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Predictive value of FRAX® for fracture in obese older women

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Abstract

Recent studies indicate that obesity is not protective against fracture in postmenopausal women and increases the risk of fracture at some sites. Risk factors for fracture in obese women may differ from those in the non-obese. We aimed to compare the ability of FRAX® with and without bone mineral density (BMD) to predict fractures in obese and non-obese older postmenopausal women who were participants in the Study of Osteoporotic Fractures. Data for FRAX clinical risk factors and femoral neck BMD were available in 6049 women, of whom 18.5% were obese. Hip fractures, major osteoporotic fractures, and any clinical fractures were ascertained during a mean follow-up period of 9.03 years. Receiving operator curve (ROC) analysis, model calibration and decision curve analysis were used to compare fracture prediction in obese and non-obese women.

ROC analysis revealed no significant differences between obese and non-obese women in fracture prediction by FRAX, with or without BMD. Predicted hip fracture risk was lower than observed risk in both groups of women, particularly when FRAX + BMD was used, but there was good calibration for FRAX + BMD in prediction of major osteoporotic fracture in both groups. Decision curve analysis demonstrated that both FRAX models were useful for hip fracture prediction in obese and non-obese women for threshold 10-yr fracture probabilities in the range of 4–10%, although in obese women FRAX + BMD was superior to FRAX alone. For major osteoporotic fracture, both FRAX models were useful in both groups of women for threshold probabilities in the range of 10–30%. For all clinical fractures, the FRAX models were not useful at threshold probabilities below 30%. We conclude that FRAX is of value in predicting hip and major osteoporotic fractures in obese postmenopausal women, particularly when used with BMD.

Keywords

Fracture prediction; FRAX®; obesity; bone mineral density; postmenopausal women

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Disclosures

The authors state that they have no conflicts of interest.

Introduction

Although obesity has been widely believed to be protective against fracture, recent studies have challenged this perception. In an audit of postmenopausal women presenting with low trauma fracture to a Fracture Liaison Service, the prevalence of obesity was 28% (1), whilst in the Global Study of Osteoporosis in Women (GLOW) the incidence of low trauma fractures was similar in obese and non-obese postmenopausal women.(2) The distribution of fracture sites differs between obese and non-obese women, fractures of the leg, ankle, and humerus being reported more commonly in obese women whereas fractures of the hip, wrist and pelvis are less common. (2–6)

FRAX® is a computer based algorithm that is widely used in clinical practice to calculate the 10-year probability of major osteoporotic fractures (hip, clinical spine, humerus or wrist fracture) and hip fractures. (7,8) Clinical risk factors (age, body mass index (BMI), previous fracture, parental history of hip fracture, glucocorticoid therapy, smoking, alcohol intake, rheumatoid arthritis and secondary causes of osteoporosis) are used alone or with hip bone mineral density (BMD) to predict 10-yr fracture probability. A number of studies have investigated its use in populations of postmenopausal women and have generally shown moderately good discrimination between fracture and non-fracture cases and reasonably close agreement between predicted and observed fracture frequency, particularly for hip fracture. (9–20) However, its utility in fracture prediction in obese women has not been reported; higher BMI, BMD and a greater frequency of falls in obese women with fracture (1,2) might be expected to affect its performance. In addition, the prevalence of obesity in the populations used to develop FRAX was 18.3%, considerably lower than the current prevalence in women of 34% and 23% in the US and Europe respectively (21,22). In this study we have compared the prediction of low trauma clinical fractures using FRAX with and without BMD in obese and non-obese older postmenopausal women.

Methods

Subjects

For this analysis we used data from The Study of Osteoporotic Fractures (SOF). SOF is a multicentre study of risk factors for fracture in women aged 65 years and over. The participants were community-based ambulatory women recruited between September 1986 through October 1988, from population-based listings at four clinical centres in Portland, Oregon; Minneapolis, Minnesota; Baltimore, Maryland; and the Monongahela Valley near Pittsburgh, Pennsylvania. (23) Women unable to walk without assistance, and women with bilateral hip replacements, were excluded. Additionally, Black women were excluded due to their low incidence of hip fracture. All participants provided informed consent and the protocol was approved by the institutional review boards of the participating sites.

Baseline examinations took place from 1986 to 1988. From January 1989 to December 1990, all participants were invited to undergo a second evaluation. 9704 women attended the first visit and 8098 women attended the second visit. 1241 women provided questionnaire data by mail and telephone without attending the clinic. For the present analysis we used the second visit for baseline data since measurement of hip BMD was first made at this time.

Measurements

The second visit included a self-administered questionnaire, questions administered by an interviewer, and BMD measurement.

The self-reported questionnaire included demographics and risk factors for fractures including age, smoking habits, alcohol consumption, family history of fractures, and

personal history of fracture after the age of 50 years. Women were also asked about medical conditions such as diabetes mellitus, rheumatoid arthritis, and glucocorticoid use.

Weight was measured in indoor clothing with shoes removed using a balance beam scale and height was measured using a standard held-expiration technique with a wall-mounted Harpenden stadiometer (Holtain Ltd., Dyved, UK). BMI was calculated by the formula weight in kilograms divided by the square of height in metres. In addition, waist and hip circumference were measured and waist to hip ratio was calculated.

BMD of the proximal femur (total hip and its subregions) was measured between 1988 and 1990 (Visit 2) using Hologic QDR 1000 scanners (Hologic, Bedford, MA). The coefficient of variation was 1.2% for both sites. (24,25)This was performed on 84 % (7959) of the initial cohort.

WHO and FRAX 10-year absolute fracture risk

10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, wrist, or humerus) was calculated for each SOF participant using the FRAX algorithm for US white women (FRAX Version 3.0). For the calculated probabilities the risk factors included were age, BMI, parental history of hip fracture, patient history of previous fracture, presence of rheumatoid arthritis, smoking status, consumption of three or more alcoholic beverages per day and current use of glucocorticoids. (26,27) The FRAX 10-year probabilities were estimated both with and without femoral neck (FN) BMD.

Ascertainment of fractures

Women were contacted every 4 months to determine their fracture status; more than 98% of these contacts were completed. All reported fractures were confirmed by radiographic report. Women who reported fractures were interviewed to determine the circumstances. Pathologic fractures (including peri-prosthetic) and fractures secondary to extreme trauma were excluded. Incident fracture outcomes include hip fracture, major osteoporotic fracture and any clinical fracture. As FRAX generates 10-year probabilities, for this analysis the follow-up was truncated to ten years in women with ≥ 10 years follow-up.

Statistical analysis

Only women with data on risk factors for the calculation of FRAX 10-year probabilities and FN BMD were included in this analysis. Obese and non-obese women were defined as women with BMI ≥ 30 kg/m^2 and < 30 kg/m^2, respectively. Receiver operating characteristic (ROC)curve analysis was used to evaluate the ability of FRAX to predict fractures in obese and non-obese women. Further analysis was also performed to assess model calibration (i.e. how close the observed rates agree with the predicted risks). This involved comparing the predicted frequencies of fractures with overall observed frequencies of fractures in both groups (obese and non-obese) and stratifying the data into categories defined by quartiles of FRAX 10-year probabilities and comparing the observed and predicted counts within each risk category. Ratios of observed to predicted counts were calculated to aid comparisons. The utility of the FRAX models in clinical practice was also assessed by calculating estimates of sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) according to The National Osteoporosis Foundation (NOF) recommended intervention thresholds of 3% for hip fracture and 20% for major osteoporotic fracture. (28) Additionally, the Hosmer-Lemeshow goodness-of-fit statistic was calculated for logistic regression models including all risk factors used to calculate FRAX 10-year probabilities. A p value <0.05 indicates a lack of good fit for the model.

A decision curve analysis method was performed in order to evaluate the clinical usefulness of the FRAX models.(29–31)Decision curves were constructed for the FRAX model with and without BMD for the outcomes of (i) hip fracture (ii) major osteoporotic fracture and (iii)all clinical fractures. This consisted of plotting the net benefit of the FRAX models compared to the strategy of treating no women at various threshold probabilities. The threshold probabilities are the predicted risks of fracture where the clinical consequences are uncertain (i.e. there is uncertainty about whether the women would be classified as a high risk of fracture or not).

Differences were considered significant when the two-tailed p-value was less than 0.05. The decision curve analysis was performed using R statistics software, version 2.14.1 (R Development Core Team (2011). R: A language and environment for statistical computing. R: Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.) All other analyses were performed using version 18 of the SPSS statistics package for Windows (SPSS/PASW for Windows, Rel. 18.0.3. 2010. Chicago: SPSS Inc.).

Results

Data for FRAX scores and FN BMD were available in 6049 women. Of those, 18.5% were obese. Incident clinical fractures occurred during the follow-up period in 26.9% and 32.7% of obese and non-obese women respectively. Non-obese women with fracture had a significantly lower FN BMD than obese women (Table 1). The mean (SD) duration of follow-up was 9.03 (2.22) years (obese women 9.12 (2.09), non-obese women 9.0 (2.26) years, p=0.121); 10 years follow-up was available in 72.5% of women. During the follow-up period 252 (22.5%) of obese women died vs. 1215 (24.6%) of non-obese women (p=0.142).

FRAX-derived probabilities in women with incident hip or major osteoporotic fractures were significantly lower in obese than in non-obese women (without BMD; 5.8 vs. 11.4% for hip and 17.6 vs. 23.6% for major osteoporotic fracture p<0.0001); with BMD: 7.1 vs. 10.9% for hip and 18.2 vs. 23.3% for major osteoporotic fracture p<0.0001). Nevertheless, ROC analysis showed no significant differences in the ability of FRAX models with or without BMD to predict fractures in obese and non-obese women (Table 2).

The sensitivity and specificity of the FRAX scores according to the NOF risk thresholds are displayed in Table 3. The sensitivity for hip fractures was lower in obese women but the specificity was higher when compared to non-obese women. There was a lower sensitivity in both obese and non-obese women for major osteoporotic fractures, particularly in obese women; but the specificity was somewhat better in obese women. Interestingly, the NPVs and PPVs for hip fracture were almost identical in obese and non-obese women and closely similar for major osteoporotic fracture. In the stratified comparison of observed and expected counts, the FRAX performance for hip fracture was less good in obese than non-obese women in the lower two risk quartiles (Table 4). Both models performed well for major osteoporotic fractures in obese and non-obese women, particularly in the three highest quartiles of risk.

The Hosmer-Lemeshow goodness-of-fit analysis demonstrated insufficient evidence that the logistic regression models fit poorly for obese women, apart from the model for hip fractures not including BMD (p=0.03); and for non-obese women apart from the model for major osteoporotic fracture not including BMD (p= 0.02).

Figure 1 shows the decision analysis curves for FRAX with and without BMD in obese and non-obese women for hip fracture, major osteoporotic fracture and all clinical fractures. For hip fracture, the FRAX models were useful in women for threshold probabilities in the range

of 4–15%. For non-obese women, there was very little difference between the FRAX models but for obese women, the net benefit of the FRAX model including BMD was clearly superior. For major osteoporotic fracture the FRAX models were useful in women with predicted probabilities in the range of 10–30%, with very little difference between the net benefit of the two FRAX models in either obese or non-obese women. In the case of all clinical fractures, the FRAX models were not useful at threshold probabilities below around 30%, with only a small net benefit at probabilities in the range of 30–40%.

Discussion

In this study we used several approaches to compare the performance of FRAX with and without BMD in predicting fracture in obese and non-obese women. We hypothesised that because of higher BMI and BMD in obese women, the predictive value of FRAX, with or without BMD, might be inferior to that in non-obese women. However, ROC analysis and calibration did not reveal any clear differences in the utility of the models between obese and non-obese women, although decision curve analysis indicated a greater net benefit in non-obese than obese women.

Differences in the results obtained by the various approaches used in this study are not unexpected, since they provide different information about prediction models. ROC analysis is widely used in evaluating prediction models as a test of discrimination, with comparison of the area under the curve AUC expressed as the c statistic or c index. This compares how well models separate cases and non-cases but does not provide information about whether a case has an accurate risk probability or about the value of the model in clinical practice. On its own, the c statistic does not consider the range of cut-point values used to compute the ROC curve, or the clinical usefulness of these cut points. In the present study AUC values ranged between 0.66 and 0.76 for hip fracture and 0.63 to 0.70 for major osteoporotic fracture, indicating only modest discrimination between fracture and non-fracture cases in both non-obese and obese women. Furthermore, the substantial differences in sensitivity and specificity shown in Table 3 were not captured by AUC data. Calibration provides information about the agreement between predicted and observed risk, but not about the clinical relevance of miscalibration. A test of statistical significance can be applied, the Hosmer-Lemeshow test, but this tests whether there is adequate evidence for miscalibration rather than if there is good calibration. Classification and reclassification are useful in the comparison of two models in the same group of patients, but not in assessing the utility of an individual model in clinical practice. Decision analytic methods are based on the different weighting of false positives and false negatives and aim to determine the net benefit of implementing prediction models in clinical practice. (29–31)

Comparison of the performance of FRAX with and without BMD in the different analyses did not reveal any consistent differences in either obese or non-obese women. ROC analysis indicated slightly better discrimination using FRAX + BMD rather than FRAX alone but the calibration data showed a closer agreement between predicted and observed frequencies of fractures when FRAX without BMD was used. Decision curve analysis demonstrated a higher net benefit associated with use of FRAX with BMD than FRAX alone in obese women for prediction of hip fracture at clinically relevant thresholds, and a smaller advantage of FRAX with BMD for prediction of major osteoporotic fracture in both obese and non-obese women. We have recently reported that obese women with fracture have significantly lower BMD than obese women without fracture, despite closely similar BMI in the two groups, indicating that BMI may be a poor surrogate for BMD in obese women with fracture. (32)

The finding that both discrimination and calibration measures were generally worse for all clinical fractures than for hip and major osteoporotic fractures is not unexpected, given that FRAX was developed to predict hip, wrist, humerus and spine fractures only. The results of the decision curve analysis also indicated that the FRAX models were not useful in predicting all clinical fractures over clinically relevant thresholds. However, although the sites at which fracture is predicted are clearly stated on the FRAX website, it may be wrongly assumed by some that the results can be extrapolated to low trauma fracture at any site. Our results suggest that this is not the case, although we did not have high enough numbers of the other fractures to analyse individual sites separately.

Strengths of our study include the prospective design and inclusion of community-based, ambulatory women. In addition, all fractures were adjudicated and BMD measurements were subjected to rigorous quality control. Although SOF is not a population-based sample, characteristics of the SOF participants are similar to, or healthier than, those of the population-based NHANES III. The prevalence of obesity in SOF (18.3%) was somewhat lower than that of White women in the general population (22.4%), although closely similar to that of women and men studied in the cohorts from which FRAX is derived (18%). (9,33) Limitations are that only White postmenopausal women aged 65 yr and older were included in this analysis, and it remains to be established whether our results can be generalized to men, younger women, and individuals of different races. Secondly, morphometric vertebral fractures were not included in the analyses. Thirdly, not all women in this study had 10 years of follow-up. Finally, fracture probability computed by FRAX incorporates death hazard whereas the estimation of fracture incidence in the SOF cohort did not take into account the fracture status of women who did not survive. However the mean duration of follow-up and the mortality were similar in obese and non-obese women.

Overall, our results indicate that FRAX with and without BMD is of similar value in predicting hip and major osteoporotic fractures in obese women vs. non-obese women. However, the net benefit values for both FRAX models are lower over clinically relevant thresholds than in non-obese women, in part, most likely because of the lower number of true positives for obese women relative to the total sample size. The lower fracture probabilities in obese women make them more likely to be below a given intervention threshold and the lower sensitivities suggest that these women are less likely to receive treatment, a contention supported by our recent finding of significantly lower rates of treatment in obese women than non-obese women with fracture. (2) However, the positive and negative predictive values, which are more clinically meaningful quantities, are very similar between obese and non-obese women. The negative predictive values for obese women are at least as high as the corresponding values for non-obese women; which means that obese women below the NOF thresholds are no more likely to have a fracture than non-obese women.

The significantly lower rates of treatment in obese women than non-obese women may reflect the perception that obese women do not suffer “osteoporotic” fractures because of their higher BMD. (2) However, the lower BMD in obese women with fractures when compared to women of a similar BMI without fracture indicates that BMD may be inappropriately low in those who fracture, and the better performance of FRAX with than without BMD in the decision curve analysis, particularly for hip fracture, supports this contention. Whether bone protective therapy is effective in obese individuals at increased risk of fracture has not been rigorously tested, and further randomized trials are required to evaluate efficacy of treatments among obese women selected by level of BMD and/or FRAX in view of the growing prevalence of obesity and the substantial contribution of obese individuals to the overall burden of fractures in the ageing population.

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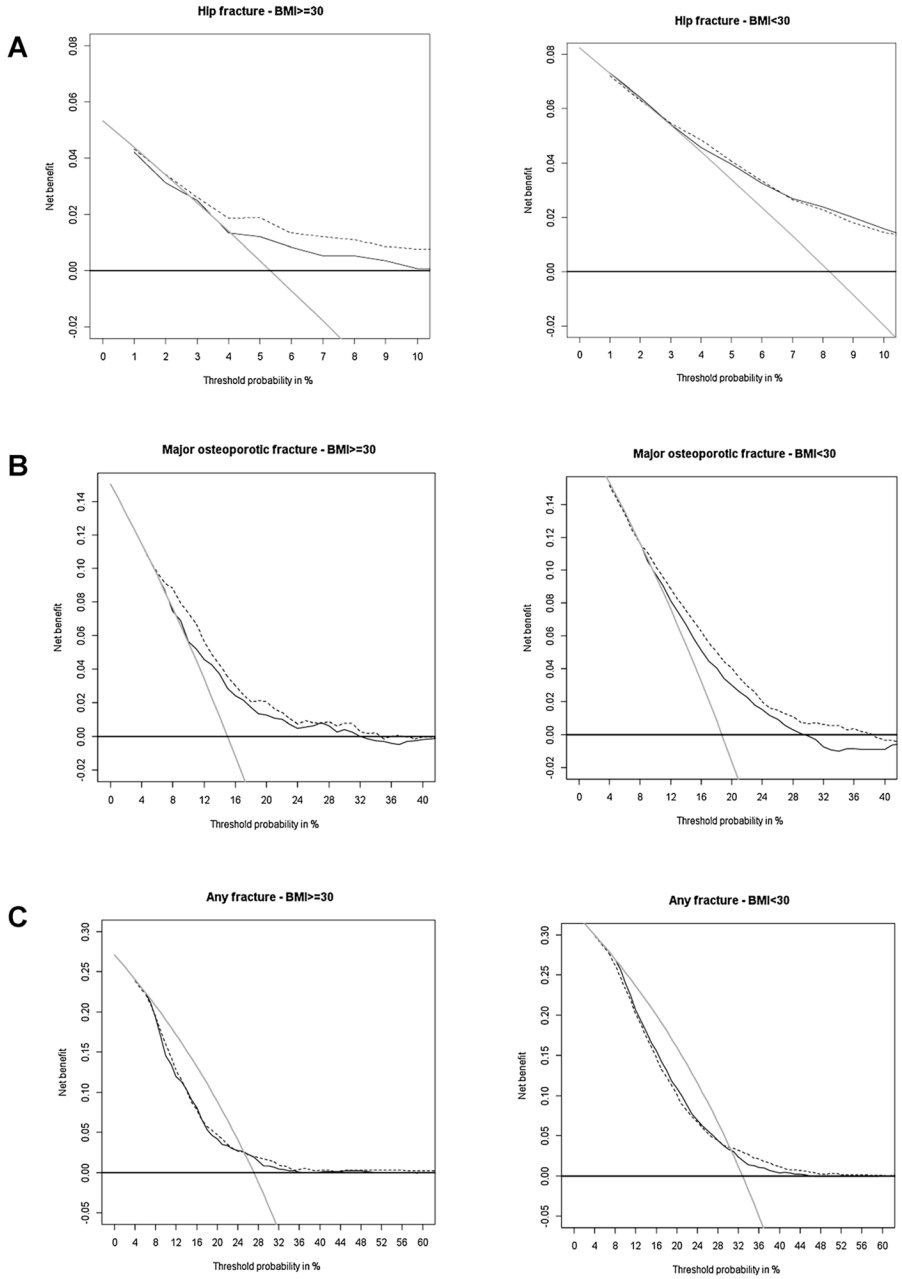

Figure 1.

Decision analysis curves for FRAX with and without BMD in obese and non-obese women for a). hip fracture b). major osteoporotic fracture c). all clinical fractures. The curves show the net benefit of using the FRAX model compared to a strategy of treating no one across a range of threshold probabilities. The threshold probabilities show the (theoretical) predicted risks of fracture where there is uncertainty about whether to classify a patient as high risk of fracture or not.

In all plots,

(i) The solid grey line represents the situation when everyone is considered to be at high risk of fracture and treated accordingly.

(ii) The horizontal solid line at y=0 represents the situation when no one is considered to be in the high risk group and no one is treated.
(iii) The solid black line shows how the benefit curve of the FRAX model changes with different threshold probabilities.
(iv) The dotted line shows the benefit curve of the FRAX model *including BMD*.

Table 1

Characteristics of obese and non-obese women with incident fracture.

	Obese women n=285	Non-obese women n=1509	p value
Age [yr: mean(SD)]	71.0 (4.8)	72.3 (5.3)	0.340
Previous fracture	45.6%	45.3%	0.948
Oral glucocorticoid therapy	3.5%	6.6%	0.057
Rheumatoid arthritis	7.0%	6.9%	0.899
Parental history of hip fracture	14.1%	17.93%	0.948
Current smoker	5.7%	9.1%	0.063
Alcohol intake ≥ units/d	1.4%	2.9%	0.166
Femoral neck BMD [g/cm^2; mean(SD)]	0.666 (0.10)	0.609 (0.10)	0.007

Table 2

Comparison of the area under the curve [AUC (95% CI)] from receiver operating characteristic curve (ROC) for the FRAX algorithm between obese and non-obese women

	Obese women	Non-obese women	P value
FRAX algorithm including BMD			
Women with hip fractures	0.76 (0.70,0.81)	0.73 (0.71,0.76)	0.48
Women with any major osteoporotic fracture (hip, clinical vertebral, wrist, and humerus)	0.70 (0.66,0.74)	0.68 (0.66,0.70)	0.18
Women with any clinical fracture (non-vertebral and clinical vertebral)	0.64 (0.60,0.67)	0.63 (0.61,0.65)	0.34
FRAX algorithm not including BMD			
Women with hip fractures	0.66 (0.59,0.73)	0.69 (0.67,0.71)	0.19
Women with any major osteoporotic fracture (hip, clinical vertebral, wrist, and humerus)	0.63 (0.59,0.68)	0.63 (0.61,0.65)	0.13
Women with any clinical fracture (non-vertebral and clinical vertebral)	0.59 (0.55,0.62)	0.60 (0.59,0.62)	0.21

Table 3

Comparison of expected and observed frequencies of fractures according to NOF thresholds.

	Hip fracture		MOP fracture	
	FRAX+BMD	**FRAX-BMD**	**FRAX+BMD**	**FRAX-BMD**
Obese				
High risk	24/38	32/43	51/51	58/54
Low risk	9/22	11/19	107/106	115/113
PPV	0.12	0.09	0.26	0.30
NPV	0.97	0.97	0.88	0.87
Sensitivity	0.63	0.69	0.32	0.31
Specificity	0.72	0.59	0.88	0.87
Non-obese				
High risk	258/341	350/374	495/445	617/492
Low risk	33/59	30/44	419/398	411/386
PPV	0.13	0.10	0.30	0.26
NPV	0.97	0.97	0.87	0.86
Sensitivity	0.85	0.89	0.53	0.56
Specificity	0.47	0.31	0.71	0.63

The figures are shown as predicted counts/observed counts

For hip fracture high risk is classified as a 10-yr fracture probability ≥ 3%

For MOP fracture high risk is classified as a 10-yr fracture probability ≥ 20%

NPV – negative predictive value; PPV – positive predictive value

Table 4

Comparison of expected and observed frequencies of fractures in obese and non-obese women using quartiles of the predicted probabilities.

	Obese women			Non-obese women		
	Predicted counts	**Observed counts***	**Observed counts/Predicted counts**	**Predicted counts**	**Observed counts***	**Observed counts/Predicted counts**
			FRAX using BMD			
Hip Fracture						
0–<1.5%	4	9 (0.02)	2.3	10	16 (0.01)	1.6
1.5–<3.0%	5	13 (0.05)	2.6	23	43 (0.04)	1.7
3.0–<6.5%	9	17 (0.08)	1.9	61	114 (0.08)	1.7
>6.5%	15	21 (0.18)	1.4	197	227 (0.17)	1.15
Major Osteoporotic Fracture						
<10%	31	21 (0.05)	0.7	75	54 (0.06)	0.7
10–<15%	42	52 (0.16)	1.2	170	162 (0.13)	0.95
15–<20%	34	33 (0.18)	0.97	174	182 (0.20)	1.05
>20%	51	51 (0.30)	1.0	495	445 (0.30)	0.9
			FRAX without BMD			
Hip Fracture						
0–<2.5%	9	16 (0.03)	1.8	20	25 (0.02)	1.3
2.5–<4.5%	10	19 (0.06)	1.9	41	64 (0.05)	1.6
4.5–<8.5%	12	15 (0.08)	1.3	84	105 (0.08)	1.3
>8.5%	12	12 (0.13)	1.0	234	224 (0.16)	0.96
Major Osteoporotic Fracture						
5–<10%	32	35 (0.10)	1.1	44	39 (0.09)	0.90
10–<15%	40	38 (0.12)	0.95	174	168 (0.13)	0.97
15–<20%	43	40 (0.17)	0.93	194	179 (0.18)	0.92
>20%	58	51 (0.26)	0.9	616	492 (0.25)	0.80

*Observed counts (observed counts/total number of patients in the risk threshold category)