

Calcium, vitamin D, milk consumption, and hip fractures: a prospective study among postmenopausal women¹⁻³

Diane Feskanich, Walter C Willett, and Graham A Colditz

ABSTRACT

Background: Short trials of calcium supplementation show that it reduces loss of bone density in postmenopausal women; longer observational studies do not generally find a lower risk of hip fracture with higher-calcium diets. Fewer studies have focused on vitamin D in preventing postmenopausal osteoporosis or fractures.

Objective: We assessed relations between postmenopausal hip fracture risk and calcium, vitamin D, and milk consumption.

Design: In an 18-y prospective analysis in 72 337 postmenopausal women, dietary intake and nutritional supplement use were assessed at baseline in 1980 and updated several times during follow-up. We identified 603 incident hip fractures resulting from low or moderate trauma. Relative risks (RRs) from proportional hazards models were controlled for other dietary and nondietary factors.

Results: Women consuming ≥ 12.5 μg vitamin D/d from food plus supplements had a 37% lower risk of hip fracture (RR = 0.63; 95% CI: 0.42, 0.94) than did women consuming < 3.5 $\mu\text{g}/\text{d}$. Total calcium intake was not associated with hip fracture risk (RR = 0.96; 95% CI: 0.68, 1.34 for ≥ 1200 compared with < 600 mg/d). Milk consumption was also not associated with a lower risk of hip fracture (P for trend = 0.21).

Conclusions: An adequate vitamin D intake is associated with a lower risk of osteoporotic hip fractures in postmenopausal women. Neither milk nor a high-calcium diet appears to reduce risk. Because women commonly consume less than the recommended intake of vitamin D, supplement use or dark fish consumption may be prudent. *Am J Clin Nutr* 2003;77:504–11.

KEY WORDS Calcium, vitamin D, milk, diet, hip fracture, osteoporosis, postmenopausal women

INTRODUCTION

Calcium has been the primary focus of nutritional research for the prevention of postmenopausal osteoporosis. Numerous clinical trials of calcium supplementation showed that it can reduce bone loss (1–4) and lower the risk of bone fractures (5–8). However, concomitant treatment with vitamin D makes it difficult to attribute benefits to calcium per se, and the increment in bone density in the first year or two of calcium supplementation may not substantially increase with continued treatment (9, 10). In contrast with the clinical data, most observational studies did not find a significant association between calcium intake and fracture risk (11–17) or bone loss (18), although a reduced risk of hip fractures was reported in one study (19). Primarily on the basis of

the clinical evidence, the Food and Nutrition Board of the National Academy of Sciences raised the adequate intake for calcium in women > 50 y of age to 1200 mg/d (20).

At low-to-moderate calcium intakes, vitamin D is essential for calcium absorption, yet vitamin D insufficiency is common among older adults (21, 22). In comparison with calcium, few clinical trials have focused on vitamin D and postmenopausal osteoporosis. Reductions in bone loss at the spine (23) and femoral neck (24, 25) were reported, although benefits from additional vitamin D may be seen only at low calcium intakes (26). For fractures, overall incidence was significantly reduced with an annual injection of vitamin D in one study (27); another found no effect of daily vitamin D supplementation on the risk of hip fractures (28). On the basis of available research on the amount of dietary vitamin D required for maintenance of normal serum concentrations of 25-hydroxyvitamin D, the Food and Nutrition Board recently set the adequate daily intake at 10 μg for women 51–70 y of age and 15 μg for women > 70 of age (20).

Milk is a primary source of calcium and vitamin D and therefore might be expected to decrease osteoporotic bone loss and fracture risk, yet research has not generally supported this assumption. Evidence from clinical trials and case-control studies has been mixed (29–34), and several observational studies found no decrease in risk of bone fracture with higher consumption of milk and dairy foods (15, 35, 36). A review of the literature concluded that there is no clear benefit of higher milk or dairy food intake on bone mass or fracture risk in women > 50 y of age but that a benefit is seen in women < 30 (37).

In the present study, we examined calcium and vitamin D intakes, milk consumption, and use of calcium supplements during 18 y of follow-up in a large cohort of postmenopausal women with repeated measures of dietary intake and supplement use. This analysis expands on our earlier research over 12 y of follow-up in this same cohort in which we reported no protective effect against

¹ From the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston (DF, WCW, and GAC), and the Departments of Nutrition (WCW) and Epidemiology (WCW and GAC), Harvard School of Public Health, Boston.

² Supported by grant CA87969 from the National Institutes of Health.

³ Address reprint requests to D Feskanich, Channing Laboratory, 181 Longwood Avenue, Boston, MA 02115. E-mail: diane.feskanich@channing.harvard.edu.

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hip fractures from higher consumption of milk or food sources of calcium during the adult years (15).

SUBJECTS AND METHODS

The Nurses' Health Study (NHS) cohort was formed in 1976 when 121 700 married female registered nurses in 11 US states responded to an initial mailed questionnaire. The women provided a medical history and information on lifestyle and other risk factors related to cancer, heart disease, and other health outcomes. Approximately 98% of the women are white. Follow-up questionnaires have been mailed every 2 y to update individual data and to identify incident diseases. Dietary intake was initially assessed in 1980 and again in 1984, 1986, 1990, and 1994. Multivitamin use was included on the questionnaire in 1980, and use of a specific calcium or vitamin D supplement was first added in 1982; multivitamin and supplement use were then included on all subsequent biennial questionnaires. At least 90% of the cohort has responded in each questionnaire cycle. Deaths are confirmed through the National Death Index (38).

This analysis began in 1980 with the postmenopausal women who responded to the initial dietary questionnaire and had not reported a previous hip fracture or a diagnosis of cancer, heart disease, stroke, or osteoporosis ($n = 27\,532$). Eligible premenopausal women entered analysis in the follow-up cycle in which they became postmenopausal. A total of 72 337 women contributed to this study with follow-up through 1998. The NHS was approved by the Institutional Review Board of the Brigham and Women's Hospital, Boston, and the subjects gave their written informed consent.

Hip fractures

Participants were asked to report all previous hip fractures (date, exact bone site, and circumstances leading to the fracture) on the 1982 questionnaire, and incident fractures were reported on subsequent biennial questionnaires. Cases in this study included only fractures of the proximal femur that were caused by low or moderate trauma (eg, slipping on ice, falling from the height of a chair). Fractures caused by high trauma (eg, skiing, falling down a flight of stairs) were excluded from analysis ($\approx 15\%$ of the reported fractures). Over the 18 y of follow-up, we identified 603 hip fracture cases among the study population. The median age at fracture was 65 y. We relied on self-reported hip fractures in this cohort of registered nurses. In a small validation study, all 30 reported hip fractures were confirmed by medical records (39).

Diet and supplement use

Diet was assessed with a semiquantitative food-frequency questionnaire (FFQ) on which participants reported their frequency of consumption for specified foods over the previous year. Dairy foods on the FFQ included milk (whole, low fat, and skim), cheese (cottage or ricotta, cream cheese, and other cheese), cream or sour cream, yogurt, ice cream, and frozen yogurt or low-fat ice cream. Dietary nutrient intakes (ie, calcium, vitamin D, retinol, protein, vitamin K, alcohol, and caffeine) were calculated on the basis of the nutrient content of foods derived primarily from US Department of Agriculture sources and supplemented with data from food manufacturers and published research.

Total nutrient intakes were calculated by adding the amounts from multivitamins and from specific supplements to the intakes from food. Participants provided the name brand of multivitamins

and the number of tablets taken per week. For calcium supplements, participants specified their dose per day (< 400 , 400–900, 901–1300, or ≥ 1300 mg). Reported use of a specific vitamin D supplement was assumed to be 10 $\mu\text{g}/\text{d}$.

Nutrient intakes that are correlated with total energy intake (all except alcohol and caffeine) were adjusted for total energy with the use of regression analysis (40). To generate the best estimates of long-term intake, values were cumulatively updated in the statistical analyses. That is, at the beginning of every 2-y follow-up cycle, each nutrient intake was calculated as the mean of all reported intakes up to that time. Cumulative updating ceased when a woman reported a diagnosis of osteoporosis because it was likely that she would then change her diet or begin using supplements. During the 18 y of follow-up, 7466 women (10%) reported a diagnosis of osteoporosis.

The accuracy of the food and nutrient intakes from the FFQ was assessed in several validation studies. In a comparison of the baseline 1980 FFQ with four 1-wk diet records among 173 NHS women, correlations were 0.81 for skim or low-fat milk and 0.62 for whole milk (41). For dietary calcium, the correlation was 0.75 when intakes from the 1986 FFQ and two 1-wk diet records were compared among 191 NHS women (42). To assess the accuracy of our measure of vitamin D intake, we compared it with serum concentrations of 25-hydroxyvitamin D among 343 NHS women. Although serum concentrations are influenced by sun exposure as well as diet, we found a positive correlation of 0.25 ($P < 0.001$).

Nondietary measures

Postmenopausal hormone use, smoking (including number of cigarettes/d), and weight data were requested on all biennial questionnaires, and body mass index (in kg/m^2) was calculated by using the height reported on the initial 1976 questionnaire. Physical activity was reported in 1980, 1982, 1986, 1988, 1992, 1994, and 1996, and the number of hours per week spent in moderate or vigorous leisure-time activities was totalled. Use of thiazide diuretics and thyroid hormone (13% and 12%, respectively, of the study population) was not associated with either calcium or vitamin D intake and was therefore not included in analyses. Steroid use was not ascertained until 1994. Although use was higher among subsequent hip fracture cases (8%) than among noncases (2%), it was unrelated to intakes of calcium and vitamin D, and results were unchanged when steroid users were excluded from analyses.

Statistical analysis

Each participant contributed person-time from the return date of the 1980 questionnaire or the questionnaire on which she first became postmenopausal until the occurrence of a hip fracture, death, or the end of follow-up on 1 June 1998. A total of 860 355 person-years was accrued from the 72 337 women in this analysis. Current exposure and covariate data were used to allocate person-time to the appropriate category for each variable at the beginning of every 2-y follow-up cycle. Age-adjusted incidence rates were calculated within categories of calcium, vitamin D, and the other food and nutrient exposures, and relative risks (RRs) were calculated as the ratio of the rate in each upper category compared with the rate in the lowest category. We used Cox proportional hazards models (43) to compute multivariate RRs, adjusting simultaneously for the other risk factors for hip fracture. To assess a dose-response effect, a P value for linear trend was determined by entering the exposure variables into the models as continuous values.

TABLE 1

Age-standardized characteristics of postmenopausal women in the Nurses' Health Study ($n = 72\,337$) in the lowest, middle, and highest consumption categories of calcium, vitamin D, and milk¹

	Total calcium (mg/d)			Dietary calcium (mg/d)			Total vitamin D ($\mu\text{g/d}$)			Dietary vitamin D ($\mu\text{g/d}$)			Milk (glasses/wk) ²		
	<600	800–999	≥ 1200	<500	625–749	≥ 900	<3.5	6.0–8.9	≥ 12.5	<2.5	3.75–4.99	≥ 6.25	<1	4–6.9	≥ 10.5
Age (y)	58.3	59.8	60.8	58.5	59.8	59.8	58.1	60.0	60.2	58.0	59.9	60.4	58.5	60.3	60.1
BMI (kg/m^2)	25.7	25.9	25.6	25.4	25.9	26.0	25.7	26.0	25.5	25.4	25.9	25.9	25.4	26.0	26.0
Physical activity (h/wk)	2.5	2.9	3.2	2.5	2.9	3.0	2.6	2.9	3.1	2.6	2.9	3.0	2.7	2.9	2.9
Current smoker (%)	27	17	14	26	18	18	27	17	17	28	18	16	25	17	18
Daily intake															
Milk (glasses) ²	0.3	1.0	1.6	0.2	0.7	1.9	0.3	1.2	1.2	0.2	0.8	1.9	0.1	0.8	2.3
Calcium (mg)															
Food + supplements	487	895	1443	543	848	1238	604	942	1116	618	858	1186	655	891	1173
Food only	475	763	1004	423	686	1089	537	791	856	502	695	1032	516	715	1030
Vitamin D (μg)															
Food + supplements	4.7	8.1	12.4	5.1	7.5	11.2	2.3	7.4	16.9	4.6	7.6	11.8	5.7	8.0	10.6
Food only	2.6	4.8	6.8	2.4	4.2	7.4	2.3	5.3	5.9	1.7	4.4	8.0	2.5	4.6	7.2
Retinol (μg)	1046	1392	2135	1139	1382	1769	653	1193	3075	1168	1378	1775	1300	1410	1589
Protein (g)	70	76	81	69	74	82	72	76	79	72	74	80	72	75	80
Vitamin K (μg)	162	189	204	160	190	195	177	184	197	180	188	185	188	187	178
Caffeine (mg)	352	345	313	328	347	334	388	330	302	383	340	301	370	330	317
Alcohol (g)	8.3	6.2	4.9	9.4	6.4	4.4	8.4	5.9	5.4	9.9	6.1	4.0	8.2	6.2	5.0
Current use (%)															
Postmenopausal hormones	26	36	45	32	36	34	28	37	39	31	36	36	32	38	34
Multivitamins	29	45	60	36	43	48	14	41	85	37	43	48	38	45	47
Calcium supplements	17	43	72	36	43	41	27	41	58	37	43	41	39	44	40
Vitamin D supplements	1	2	4	2	2	2	1	2	4	2	2	2	2	2	2

¹Values are a mean or percentage of the population within each category and are standardized to the age distribution of the study population over follow-up, 1980–1998. $P < 0.05$ in tests for linear trend in all models except the following: dietary calcium and caffeine ($P = 0.23$) and milk and vitamin D supplement use ($P = 0.15$). Total calcium and vitamin D include intakes from supplements. Dietary calcium and vitamin D include intakes from foods only. The lowest, middle, and highest categories are 3 of the 5 consumption categories used in Tables 3 and 4.

²One glass of milk = 240 mL or 8 fluid oz.

RESULTS

Milk consumption and intakes of calcium and vitamin D from food were fairly stable among the postmenopausal women in the study population over the 18 y of follow-up. Mean daily intakes were ≈ 240 mL (one glass) milk, 730 mg Ca from food, and 5 μg vitamin D from food. During follow-up, multivitamin use increased from 35% to 53% of the population and calcium supplement use increased from 14% to 51%, and <5% of the population ever reported use of vitamin D supplements.

At the final dietary assessment in 1994, calcium supplements contributed 27% of the total calcium intake and multivitamins contributed 37% of the total vitamin D intake. On the basis of the standards set by the Food and Nutrition Board of the National Academy of Sciences (20), only 36% of the NHS women had an adequate calcium intake and only 41% had an adequate vitamin D intake.

Age-standardized characteristics of the study population by calcium, vitamin D, and milk intakes are shown in **Table 1**. Multivitamin and calcium supplement use were high among the women in the highest consumption categories for total calcium (60% and 72%, respectively) and total vitamin D (85% and 58%, respectively), and multivitamin use was also more likely among women with diets that were already higher in calcium or vitamin D. Consistent with multivitamin and calcium supplement use, use of postmenopausal hormones was more common among those with the highest total calcium and vitamin D intakes. Women with the lowest milk consumption and the lowest dietary calcium and vitamin D intakes were more likely to smoke and consume alcohol.

The correlations between calcium and vitamin D intakes and the nutrients that come from common dairy and multivitamin sources and that were used as covariates in the multivariate models are shown in **Table 2**. The highest correlation was between total vitamin D and retinol intakes ($r = 0.76$). Total calcium was also highly correlated with total ($r = 0.61$) and dietary ($r = 0.58$) vitamin D.

RRs of hip fracture by calcium and vitamin D intakes are shown in **Table 3**. After age was adjusted for, the first multivariate models (multivariate 1) were adjusted for the nonnutrient covariates and the nutrients that are not supplied by dairy foods and multivitamins. Protein, retinol, and total calcium or vitamin D were

TABLE 2

Correlations between intakes of calcium, vitamin D, and nutrient covariates in multivariate models¹

	Calcium		Vitamin D	
	Total	Dietary	Total	Dietary
Total calcium	—	—	0.61	0.58
Total vitamin D	0.61	0.50	—	—
Retinol	0.42	0.27	0.76	0.30
Protein	0.32	0.40	0.24	0.34

¹Pearson's correlations on \log_e -transformed values. $P < 0.001$ for all correlations. Nutrient intakes are from 61 057 postmenopausal women at the final dietary assessment in 1994. Total calcium and vitamin D include intakes from food plus supplements; dietary calcium and vitamin D include intakes from food sources only.

TABLE 3

Relative risks of hip fracture by calcium and vitamin D intakes among postmenopausal women ($n = 603$) in the Nurses' Health Study, 1980–1998¹

	Person-years	Relative risk (95% CI)					
		Age-adjusted ²	Multivariate 1 ³	Multivariate 1 + protein ⁴	Multivariate 1 + retinol ⁵	Multivariate 1 + calcium or vitamin D ⁶	Multivariate 2 ⁷
Total calcium							
<600 mg/d ($n = 123$)	180829	1.00	1.00	1.00	1.00	1.00	1.00
600–799 mg/d ($n = 168$)	221622	1.02 (0.81, 1.29)	1.15 (0.91, 1.46)	1.16 (0.92, 1.47)	1.13 (0.89, 1.44)	1.19 (0.93, 1.53)	1.20 (0.93, 1.54)
800–999 mg/d ($n = 135$)	189803	0.92 (0.72, 1.17)	1.09 (0.84, 1.40)	1.10 (0.85, 1.43)	1.05 (0.81, 1.37)	1.14 (0.86, 1.50)	1.16 (0.88, 1.54)
1000–1199 mg/d ($n = 96$)	132031	0.89 (0.68, 1.17)	1.12 (0.85, 1.48)	1.13 (0.85, 1.51)	1.06 (0.80, 1.42)	1.16 (0.86, 1.58)	1.19 (0.88, 1.63)
≥1200 mg/d ($n = 81$)	136069	0.70 (0.52, 0.92)	0.90 (0.67, 1.21)	0.91 (0.67, 1.24)	0.83 (0.61, 1.14)	0.93 (0.67, 1.30)	0.96 (0.68, 1.34)
<i>P</i> for trend ⁸		0.003	0.34	0.40	0.13	0.42	0.52
Dietary calcium							
<500 mg/d ($n = 94$)	135799	1.00	1.00	1.00	1.00	1.00	1.00
500–624 mg/d ($n = 140$)	190524	0.99 (0.76, 1.28)	1.11 (0.85, 1.45)	1.19 (0.86, 1.46)	1.09 (0.84, 1.42)	1.13 (0.86, 1.48)	1.13 (0.87, 1.49)
625–749 mg/d ($n = 155$)	195028	1.02 (0.79, 1.32)	1.23 (0.95, 1.60)	1.25 (0.96, 1.63)	1.19 (0.92, 1.56)	1.27 (0.96, 1.67)	1.29 (0.98, 1.71)
750–899 mg/d ($n = 103$)	162783	0.80 (0.60, 1.05)	0.97 (0.73, 1.30)	0.99 (0.73, 1.33)	0.93 (0.70, 1.25)	1.00 (0.74, 1.37)	1.04 (0.76, 1.42)
≥900 mg/d ($n = 111$)	176220	0.79 (0.60, 1.04)	0.99 (0.74, 1.31)	1.00 (0.75, 1.34)	0.93 (0.69, 1.23)	1.01 (0.74, 1.38)	1.08 (0.78, 1.49)
<i>P</i> for trend ⁸		0.006	0.21	0.25	0.08	0.27	0.51
Total vitamin D							
<3.50 μg/d ($n = 122$)	175284	1.00	1.00	1.00	1.00	1.00	1.00
3.50–5.99 μg/d ($n = 149$)	215342	0.87 (0.68, 1.11)	0.93 (0.73, 1.19)	0.94 (0.73, 1.20)	0.86 (0.67, 1.11)	0.88 (0.68, 1.14)	0.82 (0.63, 1.07)
6.00–8.99 μg/d ($n = 126$)	183322	0.81 (0.63, 1.05)	0.93 (0.72, 1.20)	0.94 (0.72, 1.21)	0.80 (0.60, 1.06)	0.88 (0.67, 1.17)	0.77 (0.56, 1.04)
9.00–12.49 μg/d ($n = 98$)	135209	0.83 (0.64, 1.09)	0.96 (0.73, 1.26)	0.97 (0.74, 1.28)	0.77 (0.56, 1.07)	0.94 (0.70, 1.27)	0.75 (0.53, 1.07)
≥12.50 μg/d ($n = 108$)	151198	0.80 (0.61, 1.04)	0.92 (0.70, 1.20)	0.93 (0.71, 1.22)	0.63 (0.43, 0.90)	0.93 (0.68, 1.25)	0.63 (0.42, 0.94)
<i>P</i> for trend ⁸		0.25	0.91	0.97	0.03	0.25	0.09
Dietary vitamin D							
<2.50 μg/d ($n = 121$)	152427	1.00	1.00	1.00	1.00	1.00	1.00
2.50–3.74 μg/d ($n = 134$)	192319	0.79 (0.62, 1.01)	0.87 (0.67, 1.11)	0.87 (0.68, 1.19)	0.84 (0.66, 1.09)	0.81 (0.63, 1.05)	0.80 (0.62, 1.03)
3.75–4.99 μg/d ($n = 146$)	197719	0.76 (0.60, 0.97)	0.85 (0.66, 1.09)	0.85 (0.66, 1.10)	0.81 (0.63, 1.05)	0.76 (0.58, 0.99)	0.74 (0.56, 0.97)
5.00–6.24 μg/d ($n = 95$)	142546	0.65 (0.50, 0.86)	0.77 (0.58, 1.02)	0.77 (0.58, 1.02)	0.72 (0.54, 0.96)	0.70 (0.49, 0.91)	0.65 (0.48, 0.88)
≥6.25 μg/d ($n = 107$)	175345	0.58 (0.45, 0.76)	0.67 (0.51, 0.68)	0.67 (0.51, 0.89)	0.62 (0.47, 0.82)	0.59 (0.43, 0.81)	0.57 (0.41, 0.78)
<i>P</i> for trend ⁸		<0.001	0.004	0.004	<0.001	0.002	<0.001

¹Diet was assessed in 1980, 1984, 1986, 1990, and 1994. Nutrient intakes were cumulatively updated over follow-up. Total intakes include multivitamins and supplements. Dietary intakes are from food sources only.

²Relative risks were adjusted for age.

³Relative risks were adjusted for age, BMI, postmenopausal hormone use, physical activity, smoking, calcium supplement use (dietary calcium model only), multivitamin use (dietary vitamin D model only), and intakes of vitamin K, alcohol, and caffeine.

⁴Relative risks were adjusted for protein intake plus factors in footnote 3.

⁵Relative risks were adjusted for retinol intake plus factors in footnote 3.

⁶Relative risks were adjusted for total vitamin D intake (total and dietary calcium models only) or total calcium intake (total and dietary vitamin D models only) plus factors in footnote 3.

⁷Relative risks were adjusted for intakes of protein, retinol, total vitamin D (total and dietary calcium models only), and total calcium (total and dietary vitamin D models only) plus factors in footnote 3.

⁸*P* for linear association.

then added individually to show how each affects the RRs. The final model (multivariate 2) includes all covariates simultaneously.

Although higher total calcium intake from food plus supplements was associated with a lower risk of hip fracture in the simple age-adjusted analysis, no inverse association remained in the multivariate 1 model. The RR for hip fracture was 0.90 (95% CI: 0.67, 1.21; *P* for trend = 0.34) for women consuming ≥1200 mg/d compared with those consuming <600 mg/d. No one variable was primarily responsible for attenuation of the age-adjusted results; the addition of physical activity, smoking, and postmenopausal hormone use all increased the RR. Further addition of protein, retinol, and total vitamin D to the model had little effect on the RR associated with total calcium intake (RR = 0.96; 95% CI: 0.68, 1.34; *P* for trend = 0.52).

When calcium intake was limited to food sources only, we observed the same attenuation of the age-adjusted results when the multivariate 1 covariates were added to the model, and no

evidence of an inverse association between dietary calcium and hip fractures remained in the final multivariate 2 model with protein, retinol, and total vitamin D (RR = 1.08; 95% CI: 0.78, 1.49 for ≥900 compared with <500 mg/d; *P* for trend = 0.51). Although this analysis was adjusted for calcium supplement use, we performed an alternate analysis, excluding women when they reported using calcium supplements, to better focus on the effects of dietary calcium. However, a dietary calcium intake of ≥900 mg/d was still not associated with any reduction in fracture risk (RR = 1.33; 95% CI: 0.79, 2.23; *P* for trend = 0.67).

To further examine total calcium, we performed a separate analysis limited to women ≥65 y of age but still failed to find evidence of a reduced risk of hip fracture with a daily intake of ≥1200 mg (RR = 0.87; 95% CI: 0.54, 1.41; *P* for trend = 0.45). There was also no significant reduction in risk with intakes of ≥1500 mg/d (RR = 0.83; 95% CI: 0.50, 1.38). Previous research showed that a high calcium intake potentiates the positive

TABLE 4

Relative risks of hip fracture by frequency of consumption of milk and dark fish among postmenopausal women in the Nurses' Health Study, 1980–1998

	Person-years	Relative risk (95% CI)	
		Age-adjusted ¹	Multivariate ²
Milk³			
<1 time/wk (<i>n</i> = 137)	192409	1.00	1.00
1–3.9 times/wk (<i>n</i> = 153)	194209	1.01 (0.80, 1.27)	1.13 (0.89, 1.44)
4–6.9 times/wk (<i>n</i> = 94)	151797	0.73 (0.56, 0.95)	0.85 (0.65, 1.12)
1–1.4 times/d (<i>n</i> = 112)	154176	0.90 (0.70, 1.16)	1.02 (0.78, 1.33)
≥1.5 times/d (<i>n</i> = 107)	167763	0.75 (0.58, 0.96)	0.83 (0.61, 1.10)
<i>P</i> for trend ⁴		0.06	0.21
Dark fish⁵			
<1 time/mo (<i>n</i> = 242)	333061	1.00	1.00
1–3 times/mo (<i>n</i> = 171)	242190	0.85 (0.70, 1.04)	0.94 (0.77, 1.16)
1 time/wk (<i>n</i> = 33)	56149	0.70 (0.48, 1.00)	0.76 (0.52, 1.12)
>1 time/wk (<i>n</i> = 10)	20291	0.53 (0.28, 1.00)	0.67 (0.35, 1.28)
<i>P</i> for trend ⁴		0.002	0.03

¹Relative risks were adjusted for age.²Relative risks were adjusted for age, BMI, postmenopausal hormone use, physical activity, smoking, multivitamin use, calcium supplement use (milk model only), vitamin A supplement use (milk model only), and intakes of total calcium (dark fish model only), retinol (dark fish model only), protein, vitamin K, alcohol, caffeine, and total energy.³Consumption was assessed in 1980, 1984, 1986, 1990, and 1994, and frequency of intake was cumulatively updated over follow-up from 1980 to 1998. Frequency is based on a 240-mL (8-fluid oz) glass.⁴*P* for linear association.⁵Consumption was assessed in 1984, 1986, 1990, and 1994, and frequency of intake was cumulatively updated over follow-up from 1984 to 1998. Frequency is based on an 85–142-g (3–5-oz) serving.

effect of estrogen on bone mass (44). We did find the suggestion of a lower risk of hip fracture among women currently using postmenopausal hormones who had a total calcium intake of ≥ 1200 mg/d (RR = 0.61; 95% CI: 0.36, 1.02) than among the hormone users consuming < 600 mg/d (RR = 0.80; 95% CI: 0.49, 1.32) when both were compared with the women not taking postmenopausal hormones and with a daily calcium intake of < 600 mg, although the results were not statistically significant.

As observed for calcium, the inverse (nonsignificant) association between total vitamin D intake and hip fractures was attenuated after the multivariate 1 covariates were adjusted for (Table 3). However, after further adjustment for retinol, a significant inverse association was evident. In the final multivariate 2 model, a total intake of ≥ 12.5 μg vitamin D/d was associated with a 37% lower risk of hip fracture (RR = 0.63; 95% CI: 0.42, 0.94; *P* for trend = 0.09) than was a daily intake of < 3.5 μg . The addition of retinol to the model did not create instability; the SEs associated with the RRs for total vitamin D did not increase. We also checked for interaction between total vitamin D and retinol, but the interaction was not significant (*P* = 0.61) and it did not change the main effects of vitamin D and retinol.

Dietary vitamin D provided further evidence of a protective effect. The addition of any covariates did little to attenuate the age-adjusted results. In the final multivariate 2 model, ≥ 6.25 μg dietary vitamin D/d was associated with a 43% lower risk of hip fracture (RR = 0.57; 95% CI: 0.41, 0.78; *P* for trend < 0.001) than was an intake of < 2.5 $\mu\text{g}/\text{d}$. Although sun exposure may also contribute substantially to vitamin D status, we observed an inverse association between both total and dietary vitamin D intakes and hip fractures among women living in the southern states and among those living in the northern states.

Adequate vitamin D is necessary for maximal absorption of calcium and is most essential at lower calcium intakes. Therefore, we examined total calcium and vitamin D together as a 9-category variable, with 3 calcium intakes (< 600 , 600–999, and ≥ 1000 mg/d)

and 3 vitamin D intakes (< 5 , 5–9.9, and ≥ 10 $\mu\text{g}/\text{d}$). Women in the low-calcium but high-vitamin D category (RR = 0.54; 95% CI: 0.28, 1.05) and in the high-calcium and high-vitamin D category (RR = 0.74; 95% CI: 0.50, 1.07) had a nonsignificantly lower risk of hip fracture than did women in the low-calcium and low-vitamin D category. There was no reduction in risk among those in the high-calcium but low-vitamin D category (RR = 1.27; 95% CI: 0.77, 2.11).

Milk is a major food source of calcium and vitamin D, contributing $\approx 36\%$ of the dietary calcium and 42% of the dietary vitamin D in this population. It also contributed significant amounts of retinol ($\approx 19\%$), which was previously associated with an increased risk of hip fracture in this cohort (45). In the present study, higher milk consumption conferred a weak, nonsignificant reduction in fracture risk (Table 4). Women consuming ≥ 360 mL (1.5 glasses)/d had an RR of 0.83 (95% CI: 0.61, 1.10) compared with women who consumed < 240 mL (1 glass)/wk. However, we did not observe a dose-response relation (*P* for trend = 0.21), and with higher daily intakes of ≥ 600 mL (2.5 glasses) milk, there was still no evidence of a protective effect (RR = 0.86; 95% CI: 0.63, 1.18). These analyses were not controlled for calcium, vitamin D, or retinol intakes because milk is a package containing all these nutrients, but they were adjusted for the use of multivitamins, calcium, and vitamin A supplements. As we did for dietary calcium, we reanalyzed milk consumption among women who never used calcium supplements, but we continued to find no evidence of an inverse association with hip fractures (RR = 1.10; 95% CI: 0.73, 1.63 for ≥ 360 mL (1.5 glasses)/d).

In contrast to milk, dark fish (eg, swordfish, salmon, bluefish, mackerel, sardines), a good source of vitamin D, was associated with a 33% lower risk of hip fracture (RR = 0.67; 95% CI: 0.35, 1.28) when consumed > 1 time/wk than when consumed < 1 time/mo (Table 4). Although this categorical risk reduction was not statistically significant, the dose-response relation was significant (*P* for trend = 0.03). Dark fish contributed 12% of the dietary vitamin D in this cohort.

It is difficult to evaluate associations between calcium supplement use and hip fractures in an observational study because women at higher risk or with a family history of osteoporosis are more likely to take supplements, thereby driving a possible inverse association toward the null. Current use of calcium supplements was not associated with a lower risk of hip fracture in this population (RR = 1.01; 95% CI: 0.84, 1.23). Because previous research showed that gains in bone mineral density with calcium supplementation in older women are lost within 2 y after discontinuation of the supplement (46), we compared the women in this population who were continuous calcium supplement users during follow-up with the women who never used calcium supplements. The continuous users had a modest but not significantly reduced risk of hip fracture (RR = 0.80; 95% CI: 0.49, 1.28). The reduction was more substantial when the analysis was limited to women with dietary calcium intakes < 625 mg/d (RR = 0.38; 95% CI: 0.15, 0.99), although the interaction between calcium supplement use and dietary calcium was not significant ($P = 0.34$).

DISCUSSION

In this prospective study of postmenopausal women, we observed a significantly lower risk of hip fracture among those with higher vitamin D intakes, whether from food alone or from food plus supplements. Overall, calcium intake did not appear to be associated with fracture risk.

Adequate vitamin D is important in the prevention of postmenopausal bone loss. At low-to-moderate intakes, calcium absorption is largely dependent on the action of 1,25-dihydroxyvitamin D for active transport. Insufficient vitamin D leads to reduced calcium absorption, elevated blood concentrations of parathyroid hormone, and increased rates of bone resorption, which over time may lead to bone fracture. Case-control studies showed that older people who experience a hip fracture have lower serum concentrations of 25-hydroxyvitamin D than do those without a fracture (47).

Vitamin D insufficiency is common among older adults, with reported prevalences between 25% and 50% of the population (21, 22), and is particularly high among the institutionalized elderly. Skin exposure to sunlight is a major source of vitamin D, but older adults may spend little time in the sun, and the increased use of sunscreens to prevent skin cancers significantly reduces cutaneous production (48). Also, synthesis of vitamin D is absent during the 3 or 4 mo of winter in higher latitudes (49). With aging, vitamin D status may be further compromised by a decreased capacity of the skin to manufacture cholecalciferol (50), a reduced ability of the liver or kidney to hydroxylate vitamin D to its metabolically active form (51), or a lower consumption of dairy foods or diminished intestinal absorption of vitamin D (52).

Dietary supplementation with vitamin D in older women was shown to improve bone health. Among healthy postmenopausal women in the United States, a significantly greater improvement in spinal bone density was seen after 1 y with a daily intake of 12.5 μg (0.85%) than with 2.5 μg (0.15%) vitamin D (23), and women supplemented with 17.5 $\mu\text{g}/\text{d}$ for 2 y lost significantly less bone density at the femoral neck (1.1%) than did those with a 2.5- μg vitamin D supplement (2.5%; 24). In Denmark, supplementation in elderly women with 10 μg vitamin D/d increased bone mineral density at the femoral neck by 2.6% after 2 y (25), although in a recent trial, 15 μg 25-hydroxyvitamin D/d did not perform as well as 750 mg Ca in attenuating femoral bone loss

over 4 y because its effects were seen only at low calcium intakes (26). In an elderly Finnish population, the overall fracture rate was significantly reduced after 4 y with an annual injection of 150 000–300 000 IU ergocalciferol (27), yet incidence of hip fractures was not affected by daily supplementation with 10 μg vitamin D for > 3 y among elderly Danish men and women (28).

Vitamin D deficiency can lead to loss of muscle strength (53) and an increased likelihood of falling, which in turn increases the risk of hip fracture (54). In 1990, we asked participants if they had difficulty with their balance, and in 1998, we asked for the number of times they fell in the past year. Neither measure was associated with calcium or vitamin D intake and therefore would not be expected to influence the risk of hip fracture associated with these nutrients.

Sufficient calcium intake is necessary to replace obligatory losses. Otherwise, the body will extract calcium from the bone to maintain calcium balance. Numerous clinical trials showed reduced bone loss and fracture risk with calcium supplementation (1–10), particularly in cortical bone (55) and among older postmenopausal women and women with low-calcium diets (56). However, many of the clinical protocols also included vitamin D supplements, making it difficult to discern the relative benefits of the 2 treatments. One 4-y trial that did compare calcium (750 mg/d) and oral 25-hydroxyvitamin D (15 $\mu\text{g}/\text{d}$) treatments in older men and women found calcium to be more beneficial (26); the calcium group experienced minimal loss of bone density at the hip (1.0%), whereas the loss in the vitamin D group (2.7%) was more similar to that in the placebo group (3.0%). In the present study, our data from the NHS cohort were not consistent with this finding. We observed a lower risk of hip fracture with a higher calcium intake only when accompanied by a higher intake of vitamin D.


Longitudinal studies have not generally supported the clinical research on calcium intake. Most found no significant association with bone loss or fracture risk (11–18). One major difference between these 2 types of research is the length of study. Over the 1 or 2 y of most clinical trials, the bone remodeling space can assimilate the additional calcium, thereby slightly increasing measured bone density, typically by $\approx 2\%$. However, density does not continue to increase greatly once this space is filled, and gains in bone density are lost when the calcium supplementation ends. Several clinical trials noted that most of the reduction in bone loss with calcium supplementation occurred in the first year (9, 10), and 2 y after one of these trials ended, there were no lasting benefits in density at any bone site (46).

The lost benefit in bone density after withdrawal of calcium supplementation or a high-calcium diet might help to explain the lack of association between calcium intake and hip fractures in observational studies. Most of these studies identify hip fractures over many years, yet diet is typically assessed only once at baseline, despite the likelihood that food consumption and calcium supplement use may change over time. However, in the present study, dietary intake was assessed 5 times and supplement use was updated every 2 y over the 18 y of follow-up, and in analyses we calculated a long-term measure of total calcium intake with cumulative intake data. Still, we found no evidence that higher calcium intake is associated with a reduced risk of hip fracture. However, among the NHS women with low dietary calcium, continuous use of calcium supplements was associated with a lower risk of fracture, consistent with the hypothesis that a steady intake of sufficient calcium is necessary for maintenance of bone health.

Milk is a good source of both calcium and vitamin D, yet fortified milk also contains significant amounts of vitamin A, which

has been associated with an increased risk of hip fracture (45, 57). In this study among postmenopausal women, milk was not associated with a decreased risk of hip fracture, even among those drinking 600 mL (2.5 glasses)/d. It is possible that we did not observe an inverse association because the women who selected to consume more milk did so because they were known to be at higher risk of osteoporosis. However, previous research also did not provide clear evidence to suggest that higher milk consumption during the adult years reduces osteoporotic bone loss or fracture risk. In a review of the literature (37), only 2 of 14 studies in adults > 50 y of age showed a positive association between dairy foods and bone health. In one of these positive studies, a daily milk powder supplement containing 1 g Ca minimized loss of bone density at the femoral neck (0.2%) compared with a placebo (0.7%) after 2 y in older postmenopausal women (31); in the other, low milk consumption was a significant risk factor for hip fracture in women > 50 y of age from several southern European countries, but it did not remain significant in a multivariate analysis (33). In a subsequent clinical trial among 60 older postmenopausal women, those assigned to drink 4 glasses milk/d sustained less loss of bone density at the greater trochanter (1.5%) after 2 y than did the placebo group (3.0%), although milk did not reduce bone loss at the femoral neck (34).

The major strength of the present study is the repeated assessment of diet and supplement use over the 18 y of follow-up, which allowed us to calculate average long-term intakes. Another strength is the identification of hip fractures, rather than the measurement of bone density, because fractures are the true public health concern. Our results may be limited to white women and to those residing in latitudes similar to those of the United States.

In conclusion, our study adds to the evidence that adequate vitamin D intake is associated with a lower occurrence of osteoporotic hip fractures in postmenopausal women. A high-calcium diet appears to be of less importance. Although fortified milk is one of the few food sources of vitamin D, high consumption does not appear to substantially reduce the risk of hip fracture, perhaps because of other nutrients in the milk, such as vitamin A, that do not support bone health. Because women commonly consume less than the recommended daily intake of vitamin D and additional exposure to sunlight can increase the risk of skin cancer, use of supplements or more frequent consumption of dark fish may be prudent. 

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