulated that, because the reduction in risk associated with the total intake of calcium was the sum of the reductions in risk due to its components, that is, dietary and supplemental intake, the data supported an effect of calcium per se. Although this line of reasoning could be true, an equally plausible reason for the pattern of findings was that the results for the dietary and supplemental intakes were attenuated because some women consuming low amounts of dietary calcium were compensating by taking calcium supplements, some women not taking supplements were consuming high amounts of dietary calcium, and some women were consuming moderate amounts of each source to achieve a high total level of intake. Thus, if there were an effect of calcium, there would be attenuation of the dietary and supplemental scores that could be unmasked on stratification of dietary by supplemental intake. Therefore, if the calcium hypothesis were correct, then the stratified analyses would show reduced risks for high levels of calcium intake, whether they were from dietary or supplemental intake, that would be comparable to those for total calcium intake. Accordingly, multivariate-adjusted relative risks of ischemic heart disease death according to quartile levels of dietary intake of calcium were stratified by the previously described three levels of supplemental intake. As seen in table 5, the statistical power for some cells in this analysis was low, but there was a pattern of reduced risks for ischemic heart disease death whether the intake of calcium was high due to dietary or to supplemental sources, and these risk estimates were virtually identical to one another and to that for total calcium intake (table 4). There was no evidence to suggest that high supplementation with calcium was better than low supplementation.

DISCUSSION

The findings presented herein suggest that, among postmenopausal women, the risk of dying of ischemic

TABLE 3. Age-adjusted relative risks of ischemic heart disease mortality according to intake of various dietary components, Iowa women, 1986–1994

Category*	Total energy						Total calcium†						Dietary calcium					
	kcal/day	Cases (no.)	Person-years (no.)	Relative risk	χ^2 for trend	p value	mg/day	Cases (no.)	Person-years (no.)	Relative risk	χ^2 for trend	p value	mg/day	Cases (no.)	Person-years (no.)	Relative risk	χ^2 for trend	p value
1	<1,381	102	74,478	1.00			<696	127	74,224	1.00			<543	99	74,466	1.00		
2	1,381–1,723	86	74,574	0.85 (0.64–1.13)¶			696–1,051	84	74,497	0.66 (0.50–0.87)			543–742	103	74,446	1.03 (0.78–1.35)		
3	1,724–2,128	97	74,513	0.96 (0.73–1 27)			1,052–1,425	94	74,586	0.74 (0.57–0.97)			743–1,110	89	74,514	0.89 (0.67–1.18)		
4	>2,128	102	74,312	1.02 (0.78–1.34)	0.20	0.65	>1,425	82	74,570	0.65 (0.50–0.86)	5.75	0.02	>1,110	96	74,452	0.97 (0.73–1.28)	0.21	0.65
	Supplemental calcium						Total vitamin D†						Dietary vitamin D					
	mg/day	Cases (no.)	Person-years (no.)	Relative risk	χ^2 for trend	p value	IU/day	Cases (no.)	Person-years (no.)	Relative risk	χ^2 for trend	p value	IU/day	Cases (no.)	Person-years (no.)	Relative risk	χ^2 for trend	p value
1	0	239	153,570	1.00			<183	102	74,444	1.00			<114	94	74,426	1 00		
2	1–500	92	90,997	0.64 (0.50–0.82)			183–337	94	74,593	0.85 (0.64–1.13)			114–223	99	74,456	0.98 (0.74–1.30)		
3	>500	56	53,311	0.69 (0.52–0.92)	6.20	0.01	338–562	89	74,551	0.82 (0.62–1.09)			224–345	89	74,636	0.85 (0.64–1.14)		
4							>562	102	74,290	0.91 (0 69–1.20)	0.17	0.68	>345	105	74,361	1.02 (0.77–1.35)	0.00	0.97
	Supplemental vitamin D						Total dairy intake‡						Fat-containing dairy intake§					
	IU/day	Cases (no.)	Person-years (no.)	Relative risk	χ^2 for trend	p value	Servings/ week	Cases (no.)	Person-years (no.)	Relative risk	χ^2 for trend	p value	Servings/ week	Cases (no.)	Person-years (no.)	Relative risk	χ^2 for trend	p value
1	0	264	190,090	1.00			<9.0	114	87,404	1.00			<4.0	93	76,085	1.00		
2	1-400	87	76,109	0.81 (0.63–1.03)			9.0–14.5	110	82,978	0.98 (0.75–1.27)			4.0–7.5	140	102,080	1.14 (0.88–1.49)		
3	>400	36	31,679	0.80 (0.57–1.13)	1.56	0.21	15.0–23.5	90	73,178	0.91 (0.69–1.19)			8.0–12.5	80	69,424	0.95 (0.71–1.28)		
4							>23.5	73	54,318	1.00 (0.75–1.35)	0.01	0.92	>12.5	74	50,289	1.21 (0.89–1.64)	0.97	0.32

* Categories of all variables based on quartiles, except those for supplemental calcium and vitamin D where category 1 = no intake and remaining categories were on a low-high median split.
† Total intake = dietary sources plus supplemental sources.
‡ Milk products excluding butter.
§ Milk products other than butter containing fats, that is, the same as those in ‡ footnote minus skim milk.
¶ Numbers in parentheses, 95% confidence interval.

TABLE 4. Multivariate-adjusted relative risks of ischemic heart disease mortality according to categories of intake of various dietary components, Iowa women, 1986–1994

Category*	Total calcium†,‡			Dietary calcium‡			Supplemental calcium‡			Total vitamin D†,§		
	Relative risk	χ^2 for trend	*p* value	Relative risk	χ^2 for trend	*p* value	Relative risk	χ^2 for trend	*p* value	Relative risk	χ^2 for trend	*p* value
1	1.00			1.00			1.00			1.00		
2	0.62 (0.45–0.85)††			0.92 (0.68–1.25)			0.76 (0.58–1.00)			1.10 (0.80–1.52)		
3	0.75 (0.55–1.03)			0.81 (0.57–1.13)			0.88 (0.64–1.23)			1.06 (0.73–1.54)		
4	0.67 (0.47–0.94)	2.87	0.09	0.76 (0.53–1.11)	2.19	0.14		0.56	0.46	1.41 (0.93–2.15)	2.41	0.12
	Dietary vitamin D§			Supplemental vitamin D§			Total dairy intake¶,#			Fat-containing dairy intake¶,**		
	Relative risk	χ^2 for trend	*p* value	Relative risk	χ^2 for trend	*p* value	Relative risk	χ^2 for trend	*p* value	Relative risk	χ^2 for trend	*p* value
1	1.00			1.00			1.00			1.00		
2	1.12 (0.83–1.52)			0.86 (0.62–1.21)			1.00 (0.75–1.34)			1.14 (0.86–1.52)		
3	0.92 (0.67–1.28)			0.85 (0.54–1.34)			0.91 (0.66–1.24)			0.88 (0.60–1.22)		
4	0.99 (0.70–1.41)	0.13	0.72		0.50	0.48	0.94 (0.66–1.35)	0.22	0.64	1.14 (0.78–1.66)	0.17	0.68

* Categories of all variables based on quartiles, except those for supplemental calcium and vitamin D where category 1 = no intake and remaining categories were on a low-high median split.

† Total intake = dietary sources plus supplemental sources.

‡ Covariates included in final model for reported relative risks: age, total energy intake, body mass index, waist:ratio, history of diabetes mellitus, cigarette smoking status, postmenopausal estrogen use, alcohol intake, education, marital status, physical activity, dietary vitamin E intake, and saturated fat intake (as residuals of regression of total energy intake on saturated fat intake).

§ Covariates included in final model for reported relative risks are the same as for calcium variables in ‡ footnote except that total calcium intake was also included.

¶ Covariates included in final model for reported relative risks are the same as for calcium variables in ‡ footnote except that total fat intake was not included.

Milk products excluding butter.

** Milk products other than butter containing fat, that is, the same as in # footnote minus skim milk.

†† Numbers in parentheses, 95% confidence interval.

TABLE 5. Levels of daily supplemental calcium and dietary calcium intakes in relation to the multivariate-adjusted* relative risk of mortality from ischemic heart disease in Iowa women, 1986–1994

Dietary calcium intake by quartile	Supplemental calcium intake†								
	None			Low			High		
	Cases (no.)	Median total calcium (mg)‡	Relative risk	Cases (no.)	Median total calcium (mg)‡	Relative risk	Cases (no.)	Median total calcium (mg)‡	Relative risk
1	62	422	1.00§	22	776	0.59 (0.34–1.00)¶	15	1,400	0.66 (0.36–1.23)
2	63	641	0.79 (0.54–1.16)	26	1,057	0.72 (0.44–1.19)	14	1,608	0.63 (0.34–1.16)
3	56	886	0.73 (0.48–1.10)	19	1,265	0.50 (0.28–0.88)	14	1,834	0.71 (0.38–1.31)
4	58	1,312	0.63 (0.40–0.98)	25	1,699	0.56 (0.32–0.98)	13	2,317	0.76 (0.39–1.49)

* Single model with single reference cell with adjustment for age, body mass index, waist:hip ratio, diabetes mellitus, cigarette smoking, estrogen replacement therapy, alcohol intake, education, marital status, physical activity, dietary vitamin E intake, and saturated fat intake.
† Categories are no supplement intake and, among users of calcium-containing supplements, low and high intake based on a median split.
‡ Total = dietary plus supplemental.
§ Reference category.
¶ Numbers in parentheses, 95% confidence interval.

heart disease may be reduced by consuming relatively high levels of calcium. As shown in table 4, there was an estimated statistically significant 33 percent reduction in risk for persons in the highest quartile of total calcium intake (i.e., high whether due to diet, supplements, or both). From the traditional analysis shown in table 4 for dietary and supplemental calcium intakes, the estimated (not statistically significant) reductions in risks for ischemic heart disease for persons in the upper quartiles of calcium intakes were 24 percent and 12 percent, respectively. However, in the stratified analysis (table 5), which eliminates misclassification attenuation, the risk reductions were 37 percent and 34 percent, respectively, both estimates virtually identical to one another and to that for total calcium intake. Although the risk estimate for high dietary intake but no supplemental intake was statistically significant and that for high supplemental intake and low dietary intake was not, the pattern, though not conclusive, does provide some support for the suggestion from the total calcium findings that the reduction in risk associated with high calcium intake may be attainable by diet, supplements, or both. Because of low statistical power, the question of whether the small subset of persons (n = 13 cases) in the highest category of total calcium intake, who were also in the highest category of dietary intake and in the highest category of supplemental intake (table 5), could not be adequately addressed from these data. At the very least, the findings in this study argue against any increased risk of dying of ischemic heart disease due to calcium supplementation or a high intake of calcium. Although the findings provide no support for an association of vitamin D intake or milk product intake per se with dying of ischemic heart disease, there was a suggestion that any benefit derived from calcium from milk products is negated if the milk products contain fat.

Strengths and limitations

This study has several strengths and limitations. One limitation is that, in studies of etiology, the incidence of disease is generally preferable to mortality as an endpoint, since factors relating to mortality may or may not always be the same as those for etiology. The present study is also limited by the lack of information on sunlight exposure (of relevance to vitamin D exposure) and duration of supplemental vitamin and mineral use. Also, the findings may or may not only apply to postmenopausal women. On balance, however, it has several advantages over most previous epidemiologic studies investigating calcium, vitamin D, and milk products and ischemic heart disease, including the prospective design, the use of a large well-defined cohort derived from a general population, the validated

dietary methodology, and the collection of information on both dietary and supplemental intake.

Although we cannot eliminate the possibility that calcium intake is a marker for other dietary factors (or other "healthy lifestyle" factors) related to ischemic heart disease risk, we could not identify such a factor. Although the inverse association remained after adjustment for several risk factors, risk factor levels were self-reported and there may be some residual confounding. We also could not take into account potential risk factors such as blood lipid levels; however, cholesterol levels may, in part, be intermediary mechanisms in the relation of calcium intake to ischemic heart disease and, thus, as with a history of hypertension, be inappropriate covariates in statistical models examining the calcium-ischemic heart disease association.

Calcium, milk products, and blood pressure

There are very few epidemiologic data on the potential relation between calcium, vitamin D, and milk products and the risk of ischemic heart disease (30–36). However, there are substantial amounts of data on the association of these potential dietary risk factors, especially calcium, with blood pressure (reviewed in references 18–20) and cholesterol, both established risk factors for ischemic heart disease (1). Of more than 25 observational studies relating intake of calcium or calcium-rich foods to blood pressure, most, but not all, found some evidence of an inverse association. Notably, of the two prospective studies, the Nurses' Health Study (54) and the Health Professionals' Follow-up Study (55), the risks for developing hypertension were reduced approximately 20–25 percent. In a recent meta-analysis (56), data from 28 active treatment arms or strata from 22 randomized clinical trials with a combined total of 1,231 subjects were pooled. Pooled estimates of the effect of calcium supplementation on blood pressure were a 0.18-mmHg reduction in diastolic blood pressure (not statistically significant) and a statistically significant 0.89-mmHg reduction in systolic blood pressure; stratified by hypertension status, the estimates were systolic blood pressure reductions of 0.53 mmHg in normotensive persons (not statistically significant) and 1.68 mmHg (statistically significant) in hypertensive persons. Results of some trials and the meta-analysis suggest that calcium may be more effective in subsets of individuals. Thus, human intervention studies suggest that calcium can lower systolic blood pressure slightly (1 mmHg) and that it may do so to a greater extent in certain not yet clearly defined subsets of individuals. Possibly more importantly, there is some support for the hypothesis that long-term consumption of higher calcium, aside from its minimal ability to act pharmacologically to directly lower blood pressure, may prevent the development of hypertension.

Calcium, vitamin D, milk products, and cholesterol

The biologic plausibility for a calcium-cholesterol association is that calcium is known to bind with bile acids to form insoluble soaps and thus presumably can remove cholesterol entering the gut via the enterohepatic circulation (2–7). Experimental animal evidence supports calcium in amounts equivalent to 1,500–2,000 mg daily in humans as having a serum cholesterol-lowering effect. Supplemental calcium was found to lower serum cholesterol in rats, rabbits, and goats (3, 14, 26–29) but not in young pigs (30); was associated with an increased excretion of fecal bile acids in most (3–7) but not all (28) studies; and was most pronounced when the diet contained higher proportions of saturated fats (4, 7). Increased dietary calcium levels were also shown to reduce both aortic and cardiac cholesterol levels, as well as aortic atherosclerosis, in rabbits (6, 12, 26) (two of three studies) and in goats (14) but not in rats (27) fed hypercholesterolemic rations.

In animal experimental studies, the hypocholesterolemic effect of calcium appeared blunted by a concomitant high vitamin D intake (5, 14), and the aorta developed higher levels of atherosclerosis (14). In rats fed a hypercholesterolemic diet, the cholesterolemia was blunted by the addition of skim milk powder to the feed (57).

A few small clinical trials have been reported on the relation between calcium and vitamin D and serum lipids in humans. Several early, small, clinical trials testing the efficacy of calcium supplements in lowering total cholesterol found proportional reductions ranging from 5 percent to 34.5 percent (7, 22, 23, 25); however, all had substantial limitations (e.g., uncontrolled designs). Three more recent studies with more rigorous designs found statistically significant proportional reductions in low density lipoprotein cholesterol of 4.4–11 percent (15–17) without a reduction in high density lipoprotein cholesterol (16, 17). In a randomized, double-blind, placebo-controlled trial in 189 elderly adults, no treatment effect of a single oral dose of 2.5 mg of cholecalciferol on serum cholesterol 5 weeks later was noted (58).

Calcium, vitamin D, milk products, and ischemic heart disease

Based on the results of some ecologic studies (31–34) that populations living in hard water areas (high calcium

content) have lower cardiovascular disease mortality than people living in soft water areas, the association of calcium intake with cardiovascular and coronary heart disease mortality was investigated in a 28-year follow-up in a prospective cohort study of 2,605 Dutch civil servants who completed a limited 1-week food frequency recall in 1953–1954 (35). The findings in that study were not statistically significant, were qualitatively close to null (relative risks for men and women for cardiovascular disease mortality were 0.77 and 0.91, respectively), but were in an inverse direction as in the present study. Blood levels of 25-hydroxyvitamin D_3 were statistically significantly inversely associated with myocardial infarction in a case-control study (n = 179 cases) (37). The odds ratios across the quartiles were 1.00, 0.56, 0.33, and 0.30, with the 95 percent confidence intervals of the latter two figures excluding 1.00. The present study was limited to intake of vitamin D rather than to blood levels and was prospective, and the results were null and not statistically significant. There are few analytical observational epidemiologic data on milk product consumption and the risk of cardiovascular disease (34). Based on the present study, the ecologic data (not reviewed here, but which are mixed and on balance somewhat supportive of the calcium-ischemic heart disease hypothesis), and the limited analytical epidemiologic data available, further analytical epidemiologic investigations are warranted to determine whether there may be sufficient consistency across such studies to suspect a causal relation between calcium, and perhaps vitamin D, and cardiovascular disease.

Summary

There are biologically plausible mechanisms of action for protective effects of calcium against ischemic heart disease. Animal experimental data are supportive. Epidemiologic data are generally supportive as well. Our findings are consistent with a 30–35 percent reduction in ischemic heart disease risk with a high intake of calcium but of no association with vitamin D or milk products. These multivariate-adjusted estimates for calcium were statistically significant, and, when considered in context of the whole body of literature on this subject, we conclude that calcium, but not milk products, or some other unknown factor or factors associated with calcium may reduce the risk of death due to ischemic heart disease.

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