Hindawi Publishing Corporation
Journal of Osteoporosis
Volume 2012, Article ID 528790, 8 pages
doi:10.1155/2012/528790

Research Article

Potential Extensions of the US FRAX Algorithm

L. Joseph Melton III,[1,2] Elizabeth J. Atkinson,[3] Sara J. Achenbach,[3] John A. Kanis,[4] Terry M. Therneau,[3] Helena Johansson,[4] Sundeep Khosla,[2] and Shreyasee Amin[1,5]

[1] *Division of Epidemiology, Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, MN 55905, USA*
[2] *Division of Endocrinology, Diabetes, Metabolism and Nutrition, Department of Internal Medicine, College of Medicine, Mayo Clinic, Rochester, MN 55905, USA*
[3] *Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, College of Medicine, Mayo Clinic, Rochester, MN 55905, USA*
[4] *WHO Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Sheffield S10 2RX, UK*
[5] *Division of Rheumatology, Department of Internal Medicine, College of Medicine, Mayo Clinic, Rochester, MN 55905, USA*

Correspondence should be addressed to L. Joseph Melton III, melton.j@mayo.edu

Received 30 April 2012; Accepted 27 June 2012

Academic Editor: E. M. Lewiecki

To determine if the revised US FRAX can identify those at high risk for fractures at any skeletal site, we studied 250 women and 249 men ≥40 years old from an age-stratified random sample of Rochester, MN residents. At baseline, femoral neck (FN) bone density was assessed, as were the clinical risk factors included in FRAX, along with additional fracture risk factors such as bone turnover markers and fall history. Fracture ascertainment through periodic interviews and comprehensive medical record review was performed over 10 years of followup. In both women and men, a higher FRAX probability at baseline was associated with greater subsequent likelihood of a major osteoporotic fracture. However, a relative 10% increase in the FRAX 10-year fracture probability was also associated with a 1.4-fold increase (95% confidence interval (CI) 1.1–1.7) in other fractures in women and a 1.7-fold increase (95% CI 0.8–3.1) in men. Furthermore, FRAX predicted asymptomatic vertebral fractures and fractures generally in both sexes. The addition of risk factors not currently included in FRAX did not appear to improve the accuracy of fracture risk prediction. FRAX may provide a conservative estimate of risk for major osteoporotic fractures, but it also predicts fractures generally.

1. Introduction

Most fractures arise in the intermediate-risk "osteopenic" population rather than among those classified as having osteoporosis by dual-energy X-ray absorptiometry (DXA) [1]. To increase the assessment gradient-of-risk, and thereby improve both sensitivity and specificity [2], bone mineral density (BMD) has been combined with clinical risk factors in the World Health Organization's fracture risk assessment tool, FRAX [3], which calculates a 10-year fracture probability (%). Like most such scoring systems, discordant results inevitably arise whereby some patients at predicted low risk will fracture and vice versa [4]. This might relate to the existence of important risk factors for fracture not currently represented in FRAX. Indeed, potential changes were recently suggested to improve the accuracy of fracture prediction by FRAX, including incorporation of information about falls, additional causes of secondary osteoporosis, biochemical markers of bone turnover, BMD measurements at the lumbar spine (LS), and concurrent osteoporosis treatment [5]. Furthermore, FRAX was designed to predict the probability of a major (i.e., hip, spine, wrist, or humerus) osteoporotic fracture, but other fractures in older individuals are also related to low BMD [6], and FRAX might predict them as well. Finally, the United States version of FRAX (US FRAX) was recently revised [7], as the original version was thought to overestimate fracture probability due to the incorporation of asymptomatic vertebral fractures in the algorithm [8], but the effect of this change is not yet clear. The purpose of this study was to test the recently revised US FRAX for

long-term prediction of major osteoporotic fractures and to determine if FRAX can identify those at risk for fractures at other skeletal sites, including clinically recognized but asymptomatic vertebral fractures. We also examined whether other risk factors (e.g., bone turnover markers, fall history) add further predictive accuracy to FRAX.

2. Materials and Methods

2.1. Study Subjects. Following approval by Mayo Clinic's Institutional Review Board, subjects were recruited from age-stratified random samples of Rochester, MN women and men as described previously [9]. There were approximately 50 men per decade of age from 20–29 years to age 80 years and over (mean age ± SD, 55 ± 20 years; age-range, 22–90 years). There were also about 50 women per decade of age, including 138 premenopausal women (mean, 35 ± 9 years; range, 21–54 years) and 213 postmenopausal women (mean, 68 ± 13 years; range, 34–93 years).

2.2. Study Protocol. After providing written informed consent, subjects were interviewed using a standard protocol to collect information required for the FRAX algorithm (i.e., personal history of a moderate trauma fracture after age 35 years, rheumatoid arthritis, oral glucocorticoid use, current cigarette smoking, heavy (>2 drinks/day) alcohol use, and parental history of hip fracture). Complete (inpatient and outpatient) community medical records were reviewed to confirm prior fragility fractures and collect information about conditions predisposing to falls or to secondary (2°) osteoporosis. Since baseline data predated widespread availability of oral bisphosphonate therapy [10], concurrent osteoporosis treatment included estrogen, selective estrogen receptor modulators or calcitonin, regardless of the specific indication for therapy.

2.3. Bone Densitometry. BMD (g/cm^2) was determined for the femoral neck (FN) and LS using Hologic QDR2000 (Hologic, Waltham, MA), with coefficients of variation (CV) of 1.8% and 0.6%, respectively. FN BMD T-scores were calculated from national reference data for women [11]. In the absence of a comparable standard, we calculated LS BMD T-scores based on sex-specific young normal data from the 20–29 year-old Rochester residents [12].

2.4. Bone Turnover Markers. Fasting serum samples were obtained and, for premenopausal women, were collected during the follicular phase of the menstrual cycle. Bone formation was assessed by serum osteocalcin (OC) measured by radioimmunoassay (CIS Biointernational, Bedford, MA; interassay CV <6%), whereas bone resorption was evaluated with an ELISA kit (Osteomark NTx Serum, Ostex International, Inc., Seattle, WA; interassay CV <17%).

2.5. Fracture Follow-Up. Subjects were followed for any new fracture (prospective cohort study) by periodic interview and medical record review [13]. Since original X-rays were not available for review, the diagnosis of vertebral fracture was accepted on the basis of a radiologist's report of compression or collapse of one or more thoracic or lumbar vertebrae. We categorized vertebral deformities (~ fractures) that were only noted incidentally separately from those reported by attending physicians to be symptomatic (clinical spine fractures). Ascertainment of clinically evident fractures is believed complete [14].

2.6. FRAX Calculations. Fracture probabilities were calculated by the World Health Organization Collaborating Centre for Metabolic Bone Diseases, blinded to fracture outcome, using US FRAX models (version 3.1) that incorporated FN BMD T-scores. FRAX model US (Black) was used for 1 subject and US FRAX (Asian) for 5 others; US FRAX (Caucasian) was used for the remaining subjects. The analysis was restricted to subjects age 40 years (minimum age accommodated in FRAX) or over at baseline; those over 90 years old were set to age 90 (the maximum accommodated in FRAX).

2.7. Statistical Analysis. To address calibration, we compared the number of first major osteoporotic fractures observed with the number predicted by the sum of subject-specific FRAX models. Computations are based on the method of Berry [15], which accounts for both incomplete followup (censoring) and the competing risk of death and provides tests and confidence intervals (CI) for the observed/expected ratio that can be viewed as a standardized incidence ratio (SIR). Trends in over- and underestimation of fracture risk were evaluated by regression extensions of the Berry method using locally developed software [16]. We also used SIRs to compare the occurrence of specific fractures with that expected on the basis of site-specific incidence rates used in the revised US FRAX [8].

To address discrimination, we computed cumulative 10-year fracture incidence by quartile of the FRAX 10-year fracture probability estimates, accounting for the competing risk of death. A Cox model approach [17] allowed us to test whether factors not currently included in FRAX increase precision of the predictions. A concordance (C) statistic for time-to-event data, similar to area under the receiver operator characteristic curve (AUC) in logistic regression, is given as a secondary measure of the potential increase.

Kaplan-Meier methods assessed survival in the cohort [18], with expected death rates from the 2004 mortality tables used in US FRAX [7]. Observed and expected survival curves were compared using the log-rank test [19].

3. Results

Based in part on medical record documentation for these subjects that extended back 36 years prior to the initial assessment, baseline characteristics of the subjects are outlined in Table 1. Within the components of the FRAX algorithm, women and men were similar except for prior history of a fragility fracture (32% versus 24%; $P = 0.039$) and lower FN BMD levels (0.700 g/cm^2 versus 0.827 g/cm^2; $P < 0.001$), as well as more "other secondary osteoporosis" ($P < 0.001$),

Table 1: Fracture risk factors at baseline among 250 women and 249 men ≥40 years of age randomly sampled from the Rochester, MN population.

	Women	Men
FRAX components		
Prior fragility fracture, % yes	81 (32%)	60 (24%)
Rheumatoid arthritis, % yes	4 (2%)	2 (1%)
Other secondary osteoporosis, % yes	88 (35%)	17 (7%)
Current tobacco smoking, % yes	27 (11%)	32 (13%)
Heavy alcohol consumption, % yes	7 (3%)	8 (3%)
Parental hip fracture history, % yes	26 (10%)	29 (12%)
Femoral neck BMD (g/cm^2), $\overline{x} \pm SD$	0.700 ± 0.128	0.827 ± 0.145
Potential FRAX extensions		
Additional secondary osteoporosis[a], % yes	85 (34%)	99 (40%)
Fall history in past year, % yes	111 (45%)	91 (37%)
Risk factors for falls[b], % yes	213 (85%)	149 (60%)
Concurrent treatment, % yes	48 (19%)	0 (0%)
Lumbar spine BMD (g/cm^2), $\overline{x} \pm SD$	0.971 ± 0.159	1.129 ± 0.196
Serum NTx (nMBCE)[c], $\overline{x} \pm SD$	12.5 ± 6.0	12.6 ± 7.2
Serum osteocalcin (ng/mL), $\overline{x} \pm SD$	5.80 ± 2.64	6.52 ± 2.78

[a]Any of the following: goiter, thyroidectomy, peptic ulcer disease, gastric resection, intestinal resection, renal failure/uremia, increased parathyroid function, pancreatitis, pernicious anemia, emphysema, chronic bronchitis, or complete bed rest >7 days in a row.
[b]Any of the following: use of a cane, stroke, hemiparesis, hemiplegia, balance disorder, transient ischemic attack, cataracts, other vision problems, heart arrhythmia, postural/orthostatic hypotension, syncopal attacks, parkinsonism, polio sequelae, multiple sclerosis, or other neurological problems.
[c]Serum cross-linked N-telopeptides of type I collagen.

among the women. The latter discrepancy was accounted for by premature (<45 years) menopause; excluding that, the prevalence of the other causes of secondary osteoporosis, excluding rheumatoid arthritis, was similar in women and men (6% versus 7%). With regard to potential extensions of FRAX, women were more likely to have one or more risk factors for falling (85% versus 60%; $P < 0.001$), but the difference in reported falls in the previous year was not significant. They also had lower LS BMD (0.971 versus 1.129 g/cm^2; $P < 0.001$) and lower bone formation as assessed by serum OC levels (5.80 ng/mL versus 6.52 ng/mL; $P = 0.003$), despite comparable bone resorption as assessed by serum NTx levels (12.5 nMBCE versus 12.6 nMBCE; $P = 0.830$). None of the men, compared to 19% of the women ($P < 0.001$), were on an osteoporosis treatment at baseline.

Subjects were then followed and censored at death or loss to followup (if before 10 years) or after 10 years of followup among survivors (4455 person-years). Altogether, 74% were followed for at least 10 years, and death accounted for almost all of the shorter followup intervals (median followup of those who died was 7 years). Even so, observed survival at 10 years was 77% when 70% was expected ($P < 0.001$).

During this same 10-year followup interval, 218 subjects experienced 380 different fractures, including 165 asymptomatic, nonpathological vertebral fractures that were discovered incidentally; 4 pathologic fractures (including 2 vertebral fractures) were excluded from most analyses. Most fractures were due to no more than moderate trauma (Table 2). The primary analysis focused, however, on the major osteoporotic fractures (i.e., hip, symptomatic (clinical) spine, distal forearm, and proximal humerus). Forty-four women had at least one major osteoporotic fracture, including 11 with an incident hip fracture, as did 18 men, including 5 who had an incident hip fracture. In addition, 61 women and 33 men experienced at least one fracture at another skeletal site.

The median FRAX probability for any major osteoporotic fracture was 7% (range, 0–45%), being 10% in women (range, 0–45%) and 5% in men (range, 0–30%). The predicted risk was greater among women than men and increased in accordance with the major osteoporotic fractures actually observed (Table 3). More fractures were observed than expected in most quartiles (overall SIR = 1.6, 95% CI 1.1–2.1 in women and SIR = 1.4, 95% CI 0.8–2.2 in men). Just 5 fractures were observed in the lowest FRAX quartile (2 women due to severe trauma and 3 men due to moderate trauma), whereas 28 occurred in the highest risk quartile. Only 16 hip fractures were observed during followup so statistical power was limited, but the risk estimates for hip fractures in women (SIR = 1.5, 95% CI 0.8–2.7) and men (SIR = 1.7, 95% CI 0.6–4.0) resembled those for all major osteoporotic fractures combined.

To explore the apparent underestimation of 10-year fracture risk, we compared site-specific fracture counts with the numbers expected from the incidence rates used in revised US FRAX. For combined men and women age ≥50 years old (the age group reported for those rates), there were somewhat fewer observed first fractures of the hip (16 versus 24, $P = 0.111$), greater numbers of distal forearm (19 versus 15, $P = 0.285$) and symptomatic vertebral fractures (20 versus 15, $P = 0.166$), and similar numbers of proximal humerus fractures (8 versus 7, $P = 0.834$) compared to expected. Overall agreement between observed and expected fractures was better among the men ≥50 years of age (16

Table 2: Fracture outcomes over 10 years among Rochester, MN women and men ≥40 years of age at baseline, by precipitating trauma.

Fracture site	Women		Men	
	Moderate *n* (%)	Severe *n* (%)	Moderate *n* (%)	Severe *n* (%)
Skull/face	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)
Cervical spine	1 (0.5%)	1 (3%)	0 (0%)	0 (0%)
Other vertebrae—symptomatic[a]	20 (11%)	2 (7%)	11 (8%)	0 (0%)
Other vertebrae—asymptomatic	68 (37%)	1 (3%)	96 (67%)	0 (0%)
Ribs	29 (16%)	4 (14%)	14 (10%)	4 (21%)
Sternum/clavicle/scapula	2 (1%)	4 (14%)	2 (1%)	1 (5%)
Proximal humerus[a]	5 (3%)	2 (7%)	1 (1%)	2 (11%)
Other arm	4 (2%)	0 (0%)	2 (1%)	0 (0%)
Distal forearm[a]	16 (9%)	2 (7%)	1 (1%)	2 (11%)
Hand/fingers	8 (4%)	4 (14%)	2 (1%)	2 (11%)
Pelvis	6 (3%)	0 (0%)	3 (2%)	2 (11%)
Proximal femur[a]	12 (6%)	0 (0%)	5 (3%)	0 (0%)
Other leg	9 (5%)	3 (10%)	5 (3%)	3 (16%)
Feet/toes	4 (2%)	6 (21%)	1 (1%)	3 (16%)
Total	185	29	143	19

[a] Major osteoporotic fractures.

Table 3: First major osteoporotic fractures observed among Rochester, MN women and men compared to numbers predicted by revised US FRAX (FN BMD), by age at baseline and quartile of full 10-year fracture probability (%).

Quartile[b]	≥40 years old at baseline			≥60 years old at baseline		
	Observed	Predicted	SIR (95% CI)[a]	Observed	Predicted	SIR (95% CI)[a]
Women						
Q1 (0 to <4.7)	2	1.7	1.2 (0.2–4.4)	0	—[c]	N.A.
Q2 (4.7 to <10.4)	5	4.5	1.1 (0.4–2.6)	4	2.6	1.5 (0.4–3.9)
Q3 (10.4 to <17.9)	15	7.6	2.0 (1.1–3.3)	13	6.3	2.0 (1.1–3.5)
Q4 (17.9 to 44.9)	22	15.5	1.5 (0.95–2.3)	22	14.3	1.5 (0.96–2.3)
Subtotal	44	28.2	1.6 (1.1–2.1)	39	23.3	1.7 (1.2–2.3)
Men						
Q1 (0 to <3.6)	3	1.3	2.2 (0.5–6.6)	1	0.2	5.6 (0.1–31)
Q2 (3.6 to <5.2)	2	2.5	0.8 (0.1–2.9)	2	1.5	1.4 (0.2–4.9)
Q3 (5.2 to <8.1)	7	3.1	2.3 (0.9–4.7)	5	2.4	2.1 (0.7–5.0)
Q4 (8.1 to 29.8)	6	6.4	0.9 (0.4–2.1)	6	5.4	1.1 (0.4–2.4)
Subtotal	18	13.2	1.4 (0.8–2.2)	14	9.4	1.5 (0.8–2.5)
Total	62	41.5	1.5 (1.2–1.9)	53	32.7	1.6 (1.2–2.1)

[a] Standardized incidence ratio (SIR) and 95% confidence interval (CI).
[b] Quartiles (Q) defined using all ages.
[c] No subjects in this group.

versus 14, $P = 0.642$) than the women (41 versus 32, $P = 0.099$), but none of these differences was statistically significant.

However, FRAX predicted fractures at other sites about as well as it did major osteoporotic fracture risk (Table 4). Thus, a relative 10% increase in FRAX 10-year fracture probability was associated with a 1.9-fold increase in major osteoporotic fractures, and a 1.4-fold increase in all other fractures, in the women. Among the men, a 10% increase in the FRAX probability was associated with a 2.1-fold increase in major osteoporotic fractures and with a 1.7-fold increase in other fractures. FRAX predicted asymptomatic vertebral fractures as well as symptomatic ones, as it did fractures generally.

After forcing the full FRAX probability for each subject into a model, the potential contribution of additional risk factors was evaluated (Table 5). Although statistical power was limited, there was no additional contribution from a history of falling; the presence of risk factors for falling was associated with an increased risk that was not statistically significant, but adding them did not improve the C-statistic over that for FRAX alone (C-statistic, 0.75 in women and 0.65 in men). Results were not changed by counting the number of falls or fall risk factors (data not shown). Likewise, the presence of additional causes of secondary osteoporosis or the use of estrogen had little effect on the results. There was also no significant contribution to fracture prediction,

Table 4: First nonpathologic fracture of each type observed and hazard ratio (HR) per 10% increase in the full 10-year US FRAX (FN BMD) probability among Rochester, MN women and men ≥40 years of age, by type of fracture outcome.

Fracture type	Women		Men	
	Observed	HR (95% CI)	Observed	HR (95% CI)
Any major osteoporotic fracture[a]	44	1.9 (1.5–2.4)	18	2.1 (0.99–4.6)
Symptomatic vertebral fracture[b]	15	2.2 (1.5–3.3)	7	2.0 (0.5–7.0)
Any asymptomatic vertebral fracture[c]	44	1.8 (1.4–2.3)	78	2.4 (1.6–3.6)
Any other fracture[c]	61	1.4 (1.1–1.8)	33	1.7 (0.9–3.1)
Other axial fracture	34	1.9 (1.4–2.5)	20	2.1 (1.0–4.2)
Other appendicular fracture[d]	33	1.2 (0.9–1.6)	16	2.3 (1.0–5.0)
Any nonpathologic fracture	110	1.6 (1.4–1.9)	104	2.3 (1.6–3.3)

[a]Defined according to FRAX as proximal femur, clinical spine, distal forearm, or proximal humerus fractures.
[b]Included in major osteoporotic fractures.
[c]Not included in major osteoporotic fractures.
[d]Excluding 2 pathologic appendicular fractures.

Table 5: Effect of additional risk factors to predict first major osteoporotic fracture (Fx) over 10 years among Rochester, MN women and men ≥40 years of age, after adjusting for the full US FRAX (FN BMD) probability.

Model	Women (44 Fxs)		Men (18 Fxs)	
	HR (95% CI)[a]	C[b]	HR (95% CI)[a]	C[b]
Fall history in past year (y/n)	0.8 (0.5–1.6)	0.75	0.9 (0.4–2.4)	0.65
Fall risk factors (y/n)	1.5 (0.5–4.2)	0.74	2.0 (0.7–5.7)	0.64
Additional causes of secondary osteoporosis (y/n)	0.5 (0.3–0.98)	0.76	1.5 (0.6–3.9)	0.64
Concurrent estrogen use (y/n)	1.2 (0.6–2.7)	0.74	N.A.	—
Lumbar spine BMD (g/cm^2) (per SD ↓)	1.2 (0.8–1.8)	0.74	1.1 (0.6–1.8)	0.66
Femoral neck-lumbar spine T-score difference (per unit ↑)	1.0 (0.7–1.5)	0.75	0.8 (0.5–1.1)	0.62
Serum NTx[c] (nMBCE) (per SD ↑)	1.1 (0.8–1.5)	0.75	0.8 (0.4–1.5)	0.67
Serum osteocalcin (OC, ng/mL) (per SD ↓)	1.3 (0.9–1.8)	0.76	1.0 (0.6–1.8)	0.65
NTx/OC ratio (per SD ↑)	1.4 (1.1–1.6)	0.78	1.2 (1.04–1.4)	0.66

[a]Hazard ratio (HR) and 95% confidence interval (CI).
[b]Concordance (C) statistic.
[c]Serum cross-linked N-telopeptides of type I collagen.

once the FRAX probability was known, from the addition of LS BMD T-scores, the discrepancy between FN and LS T-scores or measures of bone resorption (NTx) or formation (OC). However, the ratio of resorption to formation (NTx ÷ OC) did predict fractures independently of FRAX in both women (HR = 1.4, 95% CI 1.1–1.6) and men (HR = 1.2, 95% CI 1.04–1.4), although the C-statistic was little changed by this addition. Generally, all of the models predicted fractures better among women than men.

4. Discussion

In a population-based cohort consisting of both sexes and all relevant ages, we found, as expected, that fractures increased with the predicted fracture probability and were more common among women than men. Few fractures were observed in the lowest quartile of FRAX probabilities, and all were attributed to severe trauma among the women. By contrast, 36% of the women and 10% of the men in the highest risk quartile had experienced a major osteoporotic fracture at 10 years. A similar result was seen for older women in the Study of Osteoporotic Fractures [20]. A more novel result is our finding that FRAX predicted fractures at other skeletal sites about as well as it did major osteoporotic fractures. This might be expected from the fact that bone density predicts fracture risk generally in older individuals [6] and, indeed, predicts fractures attributed to high-energy traumatic events as well as it does those resulting from falls [21, 22]. This is clinically relevant since the overall societal burden of fractures is not limited to the traditional osteoporotic fractures.

Although FRAX itself had been extensively validated [23], the initial version of US FRAX was revised because it seemed to overestimate fracture risk [8], particularly with respect to vertebral fractures. By contrast, the revised version underestimated fracture risk in this cohort, where we had unusually complete fracture ascertainment based on review of all community radiographs on the subjects. A priori, we had specified that agreement within 25% between observed and expected fractures would constitute a close fit with FRAX, but this conservative criterion was not met for either sex. While no single community is representative of a country-specific FRAX model [5], investigators in other settings have likewise found that FRAX may somewhat

underestimate [24–29] or, instead, overestimate [30, 31] major osteoporotic fracture risk, though some reported comparisons may be misleading [32]. Such differences may not be clinically significant since patients are usually categorized into broad risk groups [33], and FRAX better predicts fracture risk than BMD per se in any case [23].

The difference between observed and predicted fractures was partly due to more complete ascertainment of symptomatic vertebral fractures in our setting, although better than expected survival may also have played a role. The main difference between original (version 2.0) and revised (version 3.1) US FRAX was a reduction in the vertebral fracture incidence rates used in the model [8]. Comparably age- and sex-adjusted, the revised vertebral fracture incidence rates were only 27% as great as those used originally, and the corresponding overall incidence of a major osteoporotic fracture was reduced by about one-third [7], which is consistent with the discrepancy found here. The rationale for revising US FRAX was to focus on the symptomatic vertebral fractures thought to be more clinically relevant [8], although even asymptomatic vertebral fractures may lead to adverse outcomes [34]. How this latter group should be handled remains to be resolved.

In a preliminary analysis, we also evaluated several additional risk factors that have been suggested for use in an expanded FRAX model [5]. Thus, bone loading from a fall dominates skeletal fragility due to bone loss [35], but a self-reported history of falling in the previous year did not enhance prediction of a major osteoporotic fracture over FRAX alone, nor did risk factors for falling, and practical approaches for including fall risk in FRAX are lacking [36]. Likewise, risk factors for secondary osteoporosis beyond those already included in FRAX were not associated with a significant increase in fracture risk, but many exert their effects through reduced bone density [37], which was already taken into account. By contrast, some comorbid conditions predicted short-term fracture risk in a large clinical study, but the C-statistic was not better than that for FRAX alone [38], as also seen here. Discordant LS and FN BMD results in some patients prompted consideration of adding LS BMD to FRAX [39], but LS T-scores did not add significantly to fracture prediction in this study, nor did the difference between LS and FN T-scores [40]. The ratio of resorption to formation markers did predict overall risk independently of FRAX, but the accuracy of fracture prediction was not much enhanced, and many practical issues remain to be resolved [41]. Finally, FRAX pertains to untreated patients, but relatively few women and none of the men were on osteoporosis treatment at baseline.

This study has several strengths. In particular, it is a prospective study of randomly sampled community women and men with long followup and superior ascertainment of subsequent fractures. Risk factors were recorded before any knowledge of resultant fractures, and fractures were documented in detailed medical records that spanned each subject's entire period of residency in the community. The main limitation is the relatively small sample size, with correspondingly low numbers of fractures, especially hip fractures, and reduced statistical power, especially for assessing additional risk factors that might be included in FRAX in the future. In addition, these subjects were relatively healthy, with better than expected survival, although mean 10-year FRAX probabilities were in keeping with those seen in other population-based cohorts of similar age [25, 29]. To obtain a sufficient duration of followup for fracture outcomes, we studied women enrolled in 1991–93 and men in 1993–95; concurrent osteoporosis treatment at baseline was therefore mostly estrogen, as alendronate was not introduced into widespread clinical practice until 1995 [10]. Finally, our results are not generalizable to nonwhites because the study cohort and the underlying Rochester population are largely white [13]. Moreover, the local population is largely of northern European extraction, although age-adjusted secular trends and hip fracture incidence rates in this community are comparable to those for United States whites generally [42] and, indeed, consistent with the expected hip fracture incidence rate used in the revised US FRAX [7, 8].

5. Conclusions

In this study population, the revised US FRAX provided a conservative estimate of fracture probability, but much of the discrepancy between the major osteoporotic fractures predicted and those actually observed could be accounted for by unusually complete ascertainment of symptomatic vertebral fractures in this population. Agreement is likely better in routine clinical applications of FRAX. We had limited power to determine the role of other risk factors in potentially improving risk assessment by FRAX, but we did find that bone turnover markers may provide additional predictive information and be worthy of further study. While it cannot be expected that any estimate of risk will correctly identify which specific individuals will or will not experience a future fracture [4], an increased probability of fracture as determined by FRAX was associated with increased risk for a major osteoporotic fracture as well as for fractures generally, including asymptomatic vertebral fractures. Although not specifically created for assessing the risk of other types of fractures, FRAX may be equally useful in their prediction due to risk factors that these fractures share with the more typical osteoporotic fractures currently modelled in FRAX.

Conflict of Interests

The authors have no relevant conflict of interests.

Acknowledgments

The authors would like to thank Leona Bellrichard, R.N., Marcia Erickson, R.N., Wendy Gay, R.N., Julie Gingras, R.N., Joan LaPlante, R.N., Barbara Nolte, R.N., and Cynthia Nosek, R.N. for assistance with data collection and Mary Roberts for help in preparing the paper. This work was supported by research Grants AR027065 (National Institute of Arthritis, Musculoskeletal and Skin Diseases) and UL1 TR000135 (Center for Translational Scientific Activities) and made possible by the Rochester Epidemiology Project

(AG034676 from the National Institute on Aging), U.S. Public Health Service.

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