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The Relationship Between Bone Density and Incident Vertebral Fracture in Men and Women

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ABSTRACT

Bone mineral density (BMD) is an important predictor of future fracture risk in women; however, there are few prospective data in men. The aim of this analysis was to determine whether there are differences in the relationship between BMD and incident vertebral fracture in men and women. Men and women were recruited from population-based registers in 21 European centers. Those recruited were interviewed and had spinal radiographs performed. The radiographs were assessed morphometrically and prevalent vertebral deformity was defined using the McCloskey-Kanis method. Repeat spinal radiographs were performed at a mean of 3.8 years after the baseline radiographs. Incident fractures were defined using a combination of the point prevalence and 20% reduction in vertebral height (plus a 4-mm reduction in absolute height) criteria. BMD measurements were made in a subsample of those recruited. Poisson regression was used to explore the influence of gender, age, prevalent deformity, and BMD on the incidence of vertebral fracture. Thirty-four hundred sixty-one men and women had both paired spinal radiographs and bone density measurements performed. BMD at the spine and femoral neck was higher in men than in women. After adjusting for age, the risk of incident vertebral fracture was greater in women than in men (relative risk [RR] = 2.3; 95% CI, 1.5–3.6) and increased by a factor of 1.4 (95% CI, 1.2–1.8), 1.5 (95% CI, 1.2–1.8), and 1.6 (95% CI, 1.3–1.9) per decrease of 0.1 g/cm^2 in BMD at the spine, femoral neck, and trochanter, respectively. After adjusting for BMD at the spine or trochanter, the gender difference in the predicted age-specific incidence of vertebral fracture was no longer significant (RR = 1.1 and 95% CI, 0.6–1.9 at the spine; RR = 1.5 and 95% CI, 0.8–2.7 at the trochanter), although it persisted after adjusting for femoral neck BMD (RR = 1.9; 95%CI, 1.1–3.3). The presence of a prevalent vertebral deformity was a strong risk factor for future vertebral fracture, although the strength of the association was reduced after adjustment for age, sex, and spine BMD. However, adjustment for the presence of a baseline vertebral deformity did not alter the main findings. In conclusion, at a given age and spine (although not femoral neck) bone density, the risk of incident vertebral fracture is similar in men and women. Incident vertebral fractures are more common in women than men because at any age their spine BMD is lower. (J Bone Miner Res 2002;17:2214–2221)

Key words **incident vertebral fracture, bone mineral density, sex differences, prevalent vertebral deformity, population based study**

INTRODUCTION

VERTEBRAL FRACTURE is an important health problem in both men and women through its association with back pain and disability.[1–3] Over the next 50 years, the numbers of individuals with osteoporotic fracture, particularly hip but also vertebral fracture, is set to rise in both men and women because of demographic changes toward an older population.[4,5] Early identification of individuals who are at risk of fracture and targeting interventions at these individuals is an important component of any strategy to reduce the burden of disease in the population.

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Bone mineral density (BMD) is one of the most important determinants of incident vertebral fracture in women, with data from many studies suggesting a twofold increase in risk per SD reduction in BMD.[6] However, there are no published data from prospective population studies examining the relationship between BMD at either the spine or femoral neck and vertebral fracture in men. We have published a retrospective study examining the effect of gender on the relationship between bone density and prevalent vertebral fracture but there is little other data bearing on this question.[7] As a consequence, at present, it is difficult to apply a clinical value to the results of bone density measurements in men. If the relationship is similar to that observed in women, then it may be possible to use a single gender-neutral diagnostic criterion for bone density. If not, gender-specific criteria should be used. This has implications in clinical decision making, particularly because effective therapies have become available for use in treating men with osteoporosis.[8,9]

In this study, using data from the population-based European Prospective Osteoporosis Study (EPOS), our aim was to determine (i) whether there are differences in the strength of the relationship between BMD and incident vertebral fracture in men and women and (ii) if so, whether the risk of incident vertebral fractures is the same at the same absolute level of BMD in men and women.

MATERIALS AND METHODS

The subjects who took part in this analysis were recruited for participation in the EPOS. The detailed methods have been described elsewhere.[10] In brief, men and women were recruited from population-based registers in 36 centers across Europe. Stratified sampling was used with the aim of recruiting equal numbers of men and women in each of six 5-year age bands: 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, and ≥75–79 years. All subjects who agreed to take part had baseline lumbar and spinal radiographs, which were taken according to standard protocol, and an interviewer-administered lifestyle questionnaire. A subsample of those recruited to the baseline survey had BMD assessed at the spine and femoral neck. The subjects recruited were followed prospectively to ascertain new clinical fractures, and in 28 centers, subjects were invited to attend for repeat spinal radiographs, which were performed at a mean of 3.8 years after the baseline survey.

BMD

In 21 of the 36 European Vertebral Osteoporosis Study (EVOS) centers, subjects had bone densitometry performed at baseline or during the follow-up period. Eleven centers measured at both the spine and the hip, 2 centers measured the spine alone, and 8 centers measured the hip alone. Of the 2204 spine BMD measurements, 1865 measurements were made before or within 1 year of the initial radiograph, 275 measurements were made >12 months after the first radiograph but within a month of the second one, and 64 measurements were made >1 month after the second radiograph (between 1 and 2 years after, all in one center). Of the 2986 hip BMD measurements, 1452 measurements were made before or within 1 year of the initial radiograph, 1110 measurements were made >12 months after the first radiograph but within a month of the second one, and 424 measurements were made after the second radiograph (256 measurements within 6 months, 70 measurements between 6 months and 1 year, and 98 measurements >1 year after). In general, each center measured all of its participants over a short period; therefore, they were all measured either at the time of the first film, during the follow-up, or after the second film. Of subjects with two X-rays, BMD was measured in 69% of subjects in the centers that measured only spine BMD, 65% of subjects in the centers that measured only hip BMD, and 80% of subjects in the centers that measured both spine and hip BMD.

The densitometers in each center were, with one exception (a Sopha fan-beam machine), pencil beam DXA machines made by Lunar (Madison, WI, USA), Hologic (Waltham, MA, USA), or Norland (Fort Atkinson, WI, USA) and were cross-calibrated using the European Spine Phantom.[11] At least five measurements of the phantom were made on each machine and a two-parameter empirically fitted linear or exponential calibration curve was used to convert measured density values into standardized values, as described by Pearson.[12] Detailed descriptions of the densitometry procedures as they applied to the subjects are presented elsewhere.[13]

Radiographs

The radiographs at both baseline and follow-up were taken using a standard protocol. The thoracic spine films were centered at T7 and lumbar films were centered at L2. The breathing technique was used to obscure overlying lung shadows. All of the radiographs were forwarded to the central coordinating facility in Berlin for evaluation and were assessed morphometrically by one of four observers. In each subject, vertebrae from T4 to L4 were assessed and anterior, middle, and posterior heights were recorded. Using these measurements, the presence or absence of a prevalent vertebral deformity in both films was defined using the McCloskey-Kanis algorithm.[14] An incident vertebral fracture was defined as a vertebra that showed evidence of a change in absolute height (anterior, middle, or posterior height) between films of 20% or more (plus at least 4 mm), together with the requirement that the vertebra satisfy criteria for prevalent vertebral deformity on the follow-up (but not the baseline) film.[15]

Statistical analysis

Poisson regression was used to determine the relationship between incident vertebral fracture and BMD. Poisson regression predicts an incidence rate (IR) as

$$\mathrm{IR} = \exp\left(\sum_i \beta_i x_i + \mathrm{offset}\right),$$

where the x_i's represent any predictor variables and the β_i's represent the corresponding coefficients. The offset represents the duration of exposure to risk, in this case, the time

TABLE 1. SUBJECT CHARACTERISTICS

	Men (n = *1537*)	*Women* (n = *1924*)
Age (years)	63.3 (7.9)	62.2 (7.5)
Spine BMD (g/cm^2)	1.06 (0.22)	0.92 (0.20)*
Femoral neck BMD (g/cm^2)	0.83 (0.14)	0.73 (0.14)*
Trochanteric BMD (g/cm^2)	0.77 (0.14)	0.63 (0.12)*
Prevalent deformity (%)	10.9	9.7

* $p < 0.05$.

between the two radiographs. Thus Poisson regression can allow for different durations of follow-up in different individuals, which is why it was preferred to the more conventional logistic regression. The equation may be used to determine the relative risk (RR) for a unit change in x_i ($RR = \exp(\beta_i)$), and a 95% CI can be calculated from the SE of β_i. The foregoing equation can also be used to predict the IR as a function of the predictor variables. In particular, the IR can be calculated as a function of a particular variable when the other predictor variables are kept fixed at particular values. For example, if the IR is calculated as a function of BMD with age kept fixed at 65 years, this is referred to as the predicted IR adjusted to age 65 years.

In the analysis we first determined the strength of the relationship (RR) in men and women between incident vertebral fracture, age, spine BMD, femoral neck BMD, and prevalent vertebral deformity. To permit direct comparisons between men and women, the BMD values were standardized to the same unit—per 0.1 g/cm^2 (for comparison purposes we also looked at the effect of using National Health and Nutrition Examination Survey [NHANES] SDs[16]). The influence of gender on these relationships was determined in a separate model including gender as a covariate. To allow for the possibility that the strength of the association between BMD and incidence of vertebral fracture was influenced by the timing of the measurement of the BMD, the interaction between BMD and the delay between first X-ray and the BMD measurement was included in the regression models. We then determined the effect of the various risk factors identified on the predicted incidence of vertebral fracture separately in men and women.

RESULTS

Subjects

In the 21 participating EPOS centers who had performed BMD measurements, 4650 men and women had paired spinal radiographs of adequate quality to be used for the identification of incident vertebral fractures. In these 21 centers, 3461 subjects (74%) had bone mineral measurements of either the hip or the spine or both. The characteristics of subjects who had any bone density measurements are shown in Table 1. Mean age and prevalence of vertebral deformity were similar in men and women. However, for all skeletal regions, BMD values were significantly greater in men than in women. The higher than expected prevalence of deformity in men at this age in part may be related to an increased exposure to heavy activity during earlier adult life.[17] Compared with those with any BMD measurement (3461 subjects), those without (1189 subjects) were of a similar age (62.6 years vs. 62.5 years) and had a similar prevalence of vertebral deformity (10% vs. 9.1%) with no statistically significant difference between them.

Risk factors for incident vertebral fracture

In total, 26 men and 69 women had evidence of one or more incident vertebral fractures, an incidence of 9.3/1000 person-years in women (95% CI, 7.3–11.8) and 4.5/1000 person-years in men (95% CI, 3.0–6.6). Increasing age, low BMD, and the presence of a vertebral deformity at baseline were significant predictors of incident fracture in both men and women (Table 2). There was no evidence that the association between BMD and incident fracture risk depended on the time the BMD measurement was made ($p > 0.3$ for all three sites). The differences in the strength of these relationships between men and women were not statistically significant. After age adjustment, women had a twofold increased risk of vertebral fracture compared with men (RR = 2.3; 95% CI, 1.5–3.6). After adjusting for BMD at the spine or trochanter, the gender difference in the predicted age-specific incidence of vertebral fracture was no longer significant (RR = 1.1 and 95% CI, 0.6–1.9 at the spine; RR = 1.5 and 95% CI, 0.8–2.7 at the trochanter), although it persisted after adjusting for femoral neck BMD (RR = 1.9 ; 95% CI, 1.1–3.3). After adjusting for age and gender, the risk of incident vertebral fracture increased by a factor of 1.4 per 0.1 g/cm^2 reduction in spine BMD (95% CI, 1.2–1.7), 1.5 per 0.1 g/cm^2 reduction in femoral neck BMD (95% CI, 1.2–1.8), and 1.6 per 0.1 g/cm^2 reduction in trochanteric BMD (95% CI, 1.3–1.9). Further adjustment for the presence of baseline vertebral deformity reduced these estimates slightly, but they remained statistically significant (Table 3). Among those with femoral neck measurements, after adjusting for age and sex, the predictive risk of a baseline vertebral deformity for future vertebral fracture was 4.9 (95% CI, 3.1–7.8). Further adjustment for femoral neck BMD reduced this risk to 4.3 (95% CI, 2.7–6.8). Among those with spine measurements, the corresponding RRs were 3.9 (95% CI, 2.3–6.6) and 2.9 (95% CI, 1.7–5.1), respectively. There was no evidence in any of these analyses that the timing of the BMD measurement influenced the results.

Influence of age and BMD on the incidence of vertebral fracture

The incidence of vertebral fracture as a function of spine BMD was similar in men and women (Fig. 1). This shows how the predicted incidence varies with spine BMD adjusted to age 65 years. The incidence of vertebral fracture as a function of femoral neck BMD was greater in women than men (Fig. 2). Figures 3 and 4 present the predicted incidence of vertebral fracture by age separately in men and women, before and after adjusting for spine and femoral neck BMD, respectively. After adjusting for spine bone density, at all ages the incidence of vertebral fracture was similar in men and women (Fig. 3). This was true after

Table 2. RR of Incident Vertebral Fracture in Men and Women

	Men RR (95% CI)	*Women RR (95% CI)*
Age (per decade)	2.5 (1.5–4.3)	2.0 (1.5–2.8)
Spine BMD (per 0.1 g/cm^2)	1.4 (1.1–1.9)	1.5 (1.3–1.9)
Femoral neck BMD (per 0.1 g/cm^2)	1.5 (1.0–2.1)	1.8 (1.4–2.2)
Femoral neck (per SD,[a] aged 20–29 years)	1.7 (1.0–2.8)	2.0 (1.5–2.6)
Trochanteric BMD (per 0.1 g/cm^2)	1.3 (0.9–1.9)	1.9 (1.5–2.4)
Trochanteric BMD (per SD,[a] aged 20–29 years)	1.4 (0.9–2.1)	1.9 (1.5–2.4)
Prevalent deformity	5.9 (2.7–12.9)	5.2 (3.1–8.5)

Age, BMD, and prevalent vertebral deformity as univariate predictors.
[a] NHANES SDs.[16]

Table 3. RR of Incident Vertebral Fracture in Men and Women

	RR (95% CI)
Gender (female vs. male)[a]	1.2 (0.6–2.1)
Age (per decade)[b]	1.8 (1.3–2.6)
Spine BMD (per 0.1 g/cm^2)[c]	1.3 (1.2–1.6)
Femoral neck BMD (per 0.1 g/cm^2)[c]	1.4 (1.1–1.7)
Trochanteric BMD (per 0.1 g/cm^2)[c]	1.4 (1.2–1.7)
Prevalent deformity[d]	2.9 (1.7–5.1)

Gender, age, BMD, and prevalent vertebral deformity as multivariate predictors.
[a] Adjusted for age, spine BMD, and prevalent deformity.
[b] Adjusted for gender, spine BMD and prevalent deformity.
[c] Adjusted for age, gender, and prevalent deformity.
[d] Adjusted for age, gender, and spine BMD.

adjusting for trochanteric BMD, but not after adjusting for femoral neck BMD (Fig. 4).

Influence of prevalent deformity on the incidence of vertebral fracture

The predicted incidence of vertebral fracture in men and women with and without a baseline vertebral deformity by age, after adjusting for spine BMD, is shown in Fig. 5. There was no interaction between age and prevalent vertebral deformity on the incidence of vertebral fracture. The presence of a prevalent vertebral deformity significantly increased the risk of incident vertebral fracture in both men and women. There was no significant difference in the strength of the risk between men and women. A man with a prevalent vertebral fracture was 2.2 (95% CI, 1.5–3.4) times more likely to sustain an incident vertebral fracture than a woman without a prevalent deformity and 2.5 (95% CI, 1.2–5.5) times more likely to sustain an incident vertebral fracture than a woman without a prevalent deformity after adjusting for age and spine BMD.

DISCUSSION

In this study men and women of the same age and spine bone density had the same risk of sustaining an incident vertebral fracture. This was true for individuals with and without a baseline prevalent vertebral deformity. Although the increase in risk of incident vertebral fracture per unit decrease in BMD at the femoral neck was similar in men and women, the absolute risk at a given age and given level of BMD was greater in women. The presence of a baseline vertebral deformity was a stronger predictor of incident vertebral fracture than gender.

Our study had several strengths. It was both population based and used standardized approaches in the study design, conduct, and analysis. However, there are a number of methodological issues to be considered in interpreting the results. The data were collected as part of a multicenter study. Variation in survey methods between centers may have lead to variation in data quality. The effect of this though would be to dilute the strength of any observed associations toward no effect. It seems unlikely, given that similar considerations would have applied to men and women, that it would have altered our main findings in relation to the gender comparison.

In the 21 centers who participated in this study, follow-up X-rays were available in ~50% of those subjects recruited to the baseline survey, although there was considerable between-center variability in the proportion with follow-up measurements. The predominant reasons were because of resource constraints rather than subject refusal. In a separate analysis, although there were differences in the baseline characteristics between those with and without repeat spinal radiographs, these had little effect on the overall IR observed.[15] However, even if there were genuine differences in fracture risk between those with and without follow-up radiographs, this should not have impacted on the comparison of BMD effects in men and women.

In the majority of subjects, BMD was assessed at the time of the baseline survey. However, because of practical constraints a proportion of subjects had BMD assessed after the baseline survey. However, there was no evidence that the timing of the BMD measurement influenced the results. In addition, when the data were reanalyzed, using BMD data from the baseline survey only, the results remained unchanged. Finally, our data were obtained from a predominantly white group and the results may not be extrapolated with full confidence beyond this group.

Prospective studies suggest that BMD is an important risk factor for future fracture in women.[6] In contrast, relatively

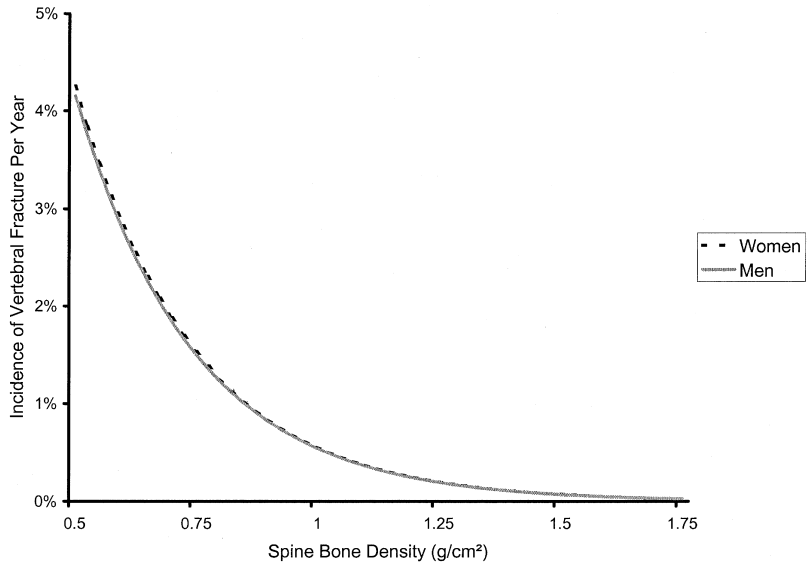

FIG. 1 Predicted incidence (%/year) of vertebral fracture with spine BMD in men and women.

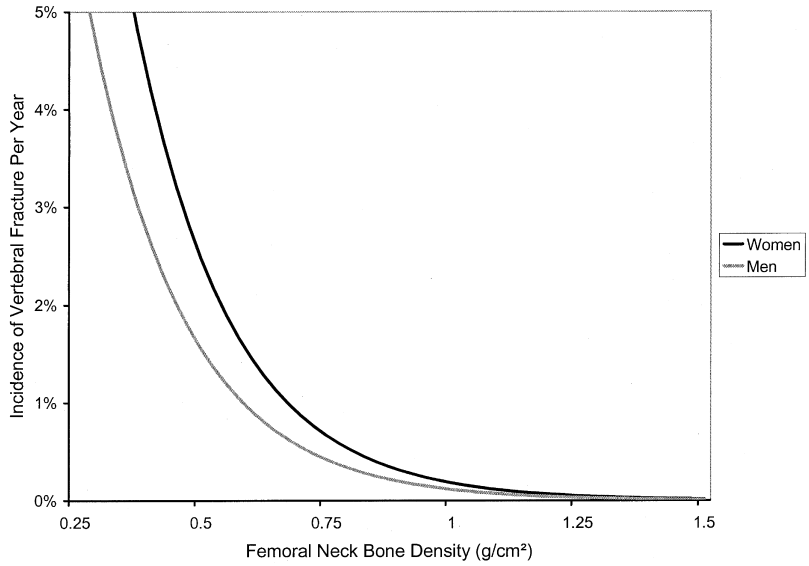

FIG. 2. Predicted incidence (%/year) of vertebral fracture with femoral neck BMD in men and women.

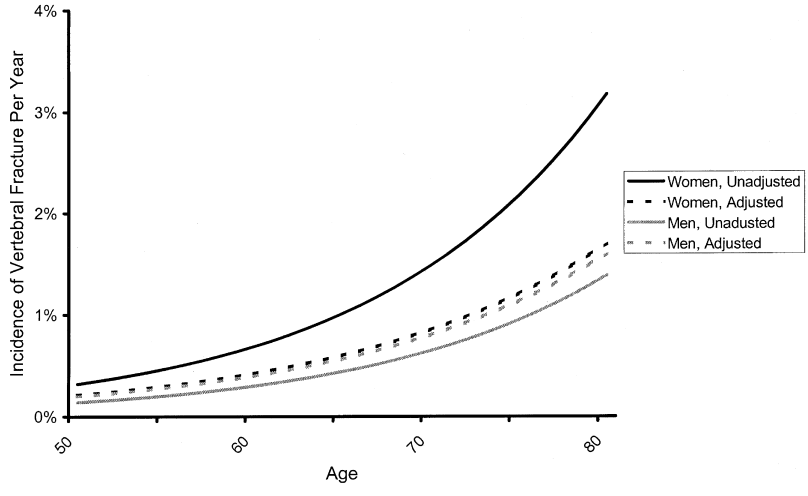

FIG. 3. Predicted incidence (%/year) of vertebral fracture with age in men and women, unadjusted and adjusted to a spine BMD of 1.0 g/cm^2.

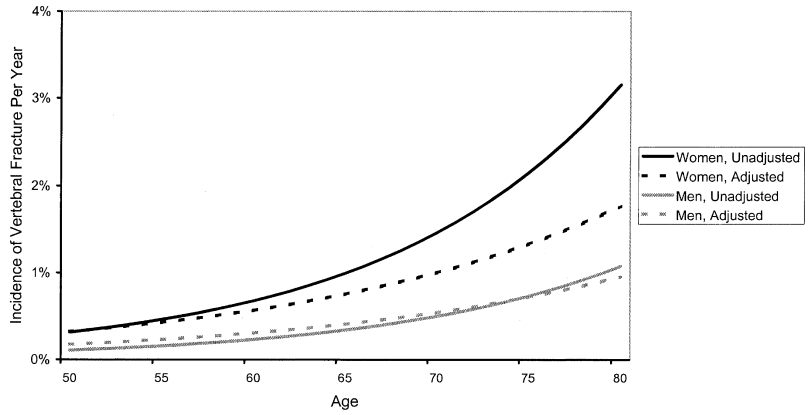

FIG. 4. Predicted incidence (%/year) of vertebral fracture with age in men and women, unadjusted and adjusted to a femoral neck BMD of 0.75 g/cm^2.

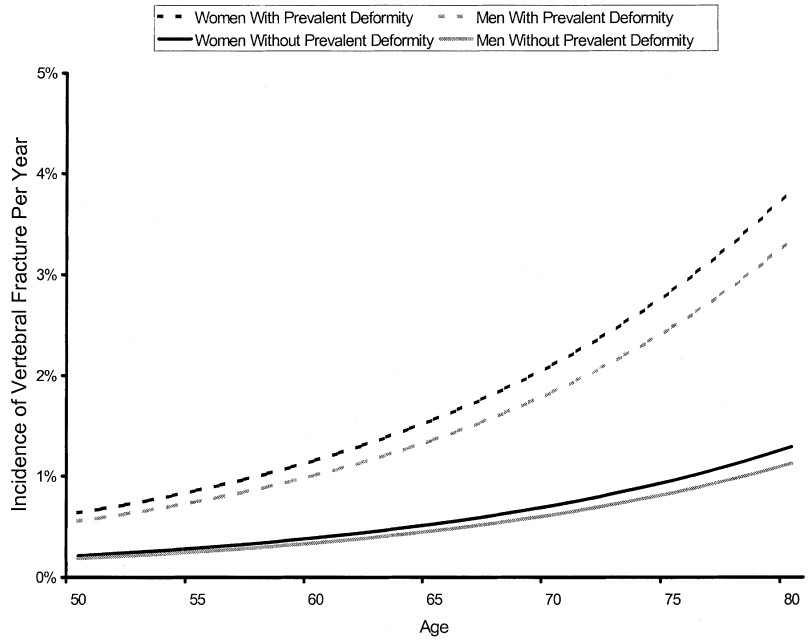

FIG. 5. Predicted incidence (%/year) of vertebral fracture with age in men and women, with and without evidence of baseline prevalent vertebral deformity, and adjusted to a spine BMD of 1.0 g/cm^2.

little is known about the strength of the relationship between fractures and BMD in men. The evidence from cross-sectional studies is somewhat conflicting. Lunt et al. found that spine BMD was an important determinant of radiographic vertebral deformity in men and women >50 years old and that the gradient of risk was similar in men and women.[7] In contrast, Melton et al. reported that the risk of fragility fractures increased with decreasing BMD in both men and women though the risk increased more rapidly in women.[18]

There are data from several prospective studies. In the Rotterdam study, De Laet et al. reported that the increase in risk of hip fracture (per SD decrease in femoral neck BMD) was similar in men and women,[19] while in the prospective Hawaii Osteoporosis Study, the increase in risk of vertebral fracture (per SD change in distal radius BMD and also calcaneal BMD) was similar in men and women.[20] Our results support these findings, indicating that for a given change in BMD (at both the spine and the femoral neck) the change in the risk of incident vertebral fracture is similar in men and women.

In addition to the gradient of risk being similar in men and women, several studies support our findings in relation to spine BMD—that the absolute risk of fracture at a given level of BMD is the same in men and women. Thus, Cheng et al. assessed calcaneal BMD in a group of men and women aged 75 years and 80 years and followed the cohort during a 5-year period for the occurrence of clinical fractures.[21] Fractures were more common in women and occurred at lower bone density; however, for a given level of bone density the probability of fracture was the same. Using data from the Hawaii Osteoporosis Study, Ross et al. reported that incident vertebral fractures occurred at the same level of calcaneal BMD in men and women.[20] While using national data concerning the incidence of hip fracture in The Netherlands and cross-sectional BMD data from the Rotter-

dam study and assuming a similar gradient of risk, De Laet et al. reported that the risk of hip fracture by age and femoral neck bone density is similar in men and women.[22]

The similarity in the relationship between BMD and incident vertebral fractures in men and women observed in our study appears at first sight somewhat surprising because it is known that men have larger vertebrae than women, even after adjusting for body size, which provides greater strength for a given level of true (volumetric) bone density.[23,24] However, because DXA measures areal BMD, any increase in vertebral size will result in a higher areal BMD for a given volumetric density (the bone mineral content increases as the cube of the change in size, while the area increases as its square). The greater strength due to the larger vertebral size in men may be offset in part by the apparent overestimation of bone density (and thus strength) in larger vertebrae when assessment is made using DXA. It is possible also that the presence of osteophytes/disc degeneration, which are more frequent in men than women, may influence the level of bone mass at which fractures occur.[25]

In our study, adjusting for femoral neck BMD reduced the difference in the predicted incidence of vertebral fracture between men and women though the difference persisted. It is possible that any degree of overestimation of bone density in men compared with women may differ at the spine and hip because of the different shapes of the bones and methods of selecting regions of interest at these sites.

Other factors that influence bone strength and that may differ in men and women and at different skeletal sites include microarchitecture,[26] bone quality, and bone turnover. However, the clinical relevance of these factors in independently determining vertebral fracture risk is unclear.

Our data confirm the importance of a previous vertebral fracture in determining susceptibility to further fractures.[27,28] In our study the risk of incident vertebral fracture was increased by a factor of fivefold in those with a baseline vertebral deformity with the risk persisting after adjusting for BMD. This was true in men and women and indeed the risk for men with a previous vertebral fracture was 2.5 times greater than for women who have not yet sustained any fractures after adjusting for age and BMD.

In 1994, the World Health Organization (WHO) established thresholds of BMD in women to define osteoporosis that is widely accepted.[29] Osteoporosis in women is defined as a BMD or bone mineral content of >2.5 SD below the young average value in women. Previous investigators have variously used thresholds for the diagnosis of osteoporosis in men derived from either male or female populations. Recently, it was suggested that the same absolute diagnostic threshold be used in men as in women using the reference standard of femoral BMD.[30] Our results, which indicate that men and women of the same age and spine bone density have the same risk of sustaining an incident vertebral fracture, suggest that the same absolute threshold of spine bone density should be used for diagnosis in men and women. However, the data in relation to femoral neck BMD suggest a different threshold might be appropriate. Further data from large-scale prospective studies are required to clarify the relationship between the occurrence of fractures and absolute BMD measured at different skeletal sites.

In conclusion, in this population-based prospective study, men and women of the same age and with the same spine (but not femoral neck) bone density had a similar risk of sustaining an incident vertebral fracture. Incident vertebral fractures are more common in middle-aged and elderly women than in men because at any age their spine bone density is lower.

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