

# Low Fractional Calcium Absorption Increases the Risk for Hip Fracture in Women with Low Calcium Intake

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**Background:** Decreased ability to absorb calcium with age limits adaptation to low calcium intake and is thought to lead to secondary hyperparathyroidism and increased risk for hip and other fractures. However, the associations between fractional calcium absorption, dietary calcium intake, and risk for fracture have never been studied.

**Objective:** To determine whether low fractional calcium absorption in women with low calcium intake increases the risk for subsequent hip and other nonspine fractures.

**Design:** Prospective cohort study.

**Setting:** Four clinical centers in Baltimore County, Maryland; Portland, Oregon; Minneapolis, Minnesota; and the Monongahela Valley, Pennsylvania.

**Participants:** 5452 nonblack women 69 years of age or older participating in the fourth examination of the Study of Osteoporotic Fractures.

**Measurements:** Fractional calcium absorption was measured by using a 3-hour single isotope ( $^{45}\text{Ca}$ ) technique. Incident fractures were identified prospectively and were confirmed by radiographic report.

**Results:** During an average of 4.8 years, 729 women (13%) experienced at least one nonspine fracture; 153 of these women had hip fractures. After adjustment for age, women with lower fractional calcium absorption were at increased risk for hip fracture (relative risk per 1-SD [7.7%] decrease in fractional calcium absorption, 1.24 [95% CI, 1.05 to 1.48]). Women with low fractional calcium absorption and low calcium intake were at greatest risk for subsequent hip fracture; among women whose dietary calcium intake was less than 400 mg/d, those who had fractional calcium absorption at or below the median value of 32.3% had a 2.5-fold (CI, 1.29-fold to 4.69-fold) increase in risk for hip fracture compared with those who had greater absorption efficiency. Fractional calcium absorption was not related to risk for other nonspine fractures (relative risk per 1-SD [7.7%] decrease in fractional calcium absorption, 1.05 [CI, 0.96 to 1.14]).

**Conclusions:** In elderly women, low fractional calcium absorption in the setting of low calcium intake increases the risk for hip fracture. Our findings support the hypothesis of type II osteoporosis, which postulates that decreased calcium absorption is an important risk factor for hip fracture in older persons.

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The fraction of calcium absorbed from the gut (fractional calcium absorption) varies widely from person to person, ranging from 10% to 70% (1–3). Cross-sectional studies in postmenopausal women have suggested that fractional calcium absorption increases with decreasing dietary calcium intake and decreases with advancing age (1, 4). It has been hypothesized that decreased ability to absorb calcium with age limits adaptation to low calcium intake and leads to secondary hyperparathyroidism, greater bone resorption, and increased risk for fracture (5, 6). However, to our knowledge, the association between fractional calcium absorption and subsequent risk for fracture has never been studied.

To test the hypothesis that decreased fractional calcium absorption in older women with low calcium intake increases the risk for hip fracture, we measured fractional calcium absorption in a cohort of 5452 elderly women enrolled in the Study of Osteoporotic Fractures and followed them prospectively for incident hip and other nonspine fractures.

## Methods

### Participants

From September 1986 to October 1988, 9704 women at least 65 years of age were recruited to participate in the baseline examination of the prospective Study of Osteoporotic Fractures. Women were recruited from population-based listings in four areas of the United States: Baltimore County, Maryland; Minneapolis, Minnesota; Portland, Oregon; and the Monongahela Valley, Pennsylvania (7). We excluded black women (because of their low incidence of hip fracture), women who were unable to walk without help, and women who had a history of bilateral hip replacement.

Beginning in August 1992, all surviving participants (93.3% of the original cohort) were invited to participate in a fourth examination, which was completed in July 1994. Of these participants, 6796 (77% of survivors) completed a fourth examination (6301 attended a clinic visit, and 495 had a home visit). Of women who completed a fourth clinic visit, 5452 (87%) had a measurement of fractional cal-

cium absorption and were followed for incident fractures occurring after the fourth examination until 31 May 1997. The appropriate institutional review boards approved the study, and written informed consent was obtained from all participants.

### Fractional Calcium Absorption

Calcium absorption testing was completed in the morning after a 5-hour fast. Participants were instructed not to take any calcium supplements for 12 hours before testing and to abstain from alcoholic beverages for 24 hours before testing. Fractional  $^{45}\text{Ca}$  absorption was estimated from the appearance of  $^{45}\text{Ca}$  in blood after ingestion of 50 g of labeled apple juice (containing 63 mg of calcium) and 120 g of unlabeled Speas Farm apple juice (Sundor Brands, Mt. Dora, Florida). The total calcium load was 215 mg. Labeled  $^{45}\text{Ca}$  was prepared by the Osteoporosis Research Center at Creighton University in Omaha, Nebraska, and was shipped to the four clinic sites, where it was mixed with the unlabeled juice. Actual dosing occurred midway through consumption of a standardized light test meal.

Blood was drawn into a serum separator tube exactly 3 hours after ingestion of the tracer and was allowed to clot at room temperature. Serum was separated within 2 hours of collection and was frozen at  $-70^\circ\text{C}$  until analysis. Frozen serum samples were later shipped on dry ice by overnight delivery to Creighton University, where fractional calcium absorption was estimated by using the single isotope method, as described elsewhere (8, 9).

### Other Measurements

Participants completed a questionnaire and were interviewed at the fourth examination. They were asked about smoking status, physical activity, self-rated health, falls during the previous year, fractures since 50 years of age, and parental history of fracture. Participants were asked to bring all current prescription and nonprescription medications, including supplements and vitamins, to the clinic. Interviewers completed a medication history for each participant, including type of medication or supplement and total daily dosage. We determined use of calcium supplements by asking questions about dose and frequency of use of multivitamins, specific vitamin and mineral supplements, and antacids with calcium. The category of vitamin D supplements included vitamin  $\text{D}_3$ , vitamin  $\text{D}_2$ , and multivitamin supplements containing vitamin D. Dietary calcium intake was estimated by using the validated 60-item Block semi-quantitative food-frequency questionnaire, which was developed from the Second National Health and Nutrition Survey (10, 11). Total calcium intake was calculated by summing dietary

calcium intake (mg/d) and daily dosage of calcium supplements (mg/d).

Body weight and height were measured by using a balance-beam scale and a stadiometer (12). Weight change was calculated by subtracting weight at the baseline examination from weight at the fourth examination. We tested neuromuscular function by determining whether the participant could rise from a chair five times without using her arms. Bone mineral density ( $\text{g}/\text{cm}^2$ ) of the proximal femur was measured by using dual-energy x-ray absorptiometry (QDR 1000, Hologic, Waltham, Massachusetts) (13, 14).

### Ascertainment of Fractures

Every 4 months, we contacted participants about fractures by postcard or by telephone. We were able to complete 98% of these follow-up contacts. All fractures were confirmed by radiographic reports; hip fractures were also confirmed by reviewing preoperative radiographs (15).

We excluded fractures that occurred because of major trauma. Self-reported vertebral fractures were also excluded because most vertebral fractures do not come to medical attention (16). The category "all nonspine fractures" included all nontraumatic, nonvertebral fractures. Wrist fractures were defined as all fractures of the distal radius or ulna, and humeral fractures were defined as fractures of only the proximal humerus. All nonspine fractures that occurred after the fourth examination and before 31 May 1997 were included in our analysis. Follow-up for fractures ranged from 0.6 years to 6.1 years (average follow-up, 4.8 years).

### Statistical Analysis

The association between fractional calcium absorption and potential covariates was assessed by calculating the correlation coefficient between fractional calcium absorption and continuous variables and by examining mean values of fractional calcium absorption according to levels of categorical variables. Potential covariates were factors physiologically related to fractional calcium absorption and known risk factors for hip fracture.

We used proportional hazards models to analyze the association between fractional calcium absorption and risk for fracture, including hip, any nonhip, wrist, and humeral fractures. The relative risk (approximated as hazards ratio) for fracture was expressed per 1-SD decrease in fractional calcium absorption.

To examine whether the effect of fractional calcium absorption on risk for hip fracture could be explained by covariates related to fractional calcium absorption (defined as factors related to fractional calcium absorption at  $P \leq 0.05$ ), we added these

covariates (health status, history of falling, previous fracture, inability to rise from a chair, dietary calcium intake, use of calcium supplements, use of vitamin D supplements, use of thiazide diuretics, bone mineral density at the femoral neck, body mass index, and weight change) to the model that contained age and fractional calcium absorption. Values for correlations between variables in multivariate models were 0.374 or less.

To further assess the effect of calcium intake (dietary and supplemental), vitamin D supplement intake, and age on the association between fractional calcium absorption and risk for fractures (including hip, any nonhip, wrist, and humeral fractures), we stratified participants by dietary calcium intake (<400 mg/d or ≥400 mg/d), use of calcium supplements (yes or no), total calcium intake (<400 mg/d or ≥400 mg/d), use of vitamin D supplements (yes or no), and age (<75 years or ≥75 years). For all of these analyses, fractional calcium absorption was expressed as a continuous variable. In addition, for analyses of hip fracture stratified by calcium intake, fractional calcium absorption was expressed as a categorical variable (≤32.3% [median] or >32.3%). By including interaction terms, we also tested for the possibility of interactions between fractional calcium absorption and such variables as dietary calcium intake (<400 mg/d or ≥400 mg/d), total calcium intake (<400 mg/d or ≥400 mg/d), and age (<75 years or ≥75 years) for the prediction of risk for hip fracture. Finally, we examined the association between fractional calcium absorption and risk for hip fracture in analyses stratified by both dietary calcium intake and use of supplemental vitamin D.

### Role of the Funding Source

Our study was funded by the National Institutes of Health, which had no role in the collection, analysis, or interpretation of the data or in the decision to submit the paper for publication.

## Results

### Characteristics of the Study Sample

Characteristics of the 5452 participants are shown in **Table 1**. Mean fractional calcium absorption (±SD) was 32.8% ± 7.7% (range, 9.7% to 64.3%). Among the 2299 women in the cohort who took supplemental vitamin D (42%), 16% took less than 400 IU/d, 71% took 400 IU/d, and 7% took more than 400 IU/d. Twenty-nine women (0.5%) reported use of calcitonin injections, 30 women (0.6%) reported use of sodium fluoride, and 102 women (1.9%) reported use of etidronate. During an average of 4.8 years of follow-up, 729 women (13%)

**Table 1. Characteristics of Participants at Fourth Examination**

Characteristic	Data
Age, <i>n</i> (%)	
69–74 y	2282 (42)
75–79 y	1871 (34)
80–84 y	890 (16)
≥85 y	409 (8)
Mean age ± SD, y	76.5 ± 4.7
White, <i>n</i> (%)	5436 (99.7)
Walks for exercise, <i>n</i> (%)	2786 (51)
Current smoker, <i>n</i> (%)	294 (5)
Self-reported health status, <i>n</i> (%)	
Excellent or good	4500 (83)
Fair	874 (16)
Poor or very poor	76 (1)
Fall in previous year, <i>n</i> (%)	1657 (30)
Any fracture since 50 years of age, <i>n</i> (%)	1914 (35)
Maternal history of hip fracture, <i>n</i> (%)	592 (11)
Mean dietary calcium intake ± SD, mg/d	598 ± 358
Mean total calcium intake ± SD, mg/d	996 ± 780
Current use of supplemental calcium, <i>n</i> (%)	2456 (45)
Current use of supplemental vitamin D, <i>n</i> (%)	2299 (42)
Current use of oral estrogen, <i>n</i> (%)	984 (18)
Current use of thiazide diuretics, <i>n</i> (%)	1066 (20)
Current use of furosemide diuretics, <i>n</i> (%)	374 (7)
Current use of thyroid hormones, <i>n</i> (%)	660 (12)
Unable to rise from chair without assistance, <i>n</i> (%)	524 (10)
Mean body mass index ± SD, kg/m <sup>2</sup>	26.5 ± 4.7
Mean weight change ± SD, kg*	−0.84 ± 5.04
Mean femoral neck bone mineral density ± SD, g/cm <sup>2</sup>	0.636 ± 0.116
Mean fractional calcium absorption ± SD, %	32.8 ± 7.7

\* Calculated as difference between weight at baseline and weight at fourth examination.

experienced at least one nonspine fracture (153 had hip fractures, 133 had wrist fractures, and 99 had humeral fractures).

### Factors Associated with Fractional Calcium Absorption

Average fractional calcium absorption steadily decreased with advancing age, from 34.3% in persons 69 to 74 years of age to 28.8% in persons at least 85 years of age ( $P < 0.001$  for trend). Decreasing fractional calcium absorption was also associated with greater total calcium intake and increasing weight loss. Increasing fractional calcium absorption was associated with greater body mass index and greater bone mineral density at the femoral neck (**Table 2**). On average, participants who reported use of calcium supplements, supplemental vitamin D, or thiazide diuretics had lower fractional calcium absorption than those who did not. On average, women whose dietary calcium intake was at least 400 mg/d had lower fractional calcium absorption than those whose dietary calcium intake was less than 400 mg/d. Several risk factors for hip fracture were associated with lower fractional calcium absorption, including falling in the past year, previous fracture, poor health status, and inability to rise from a chair. Walking for exercise; smoking status; maternal history of fracture; and use of oral estrogen, furosemide, and thyroid hormones were not related to fractional calcium absorption.

**Table 2. Potential Correlates of Fractional Calcium Absorption**

Characteristic	Participants	Pearson Correlation Coefficient ( <i>P</i> Value)	Mean Fractional Calcium Absorption	<i>P</i> Value for Difference between Means
	<i>n</i>		%	
Age	5452	-0.23 (<0.001)	-	-
Total calcium intake	5452	-0.10 (<0.001)	-	-
Body mass index	5409	0.18 (<0.001)	-	-
Weight change	5445	0.18 (<0.001)	-	-
Femoral neck bone mineral density	4503	0.06 (<0.001)	-	-
Walks for exercise				
Yes	2786	-	32.8	>0.2
No	2651		32.8	
Current smoker				
Yes	294	-	32.7	>0.2
No	5155		32.8	
Health status				
Good to excellent	4500	-	32.9	0.003
Very poor to fair	950		32.1	
Fall in previous year				
Yes	1657	-	32.0	<0.001
No	3788		33.1	
Any fracture since 50 years of age				
Yes	1914	-	32.4	0.002
No	3513		33.0	
Maternal history of hip fracture				
Yes	592	-	32.7	>0.2
No	3587		32.8	
Dietary calcium intake				
<400 mg/d	1814	-	33.3	<0.001
≥400 mg/d	3638		32.5	
Current use of supplemental calcium				
Yes	2456	-	32.0	<0.001
No	2996		33.4	
Current use of supplemental vitamin D				
Yes	2299	-	32.2	<0.001
No	3153		33.2	
Current use of oral estrogen				
Yes	984	-	32.6	>0.2
No	4468		32.8	
Current use of thiazide diuretics				
Yes	1066	-	31.7	<0.001
No	4386		33.1	
Current use of furosemide diuretics				
Yes	374	-	32.4	>0.2
No	5078		32.8	
Current use of thyroid hormones				
Yes	660	-	32.6	>0.2
No	4588		32.8	
Unable to rise from chair without assistance				
Yes	524	-	30.6	<0.001
No	4920		33.0	

### Fractional Calcium Absorption and Risk for Hip Fracture

Women with low fractional calcium absorption had an increased risk for hip fracture. After adjustment for age, each SD (7.7%) decrease in fractional calcium absorption increased the risk for hip fracture by 24% (CI, 1.05 to 1.48) (Table 3). Further adjustment for factors related to fractional calcium

absorption (health status, history of falling, previous fracture, inability to rise from a chair, dietary calcium intake, use of calcium supplements, use of vitamin D supplements, use of thiazide diuretics, bone mineral density at the femoral neck, body mass index, and weight change) did not substantially affect the association between fractional calcium absorption and hip fracture. However, this adjustment

increased the width of the CI (multivariate relative risk for hip fracture per 1-SD [7.7%] decrease in fractional calcium absorption, 1.15 [CI, 0.96 to 1.38]). No single factor explained the association between decreased fractional calcium absorption and risk for hip fracture. The relation between fractional calcium absorption and hip fracture did not change with the addition of each individual factor to a model that contained age and fractional calcium absorption as dependent variables.

The effect of fractional calcium absorption on risk for hip fracture depended on usual calcium intake; women with low fractional calcium absorption and low dietary calcium intake were at greater risk for subsequent hip fracture. Among participants with a dietary calcium intake less than 400 mg/d, women who had fractional calcium absorption at or below 32.3% (median) had a 2.5-fold increase in the risk for hip fracture (age-adjusted relative risk, 2.46 [CI, 1.29 to 4.69]) compared with those who had higher fractional calcium absorption (Figure). In contrast, among participants whose dietary calcium intake was 400 mg/d or greater, the 1.2-fold increase in risk for hip fracture in those with a fractional calcium absorption of 32.3% or less compared with those with higher absorption efficiencies did not reach statistical significance (age-adjusted relative risk, 1.24 [CI, 0.82 to 1.87]). Similar findings were observed in analyses in which fractional calcium absorption was expressed as a continuous variable (Table 4). The interaction between dietary calcium intake (<400 mg/d compared with ≥400 mg/d) and fractional calcium absorption for the prediction of

**Table 3. Association between Fractional Calcium Absorption and Fracture**

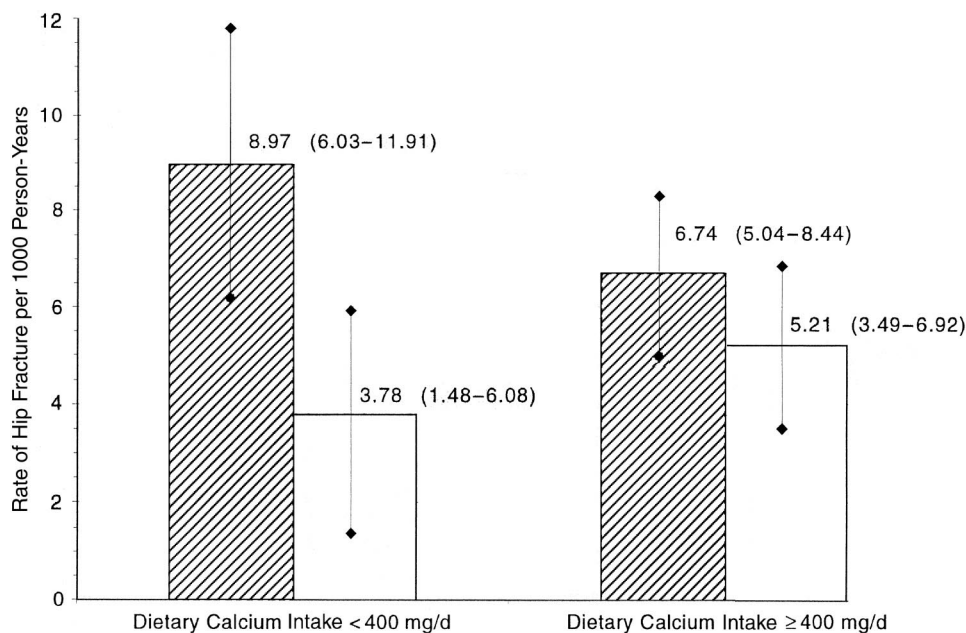
Fracture	Women with Fractures, <i>n</i>	Relative Risk (95% CI)*
Any nonspine	729	1.09 (1.01–1.18)
Hip	153	1.24 (1.05–1.48)
Any nonhip	588	1.05 (0.96–1.14)
Wrist	133	0.95 (0.80–1.14)
Humeral	99	1.04 (0.85–1.27)

\* Age-adjusted relative risk (relative hazard) per 1-SD (7.7%) decrease in fractional calcium absorption.

risk for hip fracture was significant ( $P = 0.049$  for the interaction term). Substitution of total calcium intake (<400 mg/d compared with ≥400 mg/d) for dietary calcium intake in these analyses did not substantially change our results.

Decreased fractional calcium absorption increased the risk for hip fracture among women who were not taking supplemental calcium and those who were not taking supplemental vitamin D (age-adjusted relative risks for hip fracture per 1-SD [7.7%] decrease in fractional calcium absorption, 1.33 [CI, 1.05 to 1.68] and 1.29 [CI, 1.03 to 1.62], respectively) but was not significantly related to risk for hip fracture in women who took these agents (Table 4).

Decreased fractional calcium absorption increased the risk for hip fracture in women at least 75 years of age (age-adjusted relative risk per 1-SD [7.7%] decrease in fractional calcium absorption, 1.51 [CI, 1.25 to 1.82]) but not in women younger than 75 years of age (age-adjusted relative risk per



**Figure.** Age-adjusted rates of hip fracture according to fractional calcium absorption and dietary calcium intake. Striped bars represent fractional calcium absorption of 32.3% (median) or less; white bars represent fractional calcium absorption greater than 32.3%. Numbers in parentheses are 95% CIs for fracture rates.

**Table 4. Fractional Calcium Absorption and Risk for Hip Fracture according to Risk Subgroup**

Risk Subgroup	Women with Hip Fractures, <i>n</i>	Relative Risk for Hip Fracture (95% CI)*
Age		
<75 y	31	0.94 (0.66–1.33)
≥75 y	122	1.51 (1.25–1.82)
Dietary calcium intake		
<400 mg/d	52	1.60 (1.16–2.19)
≥400 mg/d	101	1.10 (0.90–1.36)
Current use of supplemental calcium		
No	84	1.33 (1.05–1.68)
Yes	69	1.15 (0.89–1.48)
Current use of supplemental vitamin D		
No	92	1.29 (1.03–1.62)
Yes	61	1.18 (0.90–1.55)

\* Age-adjusted relative risk (relative hazard) per 1-SD (7.7%) decrease in fractional calcium absorption.

1-SD [7.7%] decrease in fractional calcium absorption, 0.94 [CI, 0.66 to 1.33]). A significant interaction was seen between age (≥75 years compared with <75 years) and fractional calcium absorption for prediction of risk for hip fracture ( $P = 0.02$  for the interaction term).

In analyses stratified by both dietary calcium intake and use of supplemental vitamin D, decreased fractional calcium absorption increased the risk for hip fracture in women with low dietary calcium intake (<400 mg/d) regardless of whether they used vitamin D (Table 5). In women whose dietary calcium intake was at least 400 mg/d, decreased fractional calcium absorption was not associated with risk for hip fracture regardless of supplemental vitamin D use. Similar results were observed when the analysis was stratified by total calcium intake and use of supplemental vitamin D.

### Fractional Calcium Absorption and Risk for Other Nonspine Fractures

Fractional calcium absorption was not related to the risk for other nonspine fractures, including any nonhip, wrist, and humeral fractures (age-adjusted relative risk per 1-SD [7.7%] decrease in fractional calcium absorption, 1.05 [CI, 0.96 to 1.14], 0.95 [CI, 0.80 to 1.14], and 1.04 [CI, 0.85 to 1.27], respectively) (Table 3). In addition, we found that fractional calcium absorption was not associated with the risk for other nonspine fractures, including any nonhip, wrist, and humeral fractures, in analyses stratified by dietary calcium intake, use of supplemental calcium, total calcium intake, use of supplemental vitamin D, and age.

## Discussion

We found that older women with decreased fractional calcium absorption and low calcium intake

had an increased risk for subsequent hip fracture. However, we did not find evidence of an association between fractional calcium absorption and risk for other nonspine fractures. Our findings support the hypothesis of type II osteoporosis, which postulates that decreased calcium absorption is an important risk factor for hip fracture. Our results suggest that supplementation with calcium and vitamin D and efforts to increase dietary calcium intake are most likely to prevent hip fractures in elderly persons with low calcium intakes.

To our knowledge, this is the first prospective study to examine the relation between fractional calcium absorption and risk for hip fracture. In agreement with the results of previous laboratory-based investigations (17, 18), we observed an inverse relation between fractional calcium absorption and calcium intake. Our findings suggest that on average, elderly women with low calcium intake experience a physiologic adaptation in calcium absorption efficiency that increases the amount of calcium absorbed from the gut. Our results indicate, however, that elderly women who do not adapt to low calcium intake with an adequate increase in absorption efficiency are at high risk for subsequent hip fracture.

Failure to adequately increase calcium absorption efficiency in the setting of low calcium intake may be due to estrogen deficiency (19, 20) or to several vitamin D–related factors (including inability of the gut to actively absorb calcium because of vitamin D deficiency caused by sunlight deprivation [21]; defects in synthesis of vitamin D due to kidney disease [22]; or intestinal resistance to vitamin D [23]). A previous randomized trial in institutionalized elderly women with low dietary calcium intake demonstrated that daily supplementation with calcium (1.2 g) and vitamin D (800 IU) reduced risk for hip fracture (24). Similarly, our results suggest that supplementation with calcium and vitamin D is most

**Table 5. Association between Fractional Calcium Absorption and Hip Fracture, Stratified by Dietary Calcium Intake and Use of Vitamin D Supplements\***

Dietary Calcium Intake	Relative Risk (95% CI)†	
	Women Who Did Not Use Vitamin D Supplements	Women Who Used Vitamin D Supplements
<400 mg/d	1.53 (1.06–2.22)	1.85 (1.00–3.40)
≥400 mg/d	1.16 (0.87–1.54)	1.04 (0.76–1.41)

\* Thirty-eight hip fractures occurred among 1122 women who did not use vitamin D supplements and had a dietary calcium intake less than 400 mg/d. Fourteen hip fractures occurred among 691 women who used vitamin D supplements and had a dietary calcium intake less than 400 mg/d. Fifty-four hip fractures occurred among 2029 women who did not use vitamin D supplements and had a dietary calcium intake of 400 mg/d or greater. Forty-seven hip fractures occurred among 1607 women who used vitamin D supplements and had a dietary calcium intake of 400 mg/d or greater.  
† Age-adjusted relative risk (relative hazard) per 1-SD (7.7%) decrease in fractional calcium absorption.

likely to effectively reduce risk for hip fracture in elderly persons with low calcium intake.

We found that decreased fractional calcium absorption increased the risk for hip fracture in women with low calcium intake regardless of use of low-dose supplemental vitamin D. These results suggest that supplementation with low-dose vitamin D alone may not effectively prevent hip fracture in women with decreased absorption and low calcium intake. Our findings are consistent with those of a clinical trial by Lips and colleagues (25), which demonstrated that daily vitamin D supplementation (400 IU) was not effective in reducing risk for hip fracture in elderly persons.

In our cohort of older women, decreased fractional calcium absorption was related to several factors that increase risk for hip fracture, including advanced age, smaller body size, weight loss, lower bone density, poor health status, history of falling, previous fracture, and impaired neuromuscular function. Cross-sectional studies (1–4) have suggested that average fractional calcium absorption steadily decreases with advancing age, and case-control studies (26, 27) have reported that average fractional calcium absorption is lower in osteoporotic persons with one or more vertebral deformities than in normal controls. However, adjustment for these factors did not substantially change the association between fractional calcium absorption and hip fracture.

Observational studies examining the relation between calcium intake and risk for hip fracture have produced conflicting results (28–43). Most studies, including one from our cohort (42), have not found clear evidence of a beneficial effect of calcium on incidence of hip fracture. Our findings suggest that the association between fractional calcium absorption and risk for hip fracture depends on the level of usual calcium intake; this indicates that fractional absorption of calcium must be considered in evaluations of the association between calcium intake and fracture.

We found no evidence that decreased fractional calcium absorption was related to risk for other nonspine fractures in elderly women. Similarly, a previous case-cohort analysis in our cohort (44) suggested that elderly women with low levels of 1,25-dihydroxyvitamin D were at increased risk for hip fractures but not for vertebral fractures. The findings from both analyses are consistent with the theory of type II osteoporosis (5, 6, 45), which postulates that hip fractures are the primary manifestation of the secondary hyperparathyroidism that results from age-related decreases in calcium intake and calcium absorption mediated by 1,25-dihydroxyvitamin D. In contrast to these findings and in support of an association between impaired metab-

olism of calcium and vitamin D and increased risk for nonhip fractures, a trial in elderly institutionalized women who had low calcium intake and were at risk for vitamin D deficiency (24) showed that daily supplementation with calcium and vitamin D reduced the risk for nonhip, nonspine fractures. In addition, another, smaller trial reported that daily supplementation with calcium and vitamin D in elderly men and women significantly reduced the risk for any nonspine fractures despite causing only modest gains in bone mineral density (46). However, neither of these trials measured fractional calcium absorption.

Our study has several limitations. The participants were elderly, community-dwelling white volunteers; our findings may not apply to other populations. We were not able to examine the association between fractional calcium absorption and risk for spine fracture because spine radiographs were not obtained at the fourth examination or during follow-up. The limited range of supplemental vitamin D doses used by the women in our cohort did not allow us to examine the relation between fractional calcium absorption and fracture according to dose of supplemental vitamin D. Although we had power of 0.8 to detect hazard ratios (per 1-SD decrease in fractional calcium absorption) of 1.30 for hip fracture and 1.12 for any nonspine fracture, our power for subgroup analyses was limited. Finally, fractional calcium absorption may affect risk for hip fracture through several mechanisms. Measurements of mediating factors, such as 1,25-dihydroxyvitamin D, endogenous estrogen levels, and renal calcium excretion, were not available for a sufficient number of participants to allow us to examine the pathway between low fractional calcium absorption and hip fracture.

We conclude that elderly women with decreased fractional calcium absorption and low calcium intake are at increased risk for hip fracture. These findings support the theory that type II (senile) osteoporosis contributes to an increased risk for hip fracture. Together with evidence from randomized trials, our results suggest that supplementation with calcium and vitamin D or interventions to increase dietary calcium intake are most likely to be effective in reducing risk for hip fracture in elderly persons with low calcium intake.

### **Appendix: Investigators in the Study of Osteoporotic Fractures Research Group**

University of California, San Francisco (Coordinating Center): S.R. Cummings (*principal investigator*), M.C. Nevitt (*co-investigator*), K. Stone (*project director*), D.M. Black (*study statistician*), H.K. Genant (*director, central*

radiology laboratory), D.C. Bauer, T. Blackwell, W.S. Browner, M. Dockrell, T. Duong, E. Edwards, C. Fox, T. Fuerst, S. Harvey, M. Jaime-Chavez, L. Laidlaw, L.Y. Lui, G. Milani, L. Palermo, H. Tabor, E. Williams, D. Tanaka, and C. Yeung. University of Maryland: M. Hochberg (*principal investigator*), J.C. Lewis (*project director*), D. Wright (*clinic coordinator*), C. Boehm, L. Finazzo, B. Hohman, H. Kelm, T. Page, S. Trusty, and C. Williams. University of Minnesota: K. Ensrud (*principal investigator*), P. Schreiner (*co-investigator*), K. Margolis (*co-investigator*), C. Bell (*project director*), E. Mitson (*clinic coordinator*), C. Bird, D. Blanks, F. Imker-Witte, K. Jacobson, K. Knauth, N. Nelson, E. Penland-Miller, and G. Saecker. University of Pittsburgh: J.A. Cauley (*principal investigator*), L.H. Kuller (*co-principal investigator*), M. Vogt (*co-investigator*), L. Harper (*project director*), L. Buck (*clinic coordinator*), C. Bashada, D. Cusick, G. Engleka, A. Flaugh, A. Githens, M. Gorecki, K. McCune, D. Medve, M. Nasim, C. Newman, S. Rudovsky, and N. Watson. The Kaiser Permanente Center for Health Research, Portland, Oregon: E. Harris (*principal investigator, project director*), W.M. Vollmer (*co-investigator*), E. Orwoll (*co-investigator*), H. Nelson (*co-investigator*), Marge Erwin (*project administrator, clinic coordinator*), J. Cogswell, A. Doherty, D. Franco, R. Garza, J. Kann, M. Klein, L. Loter, K. Redden, C. Romero, K. Snider, and J. Wallace.

From Veterans Affairs Medical Center, Minneapolis, Minnesota; University of California, San Francisco, California; University of Pittsburgh, Pittsburgh, Pennsylvania; Creighton University, Omaha, Nebraska; and Kaiser Permanente Center for Health Research, Portland, Oregon.

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... sometimes we'll see a witchdoctor with aspirins, pink pills, yellow pills, and animal pieces all laid out in neat rows on a black velvet cloth. He listens to your ailment, then tells you whether you need to buy a pill, a good-luck charm, or just go home and forget about it.

Barbara Kingsolver  
*The Poisonwood Bible*  
 New York: HarperCollins; 1998:108

Submitted by:  
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