Prediction of Vertebral Fractures Is Specific for Gender and Site of Bone Mineral Density Measurement

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ABSTRACT. ***Objective.*** To investigate basic assumptions of prediction models for future vertebral fractures.

Methods. Lateral radiographs of the spine were obtained from 314 Portuguese individuals aged 60 years or older (205 women and 109 men) with bone mineral density (BMD) measurements at several sites. Associations between BMD at various sites, participant characteristics, and vertebral fractures were investigated. For men and women separately, logistic regression analyses and analyses of areas under the receiver-operating characteristic (ROC) curves were performed to determine the accuracy of BMD measurment at predicting the presence of vertebral deformities.

Results. BMD measurements at all sites significantly predicted the presence of osteoporotic vertebral deformities in women but not in men. Similarly, in analyses of areas under ROC curves, BMD assessments were statistically significantly related to vertebral deformities in women but not in men. In multivariate analyses, BMD measurements of the lumbar spine and of the forearm, adjusted for gender, age, and body mass index, significantly predicted the presence of vertebral deformity, but BMD of the hip sites did not.

Conclusion. Prediction of fractures is specific for gender and site of BMD measurement. This challenges the use of similar algorithms for men and women as well as the use of hip BMD data to accurately estimate future vertebral fracture risk. (J Rheumatol First Release Nov 15 2009; doi:10.3899/jrheum.090731)

Key Indexing Terms:
BONE MINERAL DENSITY T-SCORE OSTEOPOROSIS
GENDER VERTEBRAL FRACTURE

Osteoporotic fractures represent a major worldwide health burden that is expected to increase remarkably over the next decades because of increasing life expectancy[1]. Therefore, predictors of the risk of fracture have long been sought in the hope that this might identify suitable targets for effective preventive measures. Bone mineral density (BMD) is the most important single predictor of fracture. Research suggests that for each decrease of 1 in T-score in postmenopausal osteoporosis, the relative risk of fracture is multiplied by a factor of 1.5 to 3, depending on the site measured[1-3]. This close relationship underlies the World Health Organization (WHO) operational definition of osteoporosis[4], which considers 4 different groups of increased risk of fracture as derived from the BMD (expressed as T-scores) and previous fracture. This concept, although extremely useful, disregards a number of risk factors for fracture that are independent of BMD, such as age, previous fracture, body mass index (BMI), and family history for osteoporotic fractures[5,6]. Moreover, calculation of relative risks of fractures based on T-scores alone is less important for clinical decision-making than absolute risks. A large group of researchers, under the auspices of WHO, set out to resolve these limitations. Following a number of systematic reviews and metaanalyses, an algorithm was derived and made available under the designation FRAX, which allows calculation of 10-year absolute risk of hip and major osteoporotic fractures, taking into account a variety of relevant risk factors[7,8].

The calculations of risks can also be performed not including BMD values. The actual algorithm used for the calculation tool was not made public and we can only derive the effects of individual factors through simulation in the available on-line calculation tool.

In seeking simplicity, the FRAX model adopted a number of principles that may bring into question its validity in practice, namely the consideration of only a single measurement site and the same reference data for men and women[9].

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The model considers only BMD measured at the femoral neck without consideration of other sites. This disregards evidence that the correlations between BMD and fracture risk depend on the site where BMD is measured[2,10]. In addition, for both male and female T-score calculation, data from the US National Health and Nutrition Examination Survey (NHANES III) of women aged 20–29 years are applied. This is different from the initial WHO definition, which was specifically derived for postmenopausal women and apparently called for gender, ethnic, and even national reference norms[11]. This approach seems consistent with the finding that, although fractures are in general more common among women for a variety of reasons[12], fracture risk is similar in men and women at the same age and areal BMD[5,13]. However, this might not be the case with the spine, as most epidemiological research shows a similar prevalence of vertebral fractures in men and women, despite the higher BMD values in males[5,14,15]. T-scores provided by densitometers are gender-specific. It is not clear whether and how T-scores for men entered into the FRAX calculation tool are converted to the new female-referenced equivalent. This is important because the difference between T-scores for men and women at a given BMD is not constant, being null at a BMD of 0.545 g/cm^2, increasingly positive below and increasingly negative above [based on NHANES III reference data for femoral neck, non-Hispanic white population, peak standard deviation) (SD) BMD for men 0.93 (0.138) and for women 0.849 (0.109)]. The considerations above led us to the research described here.

We investigated the associations among BMD assessed at various sites, participant characteristics such as gender and age, and prevalent vertebral fractures.

MATERIALS AND METHODS

Participants. The study took place in the Coimbra district of Portugal, with a population of about 25,000 people. This district has a mixture of rural and urban population, which presents epidemiological patterns of age and sex distribution, income, and consumer habits considered to be similar to those of the general Portuguese population. Residents were randomly selected from the 19,000 registered voters following a computer-generated random number list, stratified to gender and 5-year age groups. There were no exclusion criteria. People were invited to participate by mailed notices explaining the design and purpose of the study. Nonrespondents were contacted a second time. A total of 6000 notices were sent out; 1100 letters were returned because of a change in address, death, and other reasons. Altogether 1745 people agreed to participate. Participants responded to a comprehensive questionnaire regarding risk factors for osteoporosis in personal and family history. Height and weight were recorded. In all participants, dual energy x-ray absorptiometry (DEXA) scans of the spine and proximal femur sites (Hologic QDR 4500/c) were performed, of which 73 measurements were excluded because of incomplete data or unresolved technical difficulties in the DEXA scan, reducing the sample to 1672 people: 1208 women and 464 men. All participants aged 65 years or above (n = 246) were also invited to have a scan of the forearm; 233 accepted (95%). All scans were performed and analyzed according to the manufacturer's instructions.

In 2001, about 3 years [mean 2.7 (SD 0.8)] after these assessments, all participants aged ≥ 60 years on January 1, 2001 (n = 499), were invited to have lateral radiographs of the thoracic and lumbar spine. Fifty-one had died since having the DEXA scan, 55 could not be reached despite at least 2 attempts by mail and/or telephone, and 79 declined to participate. So radiographs for fracture assessment were obtained for 314 participants: 205 women and 109 men. This is the population used for this research. There were no statistically significant differences between those agreeing to have the radiographs taken (80%) and those declining (20%) regarding age, height, weight, or BMI, but fewer men (14%) than women (23%) declined ($p = 0.03$). As expected, those having radiographs were significantly younger at the time of assessment of DEXA compared to those who could not have radiographs taken because they had died: 66 and 70 years, respectively ($p = 0.002$).

Methods. For scoring of vertebral fractures, i.e., the number of deformities, the lateral radiographs of vertebrae T4 to L4 were evaluated qualitatively, semiquantitatively, and quantitatively by one of the authors. The anterior (a), medial (m), and posterior (p) height of each vertebra was measured. Because no film object and film focus distances were provided, the heights measured on the digitizing board were not corrected with film object and film focus distances and therefore were not the real vertebral heights. These heights were used to calculate the following ratios: 1 anterior ratio (a/p), 1 medial ratio (m/p), and 2 posterior ratios (p/pu and p/pl). For the posterior ratios the posterior height of a given vertebra (p) was divided by the posterior height of the vertebra above (pu) to get the ratio p/pu and was divided by the posterior height of the vertebra below (pl) to get the ratio p/pl. If 1 of the ratios (a/p, m/p, p/pu, p/pl) was below the threshold of 0.80, the vertebra was considered deformed: vertebral deformity with cutoff at the 20% level. Each vertebral deformity was defined based on radiographic characteristics alone between osteoporotic, degenerative, and traumatic reasons for the deformation[16]. Because this distinction is sometimes difficult to make, we performed additional sensitivity analyses including all vertebral deformations. For analyses, we grouped age into 4 categories: < 60, 60–65, 65–70, and > 70 years, more or less reflecting quartiles.

Statistics. Correlation coefficients (Pearson) between BMD assessments at various sites were calculated for women and men separately. In addition, for women and men separately, univariate logistic regression analyses were carried out, with the judgment of osteoporotic vertebral deformity (yes/no) as dependent variable and BMD at the different sites as independent variables; receiver-operating characteristic (ROC) curves were plotted and areas under the curve (AUC) calculated. In addition, multivariate logistic regression analyses were done with any vertebral deformity (yes/no) as a dependent variable and BMD at a specific site, gender, age, and BMI as independent variables. BMD values of the lumbar spine for women and men with or without vertebral deformity were plotted as cumulative probability plots, to gain visual insight into the gender difference in the relation between BMD and vertebral deformities. For all analyses, p values < 0.05 were considered statistically significant; all tests were 2-sided. NCSS 2007 (NCSS, Kaysville, UT, USA) and SPSS 16 were used for statistical analyses.

RESULTS

Characteristics of the participants (n = 314) are shown in Table 1. Of the women, 97% were postmenopausal, and of the men, 75% were older than 60 years. Vertebra T4 was least frequently deformed and vertebrae T11 and T12 were most frequently deformed.

Associations of BMD assessed at various sites, vertebral deformities, and gender. All BMD measurements at the various locations were correlated, but the intercorrelations between BMD at the 5 hip regions were higher compared to correlations of BMD at the individual hip regions with BMD at the lumbar spine or BMD at the total forearm with BMD at other regions. Intercorrelations of BMD at the hip

Table 1. Study participant characteristics.

	Women	Men
No. (%)	205 (65)	109 (35)
Postmenopausal, n (%)	198 (97)	NA
Duration menopause, yrs		
Median (10–90 percentiles)	16 (9–28)	NA
Age*, Median (10–90 percentiles)	66 (59–76)	66 (58–76)
Groups, n (%)		
< 60	37 (18)	27 (25)
60–65	75 (37)	27 (25)
65–70	47 (23)	22 (20)
> 70	45 (22)	33 (30)
Height, cm, median (10–90 percentiles)	155 (148–162)	167 (159–177)
Weight, kg, median (10–90 percentiles)	64 (54–81)	76 (62–93)
BMI, median (10–90 percentiles)	27 (23–33)	28 (23–32)
BMI groups, n (%)		
< 20	5 (2)	1 (1)
20–25	45 (22)	28 (26)
25–30	102 (50)	61 (56)
30–35	37 (18)	16 (15)
35–40	12 (6)	3 (3)
> 40	4 (2)	0 (0)
BMD, g/cm^2		
Lumbar spine (L1-L4)		
Median (10-90 percentiles)	0.83 (0.66–1.03)	0.95 (0.79–1.19)
Mean (SD)	0.84 (0.13)	0.97 (0.16)
Total hip		
Median (10–90 percentiles)	0.82 (0.68–0.98)	0.97 (0.82–1.13)
Mean (SD)	0.82 (0.12)	0.97 (0.13)
Femoral neck		
Median (10–90 percentiles)	0.68 (0.56–0.81)	0.79 (0.62–0.93)
Mean (SD)	0.68 (0.10)	0.79 (0.12)
Trochanter		
Median (10–90 percentiles)	0.63 (0.50–0.75)	0.74 (0.60–0.89)
Mean (SD)	0.63 (0.10)	0.75 (0.12)
Intertrochanteric		
Median (10–90 percentiles)	0.99 (0.81–1.17)	1.12 (0.95–1.37)
Mean (SD)	0.99 (0.15)	1.15 (0.16)
Ward triangle		
Median (10–90 percentiles)	0.51 (0.37–0.67)	0.57 (0.40–0.76)
Mean (SD)	0.52 (0.12)	0.58 (0.13)
Forearm**		
Median (10–90 percentiles)	0.49 (0.39–0.56)	0.61 (0.55–0.70)
Mean (SD)	0.48 (0.06)	0.61 (0.06)
Vertebral deformities per person, n (%)		
0	155 (76)	80 (73)
1	33 (16)	15 (14)
2	7 (3)	8 (7)
3	8 (4)	2 (2)
4	0 (0)	3 (3)
5	2 (1)	0 (0)
8	0 (0)	1 (1)
Participants with ≥ 1 vertebral deformity***, n (%)	50 (25)	29 (26)
≥ 1 osteoporotic deformity, n	42	22
≥ 1 degenerative deformity, n	6	7
≥ 1 traumatic deformity, n	2	0

NA: not applicable; BMI: body mass index; BMD: bone mineral density. * Age at assessment of clinical variables and BMD. ** BMD of forearm of 98 women and 58 men. *** Vertebral deformity defined at the 20% level of differences in vertebral height ratios. Different types of deformities determined from radiographs.

regions did not show a clear gender difference. However, the correlation coefficients of BMD at the lumbar spine with BMD at hip regions were clearly higher in men (range 0.62–0.78) than in women (range 0.56–0.62). For correla-

tions of BMD at the total forearm with BMD at other sites, the opposite was true: in women clearly higher coefficients were found compared to men (ranges 0.64–0.71 for women and 0.36–0.53 for men; data not shown).

Crude odds ratios (95% confidence interval) of osteoporotic vertebral deformation per g/cm^2 BMD at various sites for women and men separately are shown in Table 2. There is significantly less risk (prevalence) of vertebral deformations at a higher BMD at all the different sites for women, but not for men. In line with this finding, ROC curves for osteoporotic vertebral deformity at cutoffs of BMD are statistically significant in women for all BMD sites but one, but not in men. For women, a cutoff of BMD of the lumbar spine of 0.80, which corresponds with a T-score of –2.24, has a sensitivity of 0.67 and a specificity of 0.71 for osteoporotic vertebral deformity (Figure 1).

Multivariate logistic regression analyses with any vertebral deformity (yes/no) as dependent variable showed that BMD of the lumbar spine, corrected for gender, age, and BMI, significantly predicted the presence of vertebral deformity (regression coefficient –3.7, Wald statistic 0.0004, OR 0.024, 95% CI 0.003–0.186). This indicates that an increase in BMD of 1 g/cm^2 is associated with a decrease in the odds of the presence of vertebral deformity by a factor of 0.024 (i.e., the risk decreases about 41-fold). However, BMD at the different hip regions did not significantly predict the presence of vertebral deformity, but BMD of the total forearm did (regression coefficient –6.0, Wald statistic 0.049, OR 0.0025, 95% CI 0.00001–0.98). Allowing interaction terms (gender, age, and BMI) into the model with BMD of the lumbar spine resulted in an age/gender interaction that was statistically significant (regression coefficient –4.5, Wald statistic 0.026, OR 0.01, 95% CI 0.00–0.59). But gender and age separately were not statistically significant (Wald statistics 0.06 and 0.07, respectively), indicating a gender difference for the influence of age on vertebral deformity.

Analyses of median BMD for women and men with or without vertebral deformity separately showed that BMD in total hip, femoral neck, trochanter region, Ward's triangle, and lumbar spine was statistically significantly lower in women with vertebral deformities compared to women without deformity (data not shown). In men, however, no statistically significant differences were present between those with and those without deformities. In line with this finding, cumulative probability plots of BMD values for women and men with a vertebral deformity versus those without showed that for the whole range of actual BMD values, there was a consistent and clear difference in BMD between women with and women without vertebral deformity, while in men a difference was only observed in the higher range of BMD values, corresponding to about 40% of men (Figure 2).

DISCUSSION

Our analyses of BMD assessed at various sites in the body are in agreement with data from previous publications, indicating that the predictive power of fractures at a specific site is higher for the BMD value at that specific site[2,10]. BMD at the lumbar spine can predict vertebral fractures better than BMD of the femoral neck, and vice versa. This indicates that

Table 2. Relation of BMD values at different sites and gender with osteoporotic vertebral deformities. Univariate logistic regression analyses; n = 205 women and 109 men, except for BMD of forearm: 98 women and 58 men.

Site	ß	SE	p	OR (95% CI)	AUC (95% CI)	p
Lumbar spine						
Women	–7.4	1.7	< 0.000	0.00 (0.00–0.02)	0.74 (0.65–0.81)	< 0.000
Male	–0.5	1.5	0.73	0.59 (0.03–11)	0.51 (0.38–0.63)	0.82
Total hip						
Women	–3.3	1.5	0.02	0.04 (0.00–0.62)	0.61 (0.49–0.70)	0.045
Male	0.5	1.8	0.77	1.7 (0.05–59)	0.49 (0.33–0.62)	0.86
Femoral neck						
Women	–4.6	1.9	0.02	0.01 (0.00–0.42)	0.63(0.52–0.71)	0.01
Male	1.1	2.0	0.58	3.1 (0.06–162)	0.47 (0.31–0.60)	0.64
Trochanter						
Women	–3.8	1.7	0.03	0.02 (0.00–0.68)	0.61 (0.50–0.70)	0.03
Male	1.6	2.1	0.45	4.7 (0.08–272)	0.44 (0.29–0.58)	0.44
Intertrochanteric						
Women	–2.4	1.2	0.04	0.09 (0.01–0.90)	0.59 (0.48–0.69)	0.09
Male	0.2	1.5	0.89	1.2 (0.06–24)	0.50 (0.34–0.63)	0.95
Ward triangle						
Women	–4.7	1.6	0.003	0.01 (0.0–0.20)	0.65 (0.56–0.73)	< 0.001
Male	1.3	1.8	0.47	3.8 (0.10–138)	0.45 (0.29–0.59)	0.53
Forearm						
Women	–12.7	4.1	0.002	0.00 (0.00–0.1)	0.73 (0.60–0.82)	< 0.000
Male	3.8	5.3	0.48	43 (0.00– > 1000)	0.47 (0.26–0.64)	0.79

BMD: bone mineral density; SE: standard error; OR: odds ratio; CI: confidence interval; AUC: area under the curve.

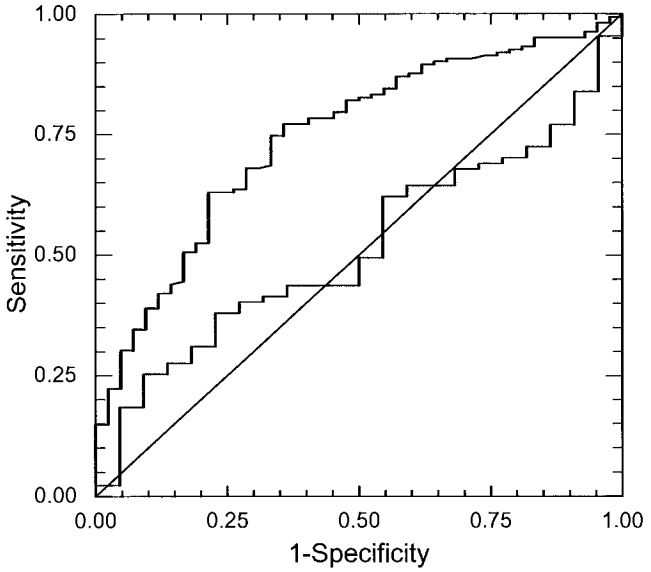

Figure 1. Receiver-operating characteristic curve for osteoporotic vertebral deformity at cutoffs of bone mineral density of the lumbar spine for women (upper curve) and men (lower curve). N = 314 (205 women, 109 men). At a cutoff of BMD of the lumbar spine of 0.80 in women, sensitivity = 0.66 and specificity 0.87 for osteoporotic vertebral deformity. The area under the curve (AUC) for women = 0.74 and men = 0.51, a statistically significant difference (p = 0.002). For men, the AUC of 0.51 compared to the AUC of 0.5 (AUC of 0.5 is "useless") is statistically not significantly different (p = 0.8). For women, AUC is statistically significantly different from 0.5 (p < 0.000).

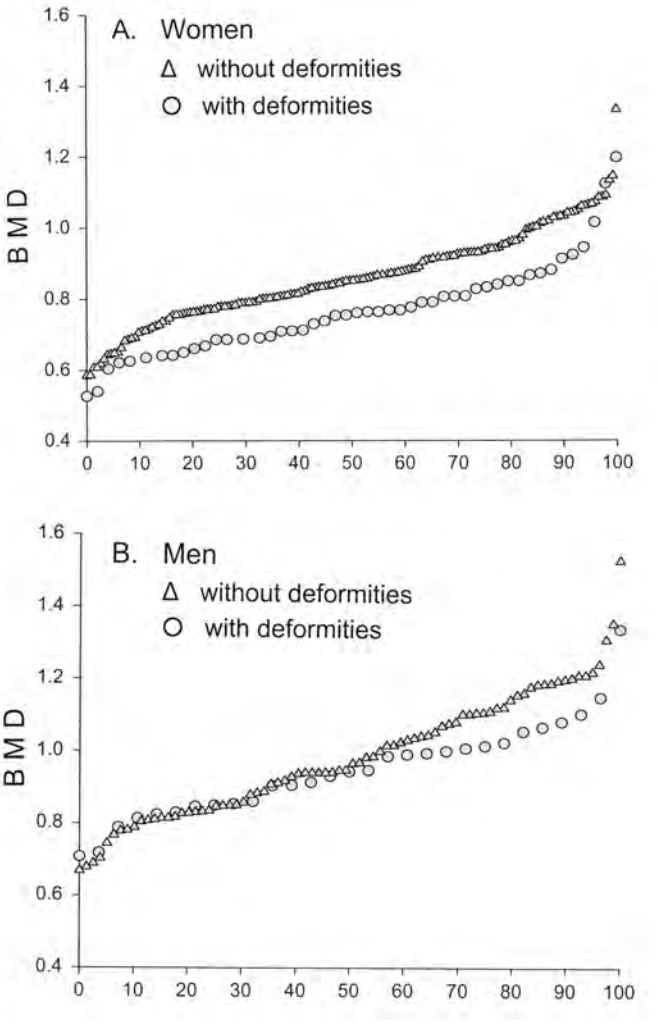

Figure 2. Cumulative probability plots of lumbar spine bone mineral density (BMD) values for those with a vertebral deformity versus those without; (A) women (n = 205) and (B) men (n = 109). For the whole range of actual BMD values, there is a consistent and clear difference in BMD between women with and those without vertebral deformity, but in men, a difference is only observed in the higher range of BMD values, corresponding to about 40% of men. X-axes: cumulative probability (%).

the FRAX prediction model using only BMD at the femoral neck would predict hip fractures more reliably than all "major osteoporotic" fractures. The CI of the latter prediction probably is wider; it could be informative if the FRAX model would show CI around the estimated risks. The FRAX Website states that total hip BMD can be used interchangeably with femoral neck BMD in women, but not in men (http://www.shef.ac.uk/FRAX/faq.htm). However, we did not find a gender-specific difference in correlation coefficients between these sites; they were 0.87 for women and 0.88 for men.

However, associations between BMD assessed at various sites and osteoporotic vertebral deformities showed a clear gender difference in our study. There were no significant differences in mean BMD values between men with and men without vertebral deformities. Further, the analyses of the areas under the ROC curves and results of univariate regression analyses exploring the relation between osteoporotic vertebral deformity and BMD were statistically significant in women but not in men. The effect of age upon the risk of prevalent fracture is also different for men and women, indicated by a significant age/gender interaction in the multivariate regression model. Therefore our data suggest that relations found between BMD and the risk of vertebral deformities and possibly also other osteoporotic fractures in women cannot be directly extended to men. An explanation for the gender difference in prediction of vertebral deformities observed in our study could be that because our data on vertebral deformities are cross-sectional, not all deformities are indeed osteoporotic. Vertebral deformities are more common in men than women until about age 65 years; many of these may be traumatic or due to childhood diseases[12]. However, the gender difference in prediction based on the AUC of the ROC curves was more pronounced when analyzing osteoporotic deformities, compared to analyzing all vertebral deformities. One could argue that the lack of statistically significant test results in men could be due to type II errors. However, the significant results for a more limited group of women with BMD of the forearm and

the visual inspection of the cumulative probability plots render this hypothesis unlikely.

In accord with data in the literature, vertebra T4 was the least frequently deformed of the vertebrae T4 to L4[17]; T11 and T12 were the most frequently deformed vertebrae. In scoring systems, T4 can be used as a reference vertebra for vertebral heights, as in the method by Minne[18].

Limitations. The subgroup of patients accepting radiographic assessment of the thoracic and lumbar spine for evaluation of spine fracture prevalence was relatively small. It could be that the study population was not representative for the general Coimbra population, even though we included 79% of those randomly selected, aged > 55 years. We did not correct BMD measurements for increased density of deformed vertebrae. However, as there was a clear relation between vertebral BMD and vertebral deformities in women (more than the relation between BMD at other sites and vertebral deformities), this seems not have been a big problem in women. For men, it could be an explanation for the lack of correlation of BMD of the lumbar spine and vertebral fractures, but not for the lack of correlation of BMD at other sites and vertebral fractures.

It can also be argued that we measured existing vertebral fractures, while the FRAX is developed to predict future fracture risk. However, previous clinical and prevalent radiological fractures, including vertebral, are among the strongest predictors of future fracture, independent of BMD[6,19,20]. The risk of subsequent fractures has been found to increase 3-fold in men and women with one prevalent vertebral fracture and up to 9-fold in those with 3 or more fractures[21]. This is also included in the FRAX model and is valued in a similar way for men and women[22].

Prediction of (vertebral) deformities is specific for gender and site of BMD measurement. This challenges the use of similar algorithms for men and women as well as the use of hip data to estimate vertebral fracture risk, as in the FRAX model.

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