

## RISK FACTORS FOR HIP FRACTURE IN WHITE WOMEN

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**Abstract Background.** Many risk factors for hip fractures have been suggested but have not been evaluated in a comprehensive prospective study.

**Methods.** We assessed potential risk factors, including bone mass, in 9516 white women 65 years of age or older who had had no previous hip fracture. We then followed these women at 4-month intervals for an average of 4.1 years to determine the frequency of hip fracture. All reports of hip fractures were validated by review of x-ray films.

**Results.** During the follow-up period, 192 women had first hip fractures not due to motor vehicle accidents. In multivariable age-adjusted analyses, a maternal history of hip fracture doubled the risk of hip fracture (relative risk, 2.0; 95 percent confidence interval, 1.4 to 2.9), and the increase in risk remained significant after adjustment for bone density. Women who had gained weight since the age of 25 had a lower risk. The risk was higher among women who had previous fractures of any type after the age of 50, were tall at the age of 25, rated their own health as fair or poor, had previous hyperthyroidism, had been

treated with long-acting benzodiazepines or anticonvulsant drugs, ingested greater amounts of caffeine, or spent four hours a day or less on their feet. Examination findings associated with an increased risk included the inability to rise from a chair without using one's arms, poor depth perception, poor contrast sensitivity, and tachycardia at rest. Low calcaneal bone density was also an independent risk factor. The incidence of hip fracture ranged from 1.1 (95 percent confidence interval, 0.5 to 1.6) per 1000 woman-years among women with no more than two risk factors and normal calcaneal bone density for their age to 27 (95 percent confidence interval, 20 to 34) per 1000 woman-years among those with five or more risk factors and bone density in the lowest third for their age.

**Conclusions.** Women with multiple risk factors and low bone density have an especially high risk of hip fracture. Maintaining body weight, walking for exercise, avoiding long-acting benzodiazepines, minimizing caffeine intake, and treating impaired visual function are among the steps that may decrease the risk. (N Engl J Med 1995; 332:767-73.)

ONE of every six white women will have a hip fracture during her lifetime.<sup>1</sup> Many potential risk factors for hip fracture, such as lower body weight, cigarette smoking, caffeine intake, use of long-acting sedatives, and inactivity, have been identified in case-control<sup>2-4</sup> and prospective<sup>5-8</sup> studies. However, the findings of case-control studies might be affected by selection and recall biases, and most previous prospective studies have examined only a small number of the many risk factors for hip fracture. To identify important risk factors, we assembled a cohort of older women, identified many potential risk factors, measured bone mass, and followed the women for hip fractures.

### METHODS

#### Subjects

From 1986 to 1988, we recruited women who were able to walk and who were at least 65 years of age in Portland, Oregon; Minneapolis; Baltimore; and the Monongahela Valley, Pennsylvania, through mailings to women on lists such as voter-registration lists.<sup>9</sup> The study group consisted of 9516 white women; black women (be-

cause of their low incidence of hip fractures) and white women who had undergone bilateral hip replacement or had an earlier hip fracture were excluded. The study was approved by the appropriate committees on human research, and all the women provided written informed consent.

#### Assessment of Risk Factors

##### Questionnaire and Interview

The women were questioned and examined in outpatient clinics. We ascertained their numbers of years of education, natural hair color as young adults, height and nonpregnant weight at the age of 25, ethnic origin, numbers of pregnancies and of children who were breast-fed, ages at the last menstrual period, parental history of fractures, falls during the previous year, smoking habits and alcohol intake, and self-rated health. We asked about physician-diagnosed fractures since the age of 50, osteoporosis, spine fracture, hyperthyroidism, osteoarthritis, gastric surgery, hysterectomy, oophorectomy, cataracts, and stroke. The women were also asked about current therapy and therapy during the previous year with estrogen, diuretics, corticosteroids, thyroid hormones, anticonvulsant agents, antacids, sleeping aids, and anxiolytic drugs. Long-acting benzodiazepines were defined as those with half-lives of at least 24 hours.<sup>10</sup>

The amount of dietary calcium was assessed by a food-frequency questionnaire,<sup>11</sup> and caffeine intake was estimated.<sup>12</sup> We also asked about walking; exercise<sup>13</sup>; the number of hours spent sitting and lying down per day; and the amount of difficulty experienced in walking, climbing and descending stairs, preparing meals, shopping, and doing housework.<sup>14</sup>

##### Examinations

We measured weight, height (by stadiometer), waist and hip circumferences, and knee height.<sup>15</sup> Body-mass index (the weight in kilograms divided by the square of the height in meters) was calculated with knee height substituted for total height. Tests of neuromuscular function included whether the subject could rise up from a chair (without using her arms) five times; the number of step-ups she completed in 10 seconds; the strength of her grip, triceps, knee extensions, and hip abduction (measured with a hand-held isometric dynamometer).

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ometer)<sup>16</sup>; her walking speed (over a 6-m course); and her ability to walk and stand in a tandem position with her eyes open and closed. We assessed cognitive function with a modified version of the Mini-Mental State Examination.<sup>17,18</sup> We measured corrected visual acuity<sup>19</sup> and contrast sensitivity<sup>20</sup> (separately averaging the scores for low and high spatial frequencies). We assessed depth perception using the Howard-Dohlman device<sup>21</sup> and scored it as the standard deviation of four trials. Blood pressure and pulse were measured with the subject supine and after she had been standing for one minute<sup>22</sup>; orthostatic hypotension was defined as a drop in systolic blood pressure of 20 mm Hg or more on standing.

We measured calcaneal bone mineral density, a measurement mainly of weight-bearing trabecular bone and a strong predictor of hip fractures,<sup>23</sup> using single-photon absorptiometry (OsteoAnalyzer, Siemens-Osteon, Wahiawa, Hawaii). During a second examination, conducted between 1988 and 1990, we measured the bone density of the proximal femur, using dual x-ray absorptiometry (QDR 1000, Hologic, Waltham, Mass.) in 7786 women (82 percent of the survivors at that time).<sup>24</sup> To determine the mean coefficient of variation for these measurements, a few staff members were measured at the four clinical centers, and the mean coefficient of variation was found to be 1.2 percent for both the calcaneus and femoral neck.<sup>24</sup>

### Ascertainment of Hip Fractures

We contacted the women about fractures by postcard or telephone every four months and were able to complete 99 percent of these contacts. We confirmed all hip fractures by reviewing radiographs.<sup>25</sup>

### Statistical Analysis

We used proportional-hazards analysis to identify potential predictors of hip fracture and best subset analysis<sup>26</sup> and backward stepwise analysis to identify independent risk factors. We found no interactions between risk factors and clinical centers. Unless specified, correlations between variables in multivariable models were less than 0.5. We report age-adjusted relative hazards as relative risks with 95 percent confidence intervals. Analyses were performed with the use of Statistical Analysis Software (SAS, Cary, N.C.).

We also explored whether the effects of certain risk factors could be explained by their effect on bone density at the hip, limiting the analyses to those variables — maternal history of hip fracture, height at age 25, and history of hyperthyroidism — that were unlikely to change from base line to the measurement of hip bone density.

## RESULTS

Characteristics of the 9516 subjects are shown in Table 1. During an average 4.1 years of follow-up, 192 women had first hip fractures not due to motor vehicle accidents, 565 died, and 92 were lost to follow-up. In multivariable analyses, we identified 16 independent risk factors for hip fracture (Table 2) besides bone density. A woman whose mother had had a hip fracture had twice the risk of hip fracture of women without such a maternal history, especially if her mother fractured her hip before the age of 80 (relative risk, 2.7; 95 percent confidence interval, 1.7 to 4.4) rather than at 80 or later (relative risk, 1.6; 95 percent confidence interval, 1.0 to 2.7).

The more weight a woman had gained since the age of 25, the lower her risk of hip fracture (Fig. 1). The women who weighed less than they had at 25 had a doubled risk of hip fracture (relative risk, 2.2; 95 percent confidence interval, 1.6 to 3.0). Women who were tall at the age of 25 also had a greater risk.

Poorer self-rated health, a history of hyperthyroidism, and therapy with long-acting benzodiazepines or anticonvulsant drugs independently increased the risk of hip fracture. None of the seven hip fractures among

Table 1. Characteristics of the 9516 Women Studied to Determine the Risk of Hip Fractures.

CHARACTERISTIC	VALUE*
Age (yr)	72±5
White race (%)	99.7
High-school graduate (%)	76.9
Mean weight (kg)	67.2±12.7
Height (cm)	159.0±6.0
History of any fracture since age of 50 (%)	35.9
History of maternal hip fracture (%)	10.0
Previous hyperthyroidism (%)	9.2
Currently taking estrogen (%)	13.9
Currently taking anticonvulsant drugs (%)	1.1
Currently taking long-acting benzodiazepines (%)	9.2
Currently taking thyroid hormone (%)	12.3
Self-reported health status (%)	
Excellent or good	83.3
Fair	15.2
Poor or very poor	1.5
Mean daily dietary calcium intake (mg)	713±425
Mean daily caffeine intake (mg)†	172±138
Walking for exercise (%)	50.5
On feet ≤4 hr/day (%)	9.7
Currently a smoker (%)	9.9
Average weight gain since age of 25 (%)	20±20
Average height at age of 25 (cm)	162.6±6.0
Resting pulse >80 beats/min (%)	12
Calcaneal bone mineral density (g/cm <sup>2</sup> )	0.41±0.10
Femoral-neck bone mineral density (g/cm <sup>2</sup> )‡	0.65±0.11

\*Plus-minus values are means ±SD.

†Caffeine intake is reported for those drinking caffeinated beverages.

‡This characteristic was measured in 7834 women whose hip bone density was determined at the second visit.

women taking anticonvulsant drugs resulted from seizures or loss of consciousness. As caffeine intake increased, so did the risk of hip fracture. Women who spent four hours per day or less on their feet had twice the risk of women who spent more than four hours per day on their feet, whereas women who regularly walked for exercise had a 30 percent lower risk of hip fracture than women who did not walk regularly. Risk tended to decrease as the distance walked per day increased (relative risk, 0.9 per five blocks walked per day; 95 percent confidence interval, 0.8 to 1.0).

Four characteristics observed in the physical examination indicated an increased risk of hip fracture: the inability to rise from a chair without using one's arms, a faster resting pulse rate, poorer depth perception, and poorer low-frequency contrast sensitivity.

### Bone Density and History of Fracture

Lower calcaneal bone density and a history of any type of fracture since the age of 50 independently increased the risk of hip fracture (Table 2). Wrist fractures (relative risk, 1.9; 95 percent confidence interval, 1.4 to 2.7), self-reported spine fractures (relative risk, 1.9; 95 percent confidence interval, 1.2 to 2.9), and all other types of fractures (relative risk, 1.5; 95 percent confidence interval, 1.0 to 2.1) were all associated with an increased risk of hip fracture.

All risk factors remained significantly associated

**Table 2. Multivariable Models of Risk Factors for Hip Fracture with and without Adjustment for Fractures and Calcaneal Bone Density among 9516 White Women.**

MEASUREMENT (COMPARISON OR UNIT)*	RELATIVE RISK (95% CONFIDENCE INTERVAL)	
	BASE MODEL†	ADD FRACTURES AND BONE DENSITY
Age (per 5 yr)	1.5 (1.3–1.7)	1.4 (1.2–1.6)
History of maternal hip fracture (vs. none)	2.0 (1.4–2.9)	1.8 (1.2–2.7)
Increase in weight since age 25 (per 20%)	0.6 (0.5–0.7)	0.8 (0.6–0.9)
Height at age 25 (per 6 cm)	1.2 (1.1–1.4)	1.3 (1.1–1.5)
Self-rated health (per 1-point decrease)‡	1.7 (1.3–2.2)	1.6 (1.2–2.1)
Previous hyperthyroidism (vs. none)	1.8 (1.2–2.6)	1.7 (1.2–2.5)
Current use of long-acting benzodiazepines (vs. no current use)	1.6 (1.1–2.4)	1.6 (1.1–2.4)
Current use of anticonvulsant drugs (vs. no current use)	2.8 (1.2–6.3)	2.0 (0.8–4.9)
Current caffeine intake (per 190 mg/day)	1.3 (1.0–1.5)	1.2 (1.0–1.5)
Walking for exercise (vs. not walking for exercise)	0.7 (0.5–0.9)	0.7 (0.5–1.0)
On feet ≤4 hr/day (vs. >4 hr/day)	1.7 (1.2–2.4)	1.7 (1.2–2.4)
Inability to rise from chair (vs. no inability)	2.1 (1.3–3.2)	1.7 (1.1–2.7)
Lowest quartile for distant depth perception (vs. other three)	1.5 (1.1–2.0)	1.4 (1.0–1.9)
Low-frequency contrast sensitivity (per 1 SD decrease)	1.2 (1.0–1.5)	1.2 (1.0–1.5)
Resting pulse rate >80 beats/min (vs. ≤80 beats/min)	1.8 (1.3–2.5)	1.7 (1.2–2.4)
Any fracture since age of 50 (vs. none)	—	1.5 (1.1–2.0)
Calcaneal bone density (per 1 SD decrease)	—	1.6 (1.3–1.9)

\*For continuous variables, the relative risks are expressed as a change in risk for each specified change in the risk factor.

†Base-model values are based on proportional-hazards analysis with backward stepwise elimination. Best subsets models yielded similar sets of risk factors, including the number of steps in a 360-degree turn and the functional-status score; some did not include low-frequency contrast sensitivity, long-acting benzodiazepine therapy, or walking for exercise.

‡Health was rated as poor (1 point), fair (2 points), or good to excellent (3 points).

with the risk of hip fracture after bone density was added to the multivariable model. Therapy with anticonvulsant drugs was no longer a significant factor after a history of fractures was also added (Table 2).

#### Adjustment for Femoral-Neck Bone Density

In analyses limited to the 7786 women in whom the bone density of the hip had been measured, 83 of whom later had hip fractures, a history of maternal hip fracture was significantly associated with an increased risk of hip fracture before (relative risk, 2.0; 95 percent confidence interval, 1.2 to 3.6) and after (relative risk, 1.9; 95 percent confidence interval, 1.1 to 3.2) adjustment for femoral-neck bone density. Similarly, adjustment for femoral-neck bone density did not affect the significant associations between height at the age of 25 or previous hyperthyroidism and the risk of hip fracture.

#### Number of Risk Factors, Bone Density, and Prediction of Hip Fracture

Fifteen percent of the women had five or more of the risk factors listed in Table 2 (including older age and previous fracture, but not low bone density); their incidence of hip fracture was 19 (95 percent confidence interval, 15 to 22) per 1000 woman-years (Fig. 2). By comparison, the 47 percent of women who had two or

fewer risk factors had an incidence of only 1.1 (95 percent confidence interval, 0.5 to 1.6) per 1000 woman-years. The 6 percent of women who had five or more risk factors and calcaneal bone density in the lowest third for their age had an incidence of hip fracture of 27 (95 percent confidence interval, 20 to 34) per 1000 woman-years and had 62 (32 percent) of the hip fractures reported.

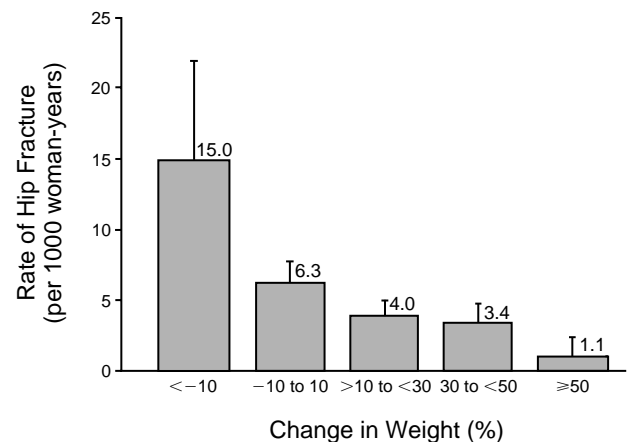
#### Factors Not Significant after Multivariate Adjustment

For a number of factors that were initially associated with the risk of hip fracture in age-adjusted models, these associations were diminished and no longer statistically significant after adjustment for other variables (Table 3). For example, current smokers had about twice as high a risk of hip fracture as nonsmokers or former smokers. The smokers had gained less (or lost more) weight, had poorer health, had more difficulty rising from a chair, spent fewer hours on their feet, were less likely to walk for exercise, and had faster heart rates. Adjusting for these effects explained most of the association between smoking and hip fracture.

Alcohol ingestion was associated with a lower risk of hip fracture (Table 3). The risk was somewhat lower among those who drank seven or fewer drinks per week (relative risk as compared with nondrinkers, 0.7; 95 percent confidence interval, 0.5 to 0.9) than among those who drank more (relative risk, 0.9; 95 percent confidence interval, 0.5 to 1.4). However, alcohol intake was no longer significantly associated with a lower risk of hip fracture after adjustment for the better self-reported health and ability to stand up from a chair among those who drank alcohol.<sup>27</sup>

Current thyroid-hormone therapy was no longer significantly associated with the risk of hip fracture after adjustment for a history of hyperthyroidism, which was reported by 36 percent of those taking thyroid hormone.

Greater weight, body-mass index, and modified body-



**Figure 1. Association between the Change in Body Weight after the Age of 25 and the Risk of Hip Fracture.**

The rate of hip fracture is adjusted for age. The T bars denote the upper 95 percent confidence limits.

mass index were all associated with a decreased risk of hip fracture, but not quite as strongly as was the percentage of weight change since the age of 25. Neither current weight nor modified body-mass index remained significantly associated with the risk of hip fracture after adjustment for weight gain. However, the percentage of weight change was correlated with current weight ( $r=0.75$ ) and body-mass index ( $r=0.76$ ).

A history of falling indicated an increased risk of hip fracture (Table 3); the risk increased 30 percent with each additional fall (relative risk, 1.30 per fall from 0 to  $\geq 5$ ; 95 percent confidence interval, 1.1 to 1.5). After adjustment for the inability to rise from a chair, spending four hours or less on one's feet, and poor health, however, a history of falling and the number of falls were no longer significantly associated with hip fracture.

Poor performance on almost every test of neuromuscular function, such as gait speed, was associated with an increased risk of hip fracture. When the models in-

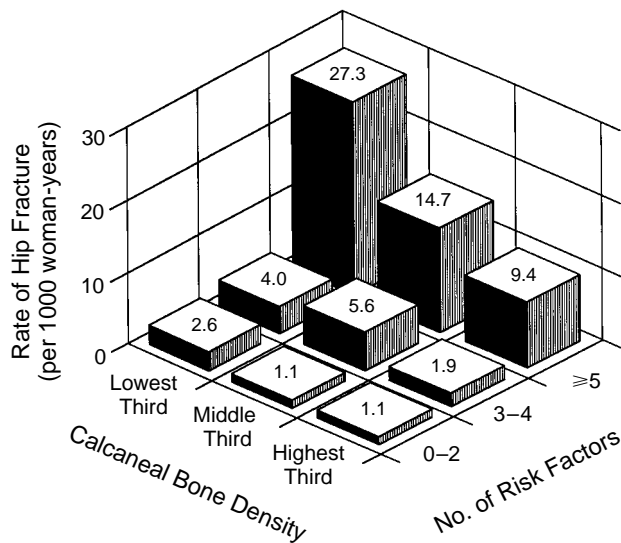


Figure 2. Annual Risk of Hip Fracture According to the Number of Risk Factors and the Age-Specific Calcaneal Bone Density. The risk factors (from Table 2) are as follows: age  $\geq 80$ ; maternal history of hip fracture; any fracture (except hip fracture) since the age of 50; fair, poor, or very poor health; previous hyperthyroidism; anticonvulsant therapy; current long-acting benzodiazepine therapy; current weight less than at the age of 25; height at the age of 25  $\geq 168$  cm; caffeine intake more than the equivalent of two cups of coffee per day; on feet  $\leq 4$  hours a day; no walking for exercise; inability to rise from chair without using arms; lowest quartile (standard deviation  $>2.44$ ) of depth perception; lowest quartile ( $\leq 0.70$  unit) of contrast sensitivity; and pulse rate  $>80$  per minute.

Table 3. Predictors Significantly Associated with Hip Fractures in Age-Adjusted Models but Not in Multivariable Models.

PREDICTOR	RELATIVE RISK (95% CONFIDENCE INTERVAL)		VARIABLES IN MULTIVARIABLE MODEL*			
	AGE-ADJUSTED MODEL	MULTIVARIABLE MODEL	WEIGHT CHANGE	HEALTH STATUS	ABILITY TO RISE FROM CHAIR	OTHER
Current smoking (vs. never having smoked)	2.1 (1.4–3.3)	1.4 (0.9–2.3)	X	X	X	X†
Any alcohol in the previous year (vs. none)	0.7 (0.5–0.9)	0.8 (0.6–1.1)		X	X	
Current thyroid hormone therapy (vs. none)	1.6 (1.1–2.3)	1.3 (0.9–2.0)				X‡
Functional-status score (per 3 points)	1.4 (1.2–1.5)	1.1 (1.0–1.3)		X	X	
Fall in the previous year (vs. none)	1.6 (1.2–2.1)	1.4 (1.0–2.1)		X	X	X§
Gait speed (per 0.22 m/sec)	1.4 (1.2–1.6)	0.9 (0.8–1.0)			X	
Current weight (per 12.7 kg)	0.8 (0.7–0.9)	1.2 (0.9–1.4)	X			

\*When these variables were included in a proportional-hazards model, the predictor variable was no longer significantly associated with the risk of hip fracture.

†Other variables included are hours on one's feet, walking for exercise, and pulse rate.

‡The other variable included is a history of hyperthyroidism.

§The other variable included is hours on one's feet.

cluded the inability to rise from a chair without using one's arms, no other measurement of neuromuscular function remained significantly associated with the risk of hip fracture.

The risk decreased with increasing numbers of births (relative risk, 0.9 per birth; 95 percent confidence interval, 0.8 to 1.0). This association was not quite statistically significant after adjustment for weight change since the age of 25.

#### Factors Not Significantly Associated with the Risk of Hip Fracture

Factors that were not significantly associated with the risk of hip fracture included hair color, ethnic ancestry, whether there was a maternal history of fractures other than hip fracture, the number of children breast-fed, the timing of menopause, past smoking status, whether the subject had cataracts, and whether she had used short-acting benzodiazepines (Table 4).

Dietary calcium intake was not related to the risk of hip fracture. There was no increased risk among the 11 percent of women who ingested 400 mg of calcium or less per day (relative risk, 1.1; 95 percent confidence interval, 0.5 to 2.3), even when women taking calcium supplements or estrogen were excluded.

Estrogen is often prescribed for osteoporosis, a fact that could lead to an underestimation in observational studies of the effectiveness of estrogen to prevent hip fracture. To minimize this bias, we analyzed the effect of estrogen in women with no previous diagnosis of osteoporosis or fracture. In this group, estrogen therapy appeared to have a strong protective effect (Table 4), but the confidence limits were wide.

Diabetes mellitus was not associated with a significantly increased risk (relative risk, 1.3; 95 percent confidence interval, 0.8 to 2.1). After adjustment for obesity, there was a trend toward an increased risk of hip fracture in diabetic women not taking insulin (rel-

Table 4. Factors Not Significantly Associated with Hip Fracture in Age-Adjusted Models.

VARIABLE	COMPARISON	RELATIVE RISK (95% CONFIDENCE INTERVAL)
Hair color (as young adult)		
Black or brown	Reference category	1.0
Red	Black or brown	0.9 (0.4–1.8)
Blond	Black or brown	1.1 (0.8–1.6)
Ancestry		
Northern European	All others	1.2 (0.9–1.6)
Southern European	All others	0.4 (0.2–1.1)
Maternal fracture other than hip fracture	No maternal fracture	1.0 (0.6–1.7)
Children breast-fed	Per child (none to $\geq 5$ )	0.9 (0.8–1.0)
Natural menopause before age of 45	Menopause at or after age of 45	1.3 (0.9–1.8)
Bilateral oophorectomy	All others	1.0 (0.7–1.6)
Past cigarette smoking	Never smoked	1.3 (1.0–1.8)
Daily dietary calcium intake	Per 425 mg*	0.9 (0.8–1.1)
Self-reported osteoarthritis	No osteoarthritis	1.1 (0.8–1.6)
Unextracted cataracts	No cataracts	1.1 (0.8–1.5)
Short-acting benzodiazepine use	No benzodiazepines	1.2 (0.8–2.1)
Aluminum-containing antacid use at least weekly	None or less frequent	1.1 (0.7–1.7)
Current estrogen use	Never used estrogen	1.0 (0.6–1.5)
No history of osteoporosis or fracture	Never used estrogen	0.3 (0.1–1.1)
History of osteoporosis or fracture	Never used estrogen	1.3 (0.8–2.2)
Current thiazide diuretic use	Never used thiazides	0.8 (0.6–1.2)
Current height	Per 6.0 cm*	1.0 (0.8–1.1)
Modified Mini-Mental State score	>5 errors	1.5 (0.9–2.3)
Poorer visual acuity with usual correction	Per 7.4 units*	1.1 (1.0–1.2)
Orthostatic hypotension†	No orthostatic change	1.2 (0.8–1.7)

\*Value is equivalent to 1 SD.

†Orthostatic hypotension was defined as a decrease in systolic blood pressure of 20 mm Hg or more on standing.

ative risk, 1.6; 95 percent confidence interval, 0.9 to 2.7). There was also a trend toward an increased risk of hip fracture among those with a history of gastric surgery (relative risk, 2.0), Parkinson's disease (relative risk, 1.6), and previous stroke (relative risk, 1.6), but these conditions were uncommon and the lower 95 percent confidence limit was less than 1.0 in each instance.

## DISCUSSION

We found that many factors influence the risk of hip fracture in older women and that the assessment of risk factors and the measurement of bone density have complementary value for the prediction of hip fracture. A small number of women with multiple risk factors and low bone density have an especially high risk. They account for a large proportion of hip fractures and should be the focus of intensive efforts to prevent them.

A woman whose mother had a hip fracture, especially before the age of 80, is at least twice as likely to have a hip fracture herself as a woman without such a maternal history. Other types of maternal fractures did not increase hip-fracture risk, and the risk was independent of bone mass, height, and weight. Inherited

characteristics of the proximal femur besides density, or perhaps a propensity to fall on the hip, may account for this familial predisposition.

Many of the other risk factors are also believed to act by reducing bone mass. However, adjustment for calcaneal bone density did not substantially affect the risk of hip fracture associated with caffeine intake, a change in weight, walking for exercise, anticonvulsant drug therapy, or a history of fracture. These factors may affect the risk of hip fracture in other ways, perhaps by influencing characteristics of bone other than density or by affecting the risk of falling.

Gaining weight reduces a woman's risk of hip fracture, and losing weight increases it. Previous studies have found that heavier women have a lower risk of hip fracture.<sup>4,5,7</sup> Weight loss may also be a marker for an underlying illness that increases risk. The high degree of correlation between weight change, current weight, and obesity limits our ability to determine whether the risk of hip fracture is affected more by previous change or by current weight.

We confirmed that women who were tall when they were young have a greater risk of hip fracture,<sup>8</sup> perhaps because they fall farther.<sup>28,29</sup> Taller women also have a longer hip-axis length (the distance from the greater trochanter to the inner pelvic brim), which has been associated with a greater risk of hip fracture.<sup>30</sup>

Hyperthyroidism may or may not reduce bone mass.<sup>12,31-34</sup> In our study, reduced bone mass did not account for the strong association between previous hyperthyroidism and the risk of hip fracture. Hyperthyroidism may cause long-lasting impairments of bone strength not detected by densitometry, or impairments of neuromuscular function not detected by our examinations. It can also reduce muscle strength. The association between resting tachycardia and hip fracture may be due to undiagnosed hyperthyroidism, although a faster pulse may also indicate decreased physical fitness or impaired cardiac function.

Our finding that caffeine consumption increases the risk of hip fracture agrees with the findings of two previous studies.<sup>6,35</sup> Although a high caffeine intake has also been associated with reduced bone mass,<sup>12,36,37</sup> our results suggest that caffeine may influence the risk of hip fracture in other ways.

Women who spent four hours or less per day on their feet had a substantially increased risk of hip fracture, whereas walking for exercise reduced the risk. Exercise may be a marker for health and functional status, but the association between activity and hip-fracture risk remained significant after adjustment for self-rated health and findings on tests of neuromuscular function.

We confirmed that therapy with long-acting benzodiazepines increases the risk of hip fracture<sup>4,10</sup>; older women should avoid these drugs. We also confirmed that women taking anticonvulsant drugs have a very high risk of hip fracture,<sup>38</sup> although none of these women had a hip fracture during a seizure. We previously found no association between the use of anticonvulsant drugs and lower appendicular bone mass in this co-

hort,<sup>12</sup> suggesting that the increased risk might be due to impairments of neuromuscular function we did not measure.

The inability to rise from a chair without using one's arms is associated with an increased risk of falls<sup>39</sup> and a twofold increase in the risk of hip fracture. None of the other assessments of neuromuscular function added significantly to the prediction of subsequent hip fracture.

Poor depth perception and a reduced ability to perceive contrast (but not poor visual acuity) increased the risk of hip fracture independently. This suggests that treatment or prevention of ophthalmologic conditions that impair depth perception and contrast sensitivity, such as cataracts, diabetic retinopathy, and glaucoma, may help prevent hip fracture.

Women who have had wrist fractures have a greater risk of hip fractures than those who have not had wrist fractures.<sup>40,41</sup> Our results indicate that any type of postmenopausal fracture signals an increased risk of hip fracture. This increased risk is independent of bone mass, implying that a history of fractures may indicate an increased risk of falling or defects in bone strength not detected by densitometry.

Our analysis suggests that smoking increases the risk of hip fracture by limiting normal weight gain and by its adverse effects on the health, neuromuscular fitness, and exercise patterns of older women.<sup>27</sup> The lower risk for former smokers implies that quitting smoking diminishes the risk of hip fracture.

Although consistent with the view that current estrogen therapy protects against hip fracture,<sup>42</sup> these results are limited by the small number of women in our study who were taking estrogen. Another analysis of estrogen therapy and fractures in this cohort has confirmed that estrogen therapy protects against osteoporotic fractures.<sup>43</sup> Our analysis illustrates the point that observational studies will underestimate the effectiveness of estrogen if they do not account for the fact that many women take estrogen for osteoporosis. Our study may underestimate the benefit in those with osteoporosis to the degree that estrogen is taken by women with more severe osteoporosis.

The results of this study do not support widely held beliefs that fair hair color, northern European ancestry, earlier natural menopause, and antacid therapy are associated with an increased risk of hip fracture. In contrast to other investigators,<sup>44,45</sup> we found that moderate alcohol intake did not increase the risk of hip fracture. Although breast-feeding temporarily decreases bone mass,<sup>46</sup> it did not increase the risk of hip fracture. Like most<sup>3,3,7</sup> but not all<sup>47</sup> prospective observational studies, ours found no relation between calcium intake and protection from hip fracture, even in women with very low intakes. However, we assessed calcium intake only once with a short questionnaire; repeated assessments may be more accurate.

This study had several limitations. The participants were community-dwelling white women over the age of 65, so these findings are not generalizable to men,

younger women, nursing home residents, or possibly women of other races.<sup>48</sup> The study had limited power to evaluate risk factors that are relatively uncommon, such as Parkinson's disease. Other risk factors, such as osteoarthritis and calcium intake, were based only on the women's own reports. Measurement of hip instead of calcaneal bone density may improve the prediction of hip fracture. In addition, some of the risk factors that are independent of calcaneal bone density may not be independent of hip bone density. Predictive models derived in one group may not perform as well in other groups; ideally, our findings should be tested prospectively in other populations.

We conclude that many factors increase the risk of hip fracture in older white women living in the community. The effect of most individual factors is moderate, but together their impact is substantial. Women with multiple risk factors and low bone density are at especially high risk. A woman may be able to minimize her risk of hip fracture in a number of ways, notably by walking for exercise, avoiding long-acting sedative-hypnotic agents, reducing caffeine intake, quitting smoking, treating impaired vision, and taking measures that maintain bone density.

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#### APPENDIX

The following investigators were members of the Study of Osteoporotic Fractures Research Group: *University of California, San Francisco (Coordinating Center)*: S.R. Cummings (principal investigator), M.C. Nevitt (project director), D. Black (study statistician), H.K. Genant (director, central radiology laboratory), C. Arnaud, W. Browner, L. Christianson, M. Dockrell, C. Fox, C. Glüer, S. Harvey, M. Jergas, L. Palermo, A. Pressman, R. San Valentin, D. Seeley, P. Steiger, and K. Stone; *University of Maryland, Baltimore*: R. Sherwin (principal investigator), J. Scott (co-investigator), K. Fox (co-investigator), J. Lewis (project coordinator), G. Greenberg (clinic coordinator), M. Bahr, S. Trusty, L. Finazzo, S. Snyder, E. Oliner, B. Hohman, and T. Page; *University of Minnesota, Minneapolis*: K. Ensrud (principal investigator), R. Grimm, Jr. (co-investigator), C. Bell (project director), E. Mitson (study coordinator), I. Chavier, K. Jacobson, S. Fillhouer, C. Shoberg, D. Michel, S. Estill, J. Hansen, and M. Baumhover; *University of Pittsburgh, Pittsburgh*: J.A. Cauley (principal investigator), L.H. Kuller (co-principal investigator), L. Harper (project director), M. Nasim (clinic coordinator), C. Bashada, L. Buck, A. Githens, A. McCune, D. Medve, S. Rudovsky, and N. Watson; *Kaiser Permanente Center for Health Research, Portland, Ore.*: T.M. Vogt (principal investigator), W.M. Vollmer and E. Orwoll (co-investigators), J. Blank (project director), F. Heimith (clinic coordinator), R. Bright, J. Downing, B. Packer, C. Souvanlauskay, L. Pudrbaugh, and D. Franco.

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