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Risk Factors for a First-Incident Radiographic Vertebral Fracture in Women ≥65 Years of Age: The Study of Osteoporotic Fractures

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ABSTRACT: Vertebral fractures in older women signal an increased risk of additional osteoporotic fractures. To identify risk factors for first vertebral fractures, we studied 5822 women ≥65 years of age who had no fracture on baseline radiographs of the spine. Several modifiable risk factors increased an older woman's risk of developing a first vertebral fracture, and women with multiple risk factors and low BMD had the highest risk. Risk factors and low BMD should be useful to help focus efforts to prevent these fractures.

Introduction: Vertebral fractures are a common cause of back pain and disability and signal an increased risk of additional osteoporotic fractures in older women. Little is known about the risk factors for the first occurrence of a vertebral fracture.
Materials and Methods: To identify risk factors for a first vertebral fracture, we studied 5822 women ≥65 years of age from the Study of Osteoporotic Fractures who had no fracture on baseline radiographs of the spine. We measured potential risk factors and BMD of the wrist and calcaneus at baseline and BMD of the spine and hip halfway through follow-up. Fractures were assessed by standard methods from spine radiographs obtained at baseline and follow-up an average of 3.7 years later.
Results and Conclusions: In multivariable analyses, older age, previous nonspine fracture, low BMD at all sites, a low body mass index (BMI), current smoking, low milk consumption during pregnancy, low levels of daily physical activity, having a fall, and regular use of aluminum-containing antacids independently increased the risk of a first vertebral fracture. Women using estrogen and those who engaged in recreational physical activity had a decreased risk. The effects of low BMI, smoking, use of estrogen and antacids, and previous fracture were partially mediated by BMD. Women in the lower third of wrist BMD with five or more risk factors had a 12-fold greater risk than women in the highest third of BMD who had zero to three risk factors. The 27% of women at highest risk suffered 60% of the incident fractures. In conclusion, several modifiable risk factors and BMD independently increase an older woman's risk of developing a first vertebral fracture. The combination of risk factors and BMD should be useful for focusing efforts to prevent vertebral fractures.
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Key words: vertebral fractures, women, spinal osteoporosis, fracture risk factors, fracture pathogenesis

INTRODUCTION

Osteoporosis is a common disorder that results in millions of fractures and a substantial burden in health care costs and disability among older women.[1] Vertebral fractures detected by radiograph are a sentinel and clinically important event in postmenopausal osteoporosis. Independently of their BMD, women with an existing radiographic vertebral fracture have a risk of subsequent vertebral fracture that is four to five times higher than

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women without an existing fracture,[2–4] and they also have an increased risk of subsequent hip[2,5–7] and other nonspine fractures.[2,6,7] Vertebral fractures cause back pain, physical disability, and reduced quality of life in older women.[8–12] A woman's first vertebral fracture usually occurs well past menopause. Less than 1 in 20 white women 50–54 years of age have had a vertebral fracture, but the proportion with an existing fracture more than doubles with each additional 10 years of age, rising to 1 in 3 among women ≥80 years of age.[13,14]

In contrast to hip fracture,[15] few risk factors for vertebral fracture in women have been established in prospective studies. Cross-sectional studies suggest that prevalent vertebral fractures are associated with older age, low BMD, a shorter reproductive span, and long-term use of oral corticosteroids,[13,14,16–18] but findings for other factors are conflicting.[19] Low BMD, older age, and a shorter fertile period are associated with the risk of vertebral fracture in recent prospective studies of older women.[20–23]

Developing a vertebral fracture signals a high risk of subsequent vertebral and nonvertebral fractures. Thus, it may be particularly valuable to identify risk factors that help target treatments to prevent the first occurrence of a vertebral fracture and avert a cascade of subsequent fractures. However, no studies have specifically examined risk factors for a first vertebral fracture in older women. Therefore, we analyzed risk factors for a first vertebral fracture in a large cohort of older women.

MATERIALS AND METHODS

Subjects

Subjects were participants in the Study of Osteoporotic Fractures, recruited from population-based listings in four U.S. metropolitan areas. Details of the design of this study, recruitment, and measurements have been published.[15,24–26] Spine radiographs were obtained in 9677 white women between the ages of 65 and 99 years (median age, 70 years) who attended the baseline examination between 1986 and 1988. Repeat radiographs suitable for vertebral morphometry were obtained for 7238 (78%) of the 9288 women surviving at the second follow-up clinic visit 3.7 ± 0.4 years (range, 1.3–5.1 years) later. The study was approved by the appropriate committees on human research, and all the women gave written informed consent.

Vertebral morphometry

Lateral radiographs of the thoracic and lumbar spine were taken in accordance with current guidelines.[27] Quantitative vertebral morphometry was performed as previously described[28,29] to calculate the anterior (H_a), middle (H_m), and posterior (H_p) height for each vertebral body from T_4 to L_4. Radiographs were first screened for probable fractures, using methods described previously,[28,30] to reduce the number undergoing morphometric measurements. Briefly, highly trained technicians separated sets of radiographs into three groups: "normal," "uncertain," and "probably fractured," using a binary semiquantitative grading scheme that classified women by the most abnormal vertebral level on her follow-up films. Those that were uncertain were further classified by the study radiologist (HKG) as "normal" or "probably fractured." Morphometry on paired films was performed for women (42%) classified as "probably fractured."

Definitions of vertebral fractures

A vertebra was classified as having a prevalent fracture on the baseline radiograph if any of the following ratios were >3 SD below the trimmed normal mean[31] for that vertebral level: (H_a/H_p), (H_m/H_p), or a combination of ($H_{pi}/H_{pi} \pm 1$) and ($H_{ai}/H_{ai \pm 1}$).[28] We defined a new (incident) fracture as a decrease of 20% or more, and at least 4 mm, in any of the three vertebral heights (H_a, H_m, or H_p) on follow-up compared with the baseline radiograph.[26] The performance of the technician triage was evaluated in a random sample of 503 women, all of whose radiographs were triaged and underwent morphometry. The sensitivity of triage for prevalent and incident fractures, as defined in this study, was 97% and 100%, respectively.[26,28,30]

Assessment of risk factors

Questionnaire and interview: Questionnaire and interview methods for our study have been previously described.[15,25,32] In brief, at baseline, we ascertained years of education, height, and nonpregnant weight at age 25, ethnic or national origin, number of pregnancies, children breast fed, hysterectomy, oophorectomy, age at last menstrual period, parental history of fractures, falls during the past year, smoking and alcohol intake, and self-rated health. We asked about physician-diagnosed medical conditions including fractures since age 50, osteoporosis, spine fracture, hyperthyroidism, osteoarthritis, gastric surgery, cataracts, and stroke. Participants were asked about current and past use of calcium supplements, estrogen, diuretics, corticosteroids, thyroid supplements, anticonvulsants, antacids, sleeping aids, and anxiolytics during the past year. Long-acting benzodiazepines were those with ≥24-h half-lives.

Dietary calcium excluding supplements was assessed by a food frequency questionnaire.[33] Past milk consumption and current caffeine intake were estimated by direct questions.[25] We asked about the number of blocks walked daily and about the number of hours spent on household chores and hours spent sitting and lying down per day, and administered the Paffenbarger questionnaire, which grades current recreational physical activities as low, moderate, or high intensity.[34] We asked about falls during the past year at baseline, and participants reported falls every 4 months by mail questionnaire during the first year of follow-up.

Examinations: We measured weight, height (by wall-mounted stadiometer), knee height, and waist and hip circumferences.[35] Knee height is the distance, measured with a sliding caliper, from the bottom of the heel to the epicondyles of the distal femur with the knee flexed to 90°.[36] Tests of physical function included standing from a chair (without use of arms) five times, grip strength, isometric triceps, quadriceps and hip abductor strength (using a hand-held dynamometer),[32] walking speed (over a 6-m course), and tandem balance. Cognitive function was assessed with a

modified version of the Mini-Mental State Examination.[37] Measures of visual function included visual acuity, low spatial frequency contrast sensitivity,[38] and distance depth perception.[39] Resting blood pressure and pulse were assessed with the participant supine.

BMD: Baseline calcaneal and distal radius BMD (g/cm^2) was measured using single photon absorptiometry (Osteo-Analyzer; Siemens-Osteon, Wahiawa, HI, USA). During the second examination (1988–1990), BMD of the proximal femur and lumbar spine was measured using DXA (QDR 1000; Hologic, Waltham, MA, USA) in 95.2% of the women who had a follow-up spine radiograph.[40]

Analysis

We used logistic regression to identify potential risk factors for first incident fractures ($p < 0.10$ after adjusting for age and clinic) and used best subset analysis[25] and backward stepwise elimination analysis to identify independent risk factors. We examined the sensitivity of our results to using $p < 0.20$ in screening potential risk factors, but this did not alter our results. Continuous measures were categorized by quintile to evaluate linearity and cut-points for nonlinear relationships. We analyzed a modified body mass index (BMI: weight in kg/height in m^2) calculated using knee height, which is highly correlated with young adult height and not altered by vertebral fractures in later life.[36] We analyzed milk consumption during pregnancy, except for nulliparous women, for whom we analyzed consumption as a teenager. Walking only one or fewer blocks per day versus two or more and spending <1 h/day on household chores versus ≥1 h were combined to form an indicator variable for low daily physical activity (positive if low on both activities). We compared woman of Southern European ethnic or national origin (Portuguese, Spanish, Italian, and Greek) with women of all other ethnic or national origins, the vast majority of which were Western, Central, or Northern European. We checked for interactions between risk factors and clinical center or age <75 versus ≥75 by including interaction terms in regression models. We also explored whether the effects of certain risk factors could be explained by their effect on BMD. We performed similar analyses of factors associated with baseline prevalent fractures. For analyses of risk factors for prevalent fractures, we excluded variables that are likely to be strongly influenced by prior fracture, including height loss, back pain, and current use of calcium supplements. Unless specified, the correlations between variables tested in multivariable models were <0.5. We report adjusted odds ratios (which are labeled relative risks in the text and tables) with 95% confidence limits (RR; 95% CI). Analyses were performed using Statistical Analysis Software (SAS, Cary, NC, USA).

RESULTS

Baseline prevalent fractures

Prevalent vertebral fractures were present at baseline in 1416 (19.6%) of the 7238 women with follow-up radiographs and in 499 (20.4%) of the 2444 women without a follow-up radiograph. Women who did not have a follow-up radiograph were older, weighed less, had a lower BMD, reported worse health status and more back pain, and walked fewer blocks than those who had a follow-up X-ray (data not shown).

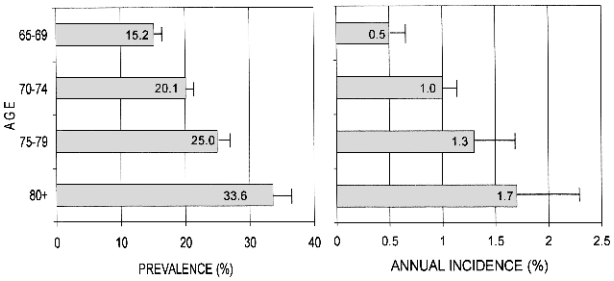

FIG. 1. Vertebral fracture prevalence (%) and annual incidence (%), with upper 95% CI, in women from the SOF cohort, by age at baseline.

The prevalence of vertebral fractures at baseline increased steadily with age, more than doubling between the age groups of 65–69 and ≥80 years (Fig. 1). A large number of factors in addition to age were independently associated ($p < .05$ in multivariable models) with prevalent vertebral fractures (Table 1), including parental history of hip fracture (paternal and maternal hip fractures carried similar risks), younger age at menopause, current smoking, use of oral corticosteroids and antacids containing aluminum, slower walking speed, and a history of nonspine fracture since age 50. Southern European ancestry and a greater weight gain from age 25 to the present were associated with a decreased risk, as was a surgical menopause despite adjustment for current and past use of estrogen. When we adjusted for distal radius BMD, all the above variables except current smoking ($p = 0.17$) remained significantly associated with prevalent fractures.

First incident vertebral fractures

Among women who did not have a baseline prevalent fracture, 181 (3.1%; annual risk, 0.9%; 95% CI, 0.7–1.0%) had a first incident vertebral fracture during follow-up. Of these, 33 (18.2%) women had two or more new fractures. The incidence of first vertebral fractures increased >3-fold between the ages of 65–69 and ≥80 years (Fig. 1). There were 118 first fractures among women ages 65–74 and 60 in women ≥75 years of age.

Risk factors for incident fracture

BMD was a strong predictor of a first vertebral fracture; this relationship was stronger for BMD of the spine than BMD at other sites. Because spine and hip BMD were measured halfway through follow-up and in only 94% of women, we included distal radius BMD in the multivariable models (Table 2).

A variety of behavioral and constitutional variables were potential risk factors for a first vertebral fracture (Table 3). Women with a previous hip fracture (RR, 2.71; 95% CI, 1.21, 6.08) and those with other nonspine fracture after age 50 (RR, 1.40; 1.02, 1.88) had an increased risk. Because

TABLE 1. BASELINE CHARACTERISTICS OF SUBJECTS BY PREVALENT VERTEBRAL FRACTURE STATUS

Characteristic	*Baseline vertebral fracture?*	
	No (n = *5822)*	*Yes* (n = *1416)*
Age, years, mean (SD)	70.8 (4.7)	72.5 (5.5)†‡
Distal radius BMD, g/cm^2; mean (SD)	0.37 (0.08)	0.33 (0.08)†
Lumbar Spine BMD, g/cm^2, mean (SD)	0.87 (0.16)	0.80 (0.16)†
Nonspine fracture after age 50, % (*n*)	32.5 (1883)	51.4 (724)†‡
Parental Hx of hip fracture, % (*n*)	11.8 (686)	14.1 (199)*‡
Mother hip fracture, % (*n*)	10.3 (597)	11.9 (169)*
Father hip fracture, % (*n*)	1.8 (106)	2.5 (36)
Southern European ancestry, % (*n*)	5.6 (328)	3.7 (52)*‡
Milk during pregnancy (or teens if nulliparous) <1 glass/day, % (*n*)	32.3 (1884)	36.7 (520)*
Age at menopause <45 years, mean, % (*n*)	12.7 (604)	17.6 (205)†‡
Bilateral oophorectomy, % (*n*)	13.2 (738)	10.5 (141)*‡
Walks ≤1 block daily and does household chores <1 h/daily, % (*n*)	47.2 (2745)	48.0 (680)
Currently does moderate or high intensity recreational physical activity at least monthly, % (*n*)	32.6 (1900)	30.2 (428)
Current smoker, % (*n*)	8.9 (515)	10.8 (152)†‡
History of gastrectomy, % (*n*)	1.3 (77)	1.8 (25)
Estrogen, current user, % (*n*)	14.8 (851)	13.7 (191)
Calcium supplements, current user, % (*n*)	41.5 (2409)	51.4 (727)†§
Oral corticosteroids, ever use for ≥1 yr, % (*n*)	2.5 (143)	4.5 (62)†‡
Antacids with aluminum, ever use ≥ weekly, % (*n*)	10.9 (636)	14.4 (204)†‡
BMI using recalled height age 25, mean (SD)	25.6 (4.5)	24.8 (4.2)†
Percent weight change since age 25, mean (SD)	20.7 (19.2)	16.6 (18.2)†‡
≥1 fall in past year, % (*n*)	28.7 (1672)	31.6 (447)
Resting pulse >80 bpm, % (*n*)	10.0 (581)	12.6 (178)*
Walking speed, m/s, mean (SD)	1.04 (0.21)	1.00 (0.22)†‡
Uses arms to rise from chair, % (*n*)	2.3 (134)	4.9 (69)†
Hip abductor strength, kg of force, mean (SD)	11.4 (3.3)	10.8 (3.3)†
Contrast sensitivity low spatial frequency, mean (SD)	1.28 (0.57)	1.17 (0.58)*
Height loss since age 25, cm, mean (SD)	2.8 (2.6)	4.5 (3.2)†§
Moderate-severe back pain in past year, % (*n*)	52.5 (3056)	60.5 (856)†§

* $p < 0.05$, † $p < 0.01$ compared with no baseline vertebral fracture, adjusted for age and clinic.
‡ Independently associated with prevalent vertebral fractures in a multivariable model that did not include BMD.
§ Probable result of prevalent vertebral fracture and therefore not included in multivariable models.

TABLE 2. ASSOCIATION OF BMD WITH FIRST INCIDENT VERTEBRAL FRACTURES

BMD site	*Adjusted OR (95% CI)**
Lumbar spine	1.89 (1.57, 2.26)
Total hip	1.54 (1.29, 1.63)
Femoral neck	1.56 (1.29, 1.87)
Distal radius	1.52 (1.28, 1.79)
Calcaneus BMD	1.46 (1.24, 1.71)

* Per –1 SD of BMD, adjusted for age and clinic.

prior hip fractures were uncommon (<1%), we combined prior hip fractures with other nonspine fractures in subsequent analyses. Several pairs of closely related variables were each associated with an increased risk, but when analyzed together, only one of the pair remained eligible for the multivariate model ($p < 0.10$). This included weight change since age 25 and BMI calculated using knee height (BMI remained eligible), hip abductor and triceps weakness (hip weakness remained eligible), and poor contrast sensitivity and reduced visual acuity (contrast sensitivity remained eligible). The protective effect of current use of estrogen did not differ by years of use, nor did it differ for women with surgical versus natural menopause. The increased risk associated with smoking was not attenuated by adjustment for variables measuring neuromuscular function. The increased risk of fracture associated with falling remained after excluding women who had a clinically detected vertebral fracture during follow-up.[9]

In multivariable models of 16 potential risk factors, not including BMD, 12 remained independent predictors ($p < 0.05$) of a first vertebral fracture (Table 3). Hip abductor strength ($p = 0.21$), back pain ($p = 0.09$), contrast sensitivity ($p = 0.07$), and gastric surgery ($p = 0.06$) were no longer significantly related to fracture risk. Results for multivariable models were similar when we analyzed either BMI calculated using knee height or BMI using young adult height.

Risk factors after adjustment for BMD

In models that adjusted for baseline distal radius BMD, smoking, use of estrogen, and frequent use of aluminum-containing antacids were no longer significant predictors of fracture, but attenuation of the relative risks for these predictors was minimal (Table 3). All other risk factors were independent of BMD. Results were essentially the same

TABLE 3. MULTIVARIABLE MODELS OF RISK FACTORS FOR FIRST VERTEBRAL FRACTURE WITH AND WITHOUT ADJUSTMENT FOR FRACTURES AND BMD

Measurement (comparison or unit)	*Odds ratios and 95% CIs*		
	Age-adjusted[§]	*Base MV model*	*Add radius BMD*
Age (+5 yrs)	1.33 (1.14, 1.55)	1.34 (1.15, 1.55)	1.28 (1.11, 1.49)
Maternal history of wrist fracture (vs. none)	0.10 (0.01, 0.71)	0.10 (0.01, 0.69)	0.09 (0.01, 0.66)
Paternal Hx of hip fracture (vs. none)	2.17 (0.99, 4.78)	2.27 (1.02, 5.07)	2.22 (1.00, 4.96)
Milk when pregnant or teen (<1 glass/day)	1.49 (1.09, 2.04)	1.43 (1.05, 1.96)	1.42 (1.04, 1.94)
Current estrogen user (vs. never user)*	0.54 (0.31, 0.95)	0.53 (0.30, 0.93)	0.60 (0.33, 1.08)
Current smoker (vs. never smoked)*	1.68 (1.04, 2.71)	1.70 (1.05, 2.76)	1.61 (0.98, 2.63)
Walks ≤1 blocks/day and does household chores <1 h/day	1.59 (1.18, 2.22)	1.59 (1.16, 2.18)	1.60 (1.16, 2.20)
High to moderate intensity recreational activity (any vs. none)	0.50 (0.31, 0.80)	0.54 (0.37, 0.80)	0.67 (0.37, 0.82)
Use of antacids with aluminum weekly (vs. < weekly)	1.54 (1.01, 2.37)	1.54 (1.02, 2.36)	1.48 (0.95, 2.28)
History of gastrectomy (vs. none)	2.46 (1.03, 5.83)	—	—
BMI with knee height, quintile 1–2 (vs. >2)[†]	1.64 (1.20, 2.22)	1.70 (1.25, 2.33)	1.53 (1.11, 2.08)
Back pain past year (all/some of time vs. less)	0.76 (0.56, 1.02)	—	—
Hip abductor weakness (per −3.3 kg[‡])	1.22 (1.04, 1.44)	—	—
Contrast sensitivity (per −0.6[‡])	1.22 (1.02, 1.46)	—	—
One or more fall in first 12 months FU (vs. none)	1.55 (1.05, 2.13)	1.71 (1.24, 2.35)	1.75 (1.27, 2.42)
Nonspine fracture since age 50 (vs. none)	1.50 (1.11, 2.03)	1.40 (1.03, 1.91)	1.32 (0.96, 1.81)
Distal radius BMD (per −1 SD)	—	—	1.40 (1.17, 1.67)

* Models include variables for past estrogen user and past smoking.
† <258.1 vs. ≥258.1 kg/m^2.
‡ Equivalent to 1 SD.
§ Candidate variables, $p \leq 0.10$ adjusted for age and clinical center.

adjusting for hip BMD, but adding spine BMD to the model more substantially attenuated the effect of a low BMI (RR, 1.18; 0.92, 1.82) and a history of nonspine fracture (RR, 1.12; 0.80, 1.56).

We used tertile cut-points for wrist BMD and 11 dichotomous risk factors to categorize women by their risk of vertebral fracture (Fig. 2). In all three BMD strata, the risk of a first vertebral fracture increased sharply with the number of risk factors present. The two highest risk subgroups combined (five or more risk factors and the low and middle BMD tertiles) included 27% of the women in the cohort and 60% of those with first incident fractures. Thirty-eight percent of women in all BMD categories combined had three or fewer risk factors, but suffered only 14% of the fractures. Results were similar using spine or hip BMD (data not shown).

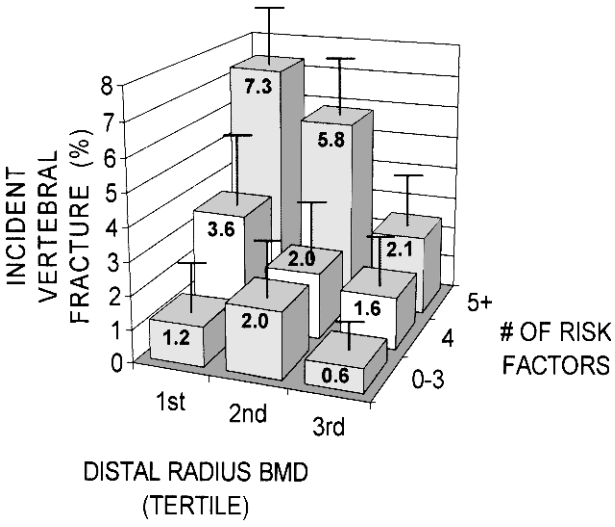

FIG. 2. Cumulative incidence of first incident vertebral fracture during 3.7 years of follow-up in women ≥65 years of age at baseline by the number of risk factors present and tertile cut-point of baseline distal radius BMD. Risk factors are age ≥ 70, a prior nonspine fracture after age 50, BMI (calculated with knee height) in the lowest 40%, current smoker, low level of physical activity (walks ≤1 block/day and does household chores <1 h/day), does no moderate or high intensity recreational physical activities, fell one or more times in the first 12 months of follow-up, not currently on estrogen replacement therapy, low milk consumption (<1 glass/day) when pregnant (or teenager for nulliparous women), ever used aluminum-containing antacids weekly, and paternal history of hip fracture. First (lowest) tertile of BMD: 0–3 risk factors, $n = 435$; 4 risk factors, $n = 423$; 5+ risk factors, $n = 861$. Second tertile of BMD: 0–3 risk factors, $n = 731$; 4 risk factors, $n = 498$; 5+ risk factors, $n = 728$. Third tertile of BMD: 0–3 risk factors, $n = 1008$; 4 risk factors, $n = 559$; 5+ risk factors, $n = 542$.

Interaction with age

An elevated resting pulse (>80 versus ≤80 bpm) was associated with an increased risk of fracture in women 65–74 years of age, but not in those older than 74 ($p < 0.05$ for interaction with age). In the younger women, a high pulse was an independent predictor (RR, 1.72; 1.03, 2.86) after adjusting for the other risk factors in Table 3 and radius BMD. There were no other interactions of risk factors with age or clinical center.

Effect of possible mild prevalent vertebral deformities

Among the women we considered at risk for a first vertebral fracture (i.e., those who did not have a ≥3 SD prevalent fracture at baseline), 403 (5.9%) had a possible mild baseline vertebral deformity (defined as vertebral height

ratios from 2.5 to 3 SD below normal). These women were no more likely to report a previous spine fracture or diagnosis of osteoporosis (2.6%) than those without a mild deformity (2.3%). Women with a possible mild deformity had an increased risk of incident vertebral fracture (10.9% versus 2.5% cumulative incidence; RR versus no mild deformity: 4.2; 2.9, 6.1) after adjusting for all other independent risk factors and spine BMD. The addition of mild deformity to the models in Table 3 did not alter the relative risks for other predictors, including radius BMD. Excluding women with mild deformities at baseline similarly had no appreciable effect on our results.

Factors not significantly associated with incident fracture

Many putative risk factors for osteoporosis were not associated with the risk of developing a vertebral fractures (Table 4). These include all reproductive history variables assessed, use of thiazide diuretics, and recent intake of calcium, caffeine, and alcohol. Past smokers and corticosteroid users did not have an increased risk. Several prominent risk factors for hip fractures were not related to first vertebral fractures, including weight, BMI calculated using height at baseline, maternal hip fracture, use of long-acting benzodiazepines, previous hyperthyroidism, cognitive impairment, and certain neuromuscular disabilities, such as inability to arise from a chair without the use of arms. Women with a history of falls in the year before baseline had a nonsignificant trend toward increased risk ($p = 0.13$).

Excluding calcium supplement users and women taking estrogen did not alter the lack of association for dietary calcium intake. The results for calcium supplement use were similar in women with, and without, a previous diagnosis of osteoporosis. Excluding women with a surgical menopause did not alter the null results for age at menopause or reproductive years.

Table 4. Variables Not Associated With a First Vertebral Fracture, After Adjusting for Age and Clinic ($p \geq 0.10$)

Variable (comparison or unit)	*Age-adjusted RR (95% CI)*
Maternal hip fracture (vs. none)	0.70 (0.39, 1.24)
Southern European ancestry (vs. other)	0.53 (0.21, 1.29)
Number of term pregnancies (per +1)	0.97 (0.88, 1.08)
Nulliparous (vs. parous)	1.09 (0.76, 1.59)
Ever breast fed ≥1 child (vs. none)	1.14 (0.84, 1.55)
Age at menarche (per +5 years)	1.14 (0.68, 1.93)
Age at menopause (per +5 years)	0.93 (0.81, 1.08)
Years from menarche to menopause (per +5 years)	0.94 (0.81, 1.08)
Bilateral oopherectomy (vs. all others)	1.02 (0.65, 1.61)
Milk intake since age 50 (per +7 glasses/week*)	0.99 (0.85, 1.15)
Current weight (per −1 SD)	1.13 (0.96, 1.33)
BMI with current height (per −1 SD)	1.13 (0.97, 1.35)
Current daily dietary calcium intake (per +425 mg*)	0.95 (0.81, 1.11)
Current use of calcium supplements (vs. none)	1.15 (0.85, 1.58)
Current daily caffeine intake (per +190 mg/day*)	0.98 (0.84, 1.14)
Past cigarette smoking (vs. never smoked)	1.15 (0.82, 1.61)
Current alcohol: 1–7 drinks per week (vs. none)	1.22 (0.89, 1.68)
Current alcohol: ≥7 drinks per week (vs. none)	1.14 (0.70, 1.91)
Current use of corticosteroids (vs. never used)	1.21 (0.44, 3.35)
Past estrogen use (vs. never used estrogen)	0.90 (0.64, 1.29)
Current thiazide diuretic use (vs. never used)	1.03 (0.74, 1.44)
Previous hyperthyroidism (vs. none)	0.85 (0.50, 1.83)
Self-rated health fair or poor (vs. good/excellent)	1.29 (0.87, 1.92)
Sedentary: ≤4 h on feet per day (vs. >4 h/day)	1.02 (0.61, 1.70)
≥1 fall in year before baseline (vs. none)	1.28 (0.95, 1.75)
Inability to rise from chair (vs. no inability)	0.86 (0.34, 2.15)

* Equivalent to 1 SD.

DISCUSSION

Among white women ≥65 years of age and free of prevalent vertebral fractures when the study began, 3.1% suffered a first vertebral fracture during an average of 3.7 years of follow-up. The risk of a first vertebral fracture was independently associated with behavioral and constitutional factors, some modifiable, of importance for both skeletal and general health. These factors may be useful in identifying women with the greatest need for interventions to prevent the development of vertebral fractures and in devising approaches to reduce this risk. Low BMD accounted, at least in part, for the effect of several variables on vertebral fracture risk, whereas other factors increased risk independently of BMD. Classifying women by their distal radius BMD and the number of risk factors they have produced a steep gradient of risk between women with high BMD and few or no risk factors and those with low BMD and multiple risk factors and permitted identification of a relatively small subgroup of women in whom most of the vertebral fractures occurred.

Our study has several unique features and strengths. It is one of only three[21,22] large, prospective population radiographic surveys of incident vertebral fractures and the only such study in North America. Ours is also the only study to evaluate risk factors for a first vertebral fracture. We achieved a high rate (75%) of radiographic follow-up in surviving women. We evaluated a comprehensive set of risk factors for osteoporosis and fracture, the same large set of risk factors that we previously examined in this cohort for association with a first hip fracture.[15] We used rigorously standardized protocols for the acquisition of spine radiographs, and our methods for defining prevalent[28] and incident[26] vertebral fractures have been extensively validated in comparison with criterion measures and alternative qualitative and morphometric approaches.[8,9,26,28,30,41,42]

Our definition of incident fracture (a 20% and at least 4-mm decrease in vertebral height) is widely used and is accepted in clinical trials by the FDA. The age-specific incidences of first vertebral fractures in our study were similar to that for first fractures in another study of white

women,[22] but direct comparisons of rates requires caution because we used a different definition of fracture and the frequency of incident vertebral fractures varies by definition.[26] Nevertheless, overall agreement among the methods for defining incident fractures is very high, and associations of risk factors and outcomes with incident fractures are broadly consistent regardless of the method used.[21,26,28,43] Thus, it is unlikely that differences in vertebral fracture determinants between ours and other studies are caused by different definitions of fracture.

Ours is the only study of risk factors for vertebral fracture focusing on women who have not already had one. About one-fifth of the full cohort had already had a vertebral fracture by our definition at study start, and our findings do not apply to the risk of recurring vertebral fracture in these women. Women with an existing vertebral fracture are known to have a very high risk of further vertebral,[2–4,22] hip, and other nonspine fractures.[2,6,7] As a result, an existing vertebral fracture by itself is usually sufficient to establish a diagnosis of osteoporosis and warrant treatment in a postmenopausal woman.[44] In addition, women with prevalent and incident vertebral fractures experience acute and chronic back pain, disability, and physical impairment,[8–12] which may alter physical activity and other health behaviors and lead to medical treatment. These consequences of fracture may bias associations of risk factors with vertebral fractures in cross-sectional studies of prevalent fractures and in prospective studies that include large numbers of women with existing vertebral fractures. In our study, for example, women with baseline prevalent vertebral fractures did not differ in physical activity compared with women without a fracture, but greater physical activity protected women without a baseline fracture from developing one.

We found that women with mild abnormalities in vertebral shape at baseline, defined as vertebral height ratios just under our threshold for defining prevalent fractures (between 2.5 and 3.0 SD below normal), had an increased risk of incident fractures. The presence of such mild abnormalities may be a marker for emergent skeletal fragility or for the presence of other biomechanical conditions in the spine that increase fracture risk. Our definition of prevalent fracture, based on vertebral height ratios $\geq$3 SD below population normal values, is widely used.[28] It is likely that vertebrae with height ratios between 2.5 and 3.0 SD below normal include a mixture of mild osteoporotic and degenerative deformities, normal vertebrae with extreme shapes, and normal vertebrae with errors in measured height. Thus, some of the women included in our analysis of first fractures may have had a mild osteoporotic deformity at baseline. In the absence of a gold standard for vertebral fracture, the number of such women is not known. Importantly, our results for other risk factors did not change after adjusting for, or excluding women with, mild baseline abnormalities of vertebral shape. Very few (3%) of the women in our study with these mild abnormalities had been told by a physician that they had a spine fracture or osteoporosis. Mild osteoporotic deformities are not identified reliably even by expert radiologists trained in standardized qualitative assessments[45] and may be associated with little pain or disability,[8] making accurate routine clinical detection unlikely. Development of accurate and inexpensive methods to detect mild osteoporotic changes in vertebral shape while maintaining a low false positive rate may help focus prevention efforts.

Relative risks of incident vertebral fracture per SD decrease in BMD were somewhat lower in our study than reported in a meta-analysis of five prospective studies.[46] In addition, in our study, the relative risk per SD for spine BMD was greater than that for BMD at other measurement sites, a pattern not seen in previous studies. These differences may reflect our focus on first fractures, whereas other studies have included women both with, and without, existing vertebral fractures. In addition, we measured hip and spine BMD part way through follow-up, and fractures occurring during follow-up may have affected the BMD at these sites. Our primary analyses used distal radius BMD, which was measured at baseline. In our study, a previous nonspine fracture predicted the risk of a first vertebral fracture and should be useful in targeting prevention efforts. However, a prior nonspine fracture did not seem to be a marker for spinal fragility independently of spine BMD.

We found that greater age and a lower BMI each independently increased the risk of vertebral fractures, confirming previous cross-sectional and prospective studies.[13,14,18,21,47,48] The rate of first fracture was more than three times higher in women $\geq$80 years of age compared with those 65–69 years of age, strong evidence that the emergence of spinal fragility occurs with increasing frequency with age. Low BMI, calculated using either knee height or young adult height, as well as smaller weight gains since age 25, were strong risk factors for vertebral fracture. These associations were largely mediated by spine BMD. Women whose BMI was <24 kg/m^2, calculated using measured baseline weight and recalled height at age 25, had a 70% increased risk of fracture. BMI calculated using height at baseline was not a risk factor, suggesting that even in women without definite vertebral fractures, height loss may bias the association of the standard measure of BMI with vertebral fracture risk.

Several lifestyle and behavioral variables were associated with the risk of a first vertebral fracture. Women who participated in any moderate- or high-intensity recreational physical activity were much less likely to develop vertebral fractures, whereas at the other end of the spectrum, those who were inactive, spending very little time walking and doing household chores, had an increased risk. These findings provide support for the skeletal and neuromuscular benefits accruing to older women who remain active and engage in moderate exercise.[49,50] Our results also support smoking cessation as an important part of efforts to prevent osteoporosis. Current cigarette smokers had a 70% greater risk of vertebral fracture, an effect that was not caused by low BMI or reduced weight gain but was partly explained by low BMD. Smoking has been found to increase risk in one previous study of vertebral fractures[23] but not in several others.[18,21,48] Less than one glass of milk per day during pregnancy (or during teenage years for nulliparous women) was associated with a greater risk of fractures occurring many years later, even after adjusting for BMD, suggesting that a permanent impairment of vertebral

strength may result from low-calcium intake during periods of high-calcium need. As previously reported,[51] we did not find a relationship of vertebral fractures with milk consumption at other periods of life nor with current dietary calcium intake and use of calcium supplements. Our findings differ from the European Prospective Osteoporosis Study (EPOS), which did not find early milk consumption, current smoking, and current physical activity related to vertebral fractures,[21] a difference that may reflect our focus on first fractures. Alcohol consumption was not related to vertebral fracture risk, consistent with other studies,[18,21,48] but few women in any of these studies reported heavy drinking.

Women in our study using estrogen at baseline had about a 40% lower risk of a first vertebral fracture, which was partly explained by their higher BMD. This is consistent with protective effects of estrogen treatment on vertebral fractures found in randomized trials[52,53] and with previous results from our cohort showing that women with very low serum estradiol levels had an increased risk of incident vertebral fractures.[54] Women who had regularly used aluminum-containing antacids had an increased risk of fracture, in part through lower BMD. Therapeutic doses of aluminum-containing antacids increase obligatory calcium loss and have been found to substantially elevate urine calcium.[55] Just over 1% of women had undergone surgery to remove part of their stomach, and they had a 2.5-fold greater risk of vertebral fracture. This was independent of smoking and weight change and may be a result of reduced vitamin D and calcium absorption after gastrectomy.

Women who fell during the first year of the study had a 70% increased risk of incident vertebral fracture. Compared with hip and other limb fractures, falls are not usually considered to play a large role in vertebral fractures. However, a significant proportion of falls may result in traumatic forces to the spine sufficient to cause vertebral fractures. In a population study of clinically diagnosed vertebral fractures, Cooper et al. found that 30% of these fractures in both genders combined were associated with a fall from a standing height or less and that women were three times as likely as men to have a vertebral fracture caused by moderate or minimal trauma, including a fall.[56] Our study extends these observations by showing that falls were associated with an increased risk of vertebral fractures detected by serial radiograph in analyses that excluded women with clinically detected vertebral fractures during follow-up. It is possible that specific diseases and impairments that increase the risk of falls and that we did not evaluate account for the association of falls and vertebral fractures.

In women <75 years old, a resting pulse >80 bpm increased the risk of vertebral fracture. An elevated pulse, which we also found associated with hip fracture in this cohort, may be caused by undiagnosed hyperthyroidism[57] or may indicate decreased fitness or impaired cardiac function. Surprisingly, we found that women who reported that their mother had a wrist fracture rarely had vertebral fractures. Mother's wrist fractures had no association with prevalent vertebral fractures in our study, so this most likely represents a chance finding, and this variable was not included in the stratification by number of risk factors.

Reproductive factors were not associated with incident vertebral fractures. This contrasts with two European prospective studies, one of which found that late menarche[21] and the other that early menopause[23] increased the risk of vertebral fracture. However, in our study, natural menopause before age 45 was independently associated with prevalent vertebral fractures, suggesting that a short fertile period may be associated with an early onset of spinal fragility.

A comparison of risk factors for first vertebral and hip fractures in our cohort[15,58,59] reveals both broad similarities and some differences in their epidemiology and pathophysiology. A variety of heterogeneous factors influenced the risk of both types of fracture, and most of these remained predictors of fracture after adjusting for BMD. Women with multiple risk factors and low BMD are at especially high risk of both vertebral fracture and hip fracture. Using BMD and risk factors that are common to both types of fractures could help focus preventive efforts more efficiently. In addition, age is a strong predictor of both types of fracture after adjusting for other risk factors and BMD, indicating that there are important age-related determinants of these fractures that remain to be elucidated.

Similar to hip fracture, factors related to bone strength (including some that are independent of BMD) and factors that result in trauma and abnormal loads on the skeleton are both likely to play a role in the pathophysiology of vertebral fractures. Nearly all hip fractures involve falls from a standing height or less.[60] Our findings confirm evidence from a previous study[61] that falls also play a role in vertebral fractures. However, the fact that several important fall-related risk factors such as measures of physical frailty, neuromuscular impairment, general poor health, and sedative use, which we found to be strong predictors of hip fracture, were not associated with first vertebral fractures is consistent with a more limited role of falls in the pathogenesis of vertebral fractures. In an osteoporotic spine, routine activities such as lifting a moderately heavy object or holding it in outstretched arms or with trunk flexed can also generate forces sufficient to result in a fracture.[62]

Obesity is protective for both vertebral and hip fractures in our cohort, an effect largely mediated by higher BMD.[58] In contrast to hip fracture, BMI but not body weight was a significant risk factor for developing a vertebral fracture, suggesting that adiposity might play a more important role than weight per se in influencing bone strength at the spine. Higher levels of physical activity are also protective for both vertebral and hip fracture.[15,59] However, in contrast to hip fracture, we did not find that extremely sedentary women (i.e., those who spent only a few hours a day on their feet) had an elevated risk, suggesting that short periods of weight-bearing per se are not sufficient to provide protection from vertebral fractures. A parental history of hip fracture increased the risk of both first vertebral and hip fractures in our cohort, but for vertebral fractures, this was limited to paternal history, whereas for hip fractures, maternal history was important.

Our study has several limitations. All of the women were ≥65 years of age at baseline, and thus our findings may not apply to younger women. However, based on tests for in-

teractions between risk factors and age, our results were largely consistent between the younger and older women within the age range of our sample. In addition, many of the risk factors that we found for first vertebral fractures were also associated with prevalent vertebral fractures at baseline. This consistency suggests that our findings for some risk factors may apply to postmenopausal women younger than those in our study, but this needs to be verified in studies of women this age. Our findings may also not apply to men, and because our cohort was nearly all white, to other racial or ethnic groups.

In conclusion, elderly women have a high risk of developing spinal fragility, as indicated by the first occurrence of a vertebral fracture, which continues to increase with age. Risk factors for a first vertebral fracture seem to be fewer in number and somewhat weaker than those for hip fracture. However, as with hip fracture, women with multiple risk factors and low BMD have the greatest risk of vertebral fracture, and this potent combination could be used to focus efforts at preventing vertebral fractures.

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