

Empirically Based Composite Fracture Prediction Model From the Global Longitudinal Study of Osteoporosis in Postmenopausal Women (GLOW)

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Context: Several fracture prediction models that combine fractures at different sites into a composite outcome are in current use. However, to the extent individual fracture sites have differing risk factor profiles, model discrimination is impaired.

Objective: The objective of the study was to improve model discrimination by developing a 5-year composite fracture prediction model for fracture sites that display similar risk profiles.

Design: This was a prospective, observational cohort study.

Setting: The study was conducted at primary care practices in 10 countries.

Patients: Women aged 55 years or older participated in the study.

Intervention: Self-administered questionnaires collected data on patient characteristics, fracture risk factors, and previous fractures.

Main Outcome Measure: The main outcome is time to first clinical fracture of hip, pelvis, upper leg, clavicle, or spine, each of which exhibits a strong association with advanced age.

Results: Of four composite fracture models considered, model discrimination (c index) is highest for an age-related fracture model (c index of 0.75, 47 066 women), and lowest for Fracture Risk Assessment Tool (FRAX) major fracture and a 10-site model (c indices of 0.67 and 0.65). The unadjusted increase in fracture risk for an additional 10 years of age ranges from 80% to 180% for the individual bones in the age-associated model. Five other fracture sites not considered for the age-associated model (upper arm/shoulder, rib, wrist, lower leg, and ankle) have age associations for an additional 10 years of age from a 10% decrease to a 60% increase.

Conclusions: After examining results for 10 different bone fracture sites, advanced age appeared the single best possibility for uniting several different sites, resulting in an empirically based composite fracture risk model. (*J Clin Endocrinol Metab* 99: 817–826, 2014)

Multivariable statistical models combine patient characteristics to create decision tools for clinicians to identify women at increased risk of future fracture. Most widely cited and used are 10-year prediction tools for Fracture Risk Assessment Tool (FRAX) major osteoporotic fracture (clinical spine, forearm, hip, or shoulder) (1)

and the Garvan model (hip, symptomatic spine, forearm, metatarsal, humerus, scapula, clavicle, distal femur, proximal tibia, patella, pelvis, or sternum) (2). It is unclear whether these particular fractures were combined based on empirical data or on some other basis, such as how common, severe, or osteoporotic the fractures are. Their

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Abbreviations: BMD, bone mineral density; EQ-5D, five dimension EuroQol; FRAX, Fracture Risk Assessment Tool; GLOW, Global Longitudinal Study of Osteoporosis in Postmenopausal Women; HR, hazard ratio; QOL, quality of life; UAS, upper arm or shoulder.

model discrimination reflects limited clinical utility (*c*-statistics <0.7) (3), perhaps because the chosen fractures have distinct risk profiles. Although combining disparate fractures may appear to increase model efficiency by increasing the volume of fractures, model performance may suffer without an empirical rationale for the chosen fracture sites. Models for hip fracture alone, in contrast, provide much better patient discrimination [*c*-statistics for hip fracture with or without bone mineral density (BMD) ≥ 0.75 in Study of Osteoporotic Fractures (4) and ≥ 0.70 for 9 of 10 studies with BMD (5)].

A previous Global Longitudinal Study of Osteoporosis in Postmenopausal Women (GLOW) paper examined associations between characteristics of older women and 10 bone fracture sites [hip, pelvis, upper leg, spine, clavicle, upper arm or shoulder (UAS), rib, lower leg, wrist, ankle] over a 3-year period (6). Several factors were associated with more than one fracture site in adjusted results: advanced age (eight sites), prior fracture of the same or a different bone (all 10 sites), low weight (five sites), falls (nine sites), weight loss of 10 lb or more in a year (three sites), and poor health or reduced activity (six sites). The fracture risk associated with advanced age is, however, unique. No other modeled factor showed comparable variation over fracture sites, from an estimated 20% adjusted decrease in ankle fracture hazard to an estimated 130% adjusted increased hip fracture hazard per 10 additional years of age. Second, no other factor showed comparable discriminative ability in as many different site models, advanced age being the dominant factor in five of 10 sites.

Accordingly, this paper introduces a risk profile-based, 5-year composite fracture model whose five fracture sites (hip, pelvis, upper leg, clavicle, and spine) are all strongly associated with advanced age, whereas the five fracture sites not included (rib, upper arm, lower leg, wrist, and ankle) have moderate to inverse age associations.

Using 5-year data from the GLOW study, the new model's performance and risk factor estimates are compared with a model that combines the four FRAX major osteoporotic fractures, and with new models of seven and 10 fracture sites, to illustrate the principle that increasing

the number of fracture outcomes may have unintended model performance consequences.

Materials and Methods

The GLOW study has been described elsewhere (7). In brief, 60 393 women aged 55 years or older were recruited by physician letter from 17 sites in 10 countries. About 90% of the women contributed at least 1 year of follow-up information after baseline. Women were followed up at 1, 2, 3, and 5 years after study baseline, with the 5-year follow-up to include information since the last completed written survey. All study information, including clinical fractures from any cause and their dates, are self-reported. We did not collect information on BMD.

Analytical methods

Women with at least one follow-up survey after baseline were analyzed. To include women with gaps in follow-up surveys, we used the counting process approach (8). Fracture rate estimates use the Kaplan-Meier method, adjusted for estimated deaths. The estimated deaths were obtained using the US Social Security Period Life Table (2007). Fracture rates are approximately 3% lower after adjustment for estimated deaths.

Outcomes are time to first fracture of the specified type. Unadjusted hazard ratios (HRs) are presented for potential fracture risk factors for 10 individual fracture sites and four site combinations. Adjusted risk factor estimates, as well as their model χ^2 values (indicative of factors' relative strengths within a given model), are from Cox multiple regression models. All Table 1 risk factors were considered. Factors were grouped (medical history, health/vitality/physical function) to eliminate possible redundant factors before adding other factors. Nonlinear (on log scale) associations with continuous variables were considered, using the methods of fractional polynomials (9) and restricted cubic splines (10). The only interactions considered were with age. Because data extend to 5 years past baseline, we checked the proportional hazards assumption for final model covariates; no violations were found.

Model covariates for composite indices [five dimension EuroQol (EQ-5D) (11), physical function, vitality] were compared with individual index components with the largest unadjusted fracture associations; final model choices were determined by the best model log likelihood. The EQ-5D has a maximum value of 1 [excellent quality of life (QOL)] and is negative if the QOL is worse than death. The vitality index scale of 0 (low) to 100 (high) was converted to $(100 - \text{vitality})/20$ to obtain a positive association with fracture. Moderate activity, defined as the ability to move a table, push a vacuum cleaner, bowl,

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Table 1. Unadjusted Results for 5-Year Fracture Combinations (53 896 Women)

			Fracture Outcome			
			F5	F7	F10	Major
Total observations, n			55 163	55 150	55 132	55 220
Fractures, n			1783	3082	5040	3169
Five-year estimated fracture rate, %			4.0	7.0	11.2	7.4
	% Missing	Median	HR			
Risk factor at study baseline						
Age per 10 y past 55 y	0	67 y	2.06	1.76	1.44	1.58
Weight per 10 kg	2.3	68 kg	0.87	0.91	0.94	0.91
BMI per 10 kg/m ²	4.4	26 kg/m ²	0.74	0.84	0.89	0.83
Height per 10 cm	3.0	161 cm	0.84	0.84	0.92	0.89
Physical function (0–100) per 10-point decrease	1.3	83	1.2	1.17	1.12	1.12
Vitality index (0–100) per 10-point decrease	1.8	63	1.21	1.18	1.13	1.12
EQ-5D index (–0.20 to –1.00) per 0.10-point decrease	8.6	0.81	1.17	1.15	1.12	1.12
	% Missing	% With RF	HR			
Risk factor at study baseline						
Age 80 y or older	0	12	3.29	2.66	2.03	2.28
Prior F10	2.3	23	3.05	2.8	2.37	2.37
Prior hip fracture	0.8	1.7	5.52	4.34	3.03	3.59
Prior wrist fracture	0.7	8.4	2.37	2.28	2.19	2.37
One fall	1.1	23	1.5	1.42	1.39	1.36
Two or more falls		15	2.28	2.22	2.06	1.94
Maternal hip fracture	6.0	13	1.39	1.28	1.26	1.27
Paternal hip fracture	9.9	3.9	1.45	1.26	1.11	1.16
Medical history						
Asthma	1.1	11	1.31	1.37	1.24	1.18
Emphysema	2.4	8.6	1.69	1.67	1.54	1.51
Osteoarthritis	1.9	40	1.55	1.54	1.42	1.41
Rheumatoid arthritis	7.9	0.8	2.11	1.84	1.55	1.44
Colitis	1.4	2.0	1.65	1.52	1.51	1.39
Celiac disease	1.8	0.6	1.47	1.4	1.4	1.57
Stroke	1.3	3.9	2.03	1.83	1.46	1.61
Parkinson's disease	1.1	0.5	4.14	3.06	2.46	2.43
Multiple sclerosis	1.1	0.6	1.69	1.87	1.72	1.76
Cancer	1.1	14	1.4	1.3	1.24	1.15
Type 1 diabetes	0.4	0.8	1.56	1.46	1.44	1.64
General health (poor vs excellent)	1.2	2.7	5.69	4.52	3.31	3.45
Moderate activities (very limited vs not)	2.3	12	2	1.76	1.5	1.52
EQ-5D (unable to perform usual activities)	0.8	1.8	2.35	2.01	1.71	1.76
Days walked past month						
0	1.8	15	2.03	1.66	1.4	1.39
1–9 (vs ≥10)		37	1.43	1.28	1.13	1.05
Active (not at all vs very)	1.1	4.4	2.44	2.12	1.73	1.74
Current smoker	0.8	8.9	1.01	1.11	1.1	1.04
Alcohol (>20 vs 0 drinks/wk)	0.8	0.5	1.19	1.02	1.18	1.25
Lost 10 lb in last y	1.5	9.2	1.98	1.77	1.51	1.57

Abbreviations: BMI, body mass index; F5, any 5-year fracture of hip, pelvis, upper leg, clavicle, or spine; F7, any 5-year fracture of hip, pelvis, upper leg, clavicle, spine, UAS, or rib; F10, any 5-year fracture of any of the 10 bones in Table 2; Major, any 5-year fracture of hip, spine, UAS, or wrist (FRAX major osteoporotic fracture).

or play golf, is defined as being limited a lot, limited a little, or not at all limited (coded –1, –2, and –3, respectively). In her performance of usual activities (work, study, housework, family, or leisure activities), a woman may have no problems, some problems, or be unable to perform them (coded 1, 2, and 3, respectively).

Prior cancer includes cancer of any kind, including skin cancer.

Weight was modeled as 100/weight in kilograms. No other nonlinear associations were found.

Because prior fracture at the same site is more strongly associated with future fracture than is prior fracture at a different site, each composite model includes baseline fracture of a site in that composite as well as fracture at a different site.

The modeling process was performed once for the composite outcome of the five most strongly age-associated fractures (F5 model: hip, pelvis, upper leg, spine, or clavicle) and once for major osteoporotic fracture to assess for each the best possible model using GLOW survey data. The two other reported models (F7: F5 plus UAS or rib, and F10: F7 plus lower

leg, wrist, or ankle) use the same final risk factors as found in the age-associated fracture model because they include the same five fractures and are presented for comparison with that model.

Model performance was assessed by the May-Hosmer goodness-of-fit test (12) and Harrell's c index (13). This index measures whether pairs of model observations with different risk profiles have expected relative outcomes; for example, a pair of women is concordant if a woman with lower modeled risk has

not fractured by the time (since study baseline) a higher-risk woman fractures. Its range is typically 0.5 (a model equivalent to random chance) to 1.0. These measures were calculated on the 88% of women with no interruptions in follow-up since study baseline.

Table 2 parameter estimates (β -hats) can be converted into a 5-year cumulative fracture risk for an individual woman as shown in the technical note following the body of this paper.

Site of recruitment was not included in these models.

Table 2. Unadjusted Results for 5-Year Individual Fractures (53 896 Women)

	Fracture Outcome									
	Hip	Pelvis	Upper Leg	Clavicle	Spine	UAS	Rib	Wrist	Lower Leg	Ankle
Total observations, n	55 224	55 280	55 270	55 273	55 296	55 294	55 283	55 304	55 248	55 219
Fractures, n	513	278	254	226	701	760	878	1426	362	834
Five-year estimated rate, %	1.2	0.6	0.6	0.5	1.6	1.7	2.0	3.2	0.8	1.8
Hazard ratios										
Risk factor at study baseline										
Age per 10 y past 55 y	2.76	2.13	2.04	1.79	1.77	1.56	1.45	1.29	1.05	0.87
Weight per 10 kg	0.78	0.81	0.96	0.87	0.92	0.98	0.92	0.91	1.09	1.12
BMI per 10 kg/m ²	0.57	0.57	1.04	0.83	0.81	1.05	0.86	0.81	1.23	1.32
Height per 10 cm	0.85	0.86	0.77	0.70	0.89	0.78	0.85	0.94	1.07	1.07
Physical function per 10-point decrease	1.24	1.18	1.24	1.21	1.19	1.12	1.16	1.06	1.15	1.07
Vitality index per 10-point decrease	1.21	1.19	1.18	1.23	1.23	1.12	1.23	1.06	1.13	1.08
EQ-5D index per 0.1-point decrease	1.20	1.16	1.19	1.17	1.16	1.10	1.19	1.09	1.15	1.08
Age 80 y or older	5.15	3.37	3.08	2.99	2.59	1.93	2.20	1.64	1.36	0.77
Prior F10	2.90	3.81	3.24	2.62	3.20	2.37	3.37	2.03	2.68	1.77
Prior hip fracture	9.10	4.89	5.18	2.41	3.79	2.35	3.17	2.06	2.50	0.83
Prior wrist fracture	2.59	3.69	2.37	1.98	2.01	2.41	2.40	2.52	1.96	1.52
One fall	1.53	1.81	1.46	1.82	1.43	1.39	1.36	1.32	1.38	1.49
Two or more falls	2.34	3.00	2.57	2.81	2.00	1.98	2.45	1.88	2.46	2.21
Maternal hip fracture	1.46	1.70	1.38	1.24	1.36	1.25	1.21	1.20	1.06	1.29
Paternal hip fracture	1.61	1.40	1.05	1.98	1.43	1.23	1.17	0.93	0.95	0.94
Medical history										
Asthma	1.02	1.02	1.55	1.11	1.59	1.25	1.74	1.05	1.32	1.34
Emphysema	1.60	1.09	1.73	1.77	1.99	1.39	2.03	1.29	1.16	1.71
Osteoarthritis	1.37	1.39	1.79	1.28	1.77	1.32	1.79	1.36	1.37	1.17
Rheumatoid arthritis	2.43	2.88	2.17	1.21	1.77	1.79	2.01	0.66	4.64	1.30
Colitis	2.04	1.15	1.04	2.72	1.87	1.13	1.60	1.29	1.49	2.00
Celiac disease	1.91	1.76	n/e	1.46	1.40	1.29	1.34	1.75	0.91	0.99
Stroke	2.30	1.87	1.39	1.32	2.16	1.64	1.82	1.10	0.97	1.13
Parkinson's disease	4.04	3.27	4.34	4.01	3.98	1.18	3.20	1.75	1.22	1.07
Multiple sclerosis	2.30	0.59	1.96	2.24	1.90	2.21	1.34	1.52	3.27	1.81
Cancer	1.31	1.58	1.78	1.30	1.33	1.11	1.33	1.05	1.29	1.32
Type 1 diabetes	2.04	0.94	2.06	2.34	1.31	2.07	0.89	1.66	1.45	1.57
General health (poor vs excellent)	3.93	3.26	3.52	3.58	12.5	2.47	4.91	2.01	5.24	2.25
Moderate activity (very limited vs not)	2.24	1.84	2.15	2.01	1.96	1.43	1.76	1.22	1.61	1.23
EQ-5D (unable to perform usual activities)	2.75	2.03	2.50	2.34	2.32	1.58	1.92	1.40	2.01	1.43
Days walked past month										
0	2.58	1.66	2.48	1.97	1.83	1.29	1.59	1.04	1.70	1.25
1–9 (vs ≥ 10)	1.64	1.42	1.74	1.58	1.28	1.04	1.29	0.87	1.11	1.25
Active (not at all vs very)	3.07	1.91	3.27	2.13	2.77	1.78	2.27	1.30	3.16	1.83
Current smoker	0.99	0.68	0.93	1.19	1.26	1.12	1.26	0.90	1.17	1.34
Alcohol (>20 vs 0 drinks/wk)	1.32	0.67	1.84	2.36	0.51	0.74	1.10	1.65	0.50	0.91
Lost 10 lb in last y	2.24	1.66	1.71	2.26	1.85	1.54	1.61	1.23	1.04	1.24

BMI, body mass index; F10, fracture of any of 10 bones listed.

All analyses were conducted using the SAS software package, version 9.2 (SAS Institute).

Results

Estimated 5-year fracture rates among the 53 896 women with at least one follow-up survey range from 0.5% (clavicle) to 3.2% (wrist; Table 2). The median age was 67 years, weight was 68 kg, 23% had a prior baseline fracture of at least one of the 10 individual bones since age 45 years, and 38% reported falling one or more times in the year prior to baseline (Table 1). Only 2.7% reported poor general health, 4.4% were not at all active compared with the same-aged women, 1.8% were unable to perform usual activities, and 12% reported being very limited in moderate activities.

Compared with women with complete 5 years of follow-up, women without complete 5 years of follow-up tended to be older (70 vs 67 y), have lower mean baseline physical function and vitality (56 vs 63 and 65 vs 77, respectively), and worse general health (6.2% vs 10% excellent; data not shown). Fracture risk factors were more likely to be present in women without complete follow-up, in particular a prior fracture of any of the 10 bones (28% vs 21%).

Tables 1 and 2 also present unadjusted HRs for 10 individual bone fractures and four fracture combinations. Individual fractures (Table 2) are listed in descending order of age association, with HRs ranging from 0.9 (ankle) to 2.8 (hip) for 10 additional years after age 55 years (see also Figure 1). Model F5 (Table 1) combines hip, pelvis, upper leg, clavicle, and spine (unadjusted age HRs from 1.8 to 2.8), F7 combines these five plus upper arm/shoulder (UAS) and rib (age HRs 1.5–2.8), F10 combines all 10 bones (age HRs 0.9–2.8). Major osteoporotic fracture combines hip, spine, UAS, and wrist (unadjusted age HRs 1.3–2.8 per 10 y).

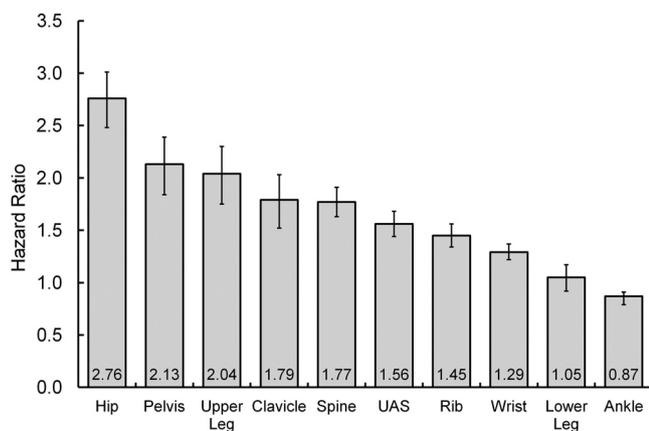


Figure 1. Unadjusted HRs and 95% confidence intervals per 10 years of age (past 55 y) for 10 fracture sites.

Because wrist fractures are relatively common ($n = 1426$), fracture of at least one major bone is more common than an F5 or F7 fracture ($n = 2594$ vs 1455 and 2547). Kaplan-Meier 5-year estimated mean fracture rates are 4.0%, 7.0%, 7.4%, and 11.2% for F5, F7, major, and F10 composites, respectively. Median 5-year fracture rates are somewhat lower due to the right-skewed nature of risk (2.4%, 4.9%, 5.4%, and 9.0%, respectively).

As one might expect, the five age-associated fractures show fairly large unadjusted individual associations with reduced physical function, vitality, EQ-5D (QOL), not walking, and prior fractures compared with the remaining five fractures (although rib fracture has an HR of 3.4 with prior F10). Parkinson's disease, although affecting only 0.5% of women, has HRs greater than 3 for each F5 fracture (3.3–4.3), less than 2 for all other fractures except rib (HR 3.2). Hip, pelvis, and clavicle are most highly associated with lower weight (HRs from 0.78 to 0.87 per 10 additional kg), whereas lower leg and ankle fractures are associated with higher weight (HR 1.1).

Table 3 presents results for the four composite fracture Cox regression models. Approximately 85% of available data were used to fit the models, the remainder having one or more missing covariate values. Because F5 fractures were selected based on their relatively strong unadjusted associations with age, this composite outcome has the largest adjusted association with age (linear age HR of 1.6 per additional 10 y, ignoring age interactions; data not shown), and age is the strongest model factor. F7 and major fracture composites have somewhat smaller adjusted linear age HRs of 1.4, whereas F10's linear age HR is 1.2 per additional 10 years (ignoring age interactions; data not shown). In F7, F10, and major fracture models, the single strongest risk factor is not age but prior fracture of at least one bone in the composite (based on χ^2 values ignoring age interactions; data not shown). F5 risk factors remain statistically significant in the F7 and F10 models, with somewhat reduced HRs for associations with age, weight, maternal hip fracture, Parkinson's disease, unintended weight loss, and reduced usual activity. Baseline falls appear similarly strong in all four composite fracture models.

The major osteoporotic fracture model was fitted independently of the F5 model, allowing for the possibility of identifying a different set of risk factors. Vitality, Parkinson's disease, and decreased moderate activity were not statistically significant, whereas osteoarthritis and reduced general health were.

F5, F7, and F10 models have two statistically significant age interactions (Table 3 and Figure 2). Advanced age has a stronger F5 fracture association for women with no prior F5 fracture (estimated cumulative F5 fracture prob-

Table 3. Cox Regression Models for 5-Yr Fracture Combinations

Model Summary	F5			F7			F10			Major		
Total observations, n	47 066			47 069			47 245			47 429		
Fractures, n	1455			2547			4199			2638		
May-Hosmer goodness of model fit (<i>P</i>)	.44			.28			.09			.99		
Harrell's c index	0.753			0.709			0.653			0.667		
	β -Hat	χ^2	HR (CI)									
Model covariates at study baseline												
1. 10 y of age past 55 y	0.9939	154	^a	0.7068	133	^a	0.3750	58	^a	0.4660	60	^a
2. 20 points less vitality	0.1156	14	1.1 (1.1–1.2)	1.1297	30	1.1 (1.1–1.2)	0.0788	18	1.1 (1.0–1.1)	NA	NA	NA
3. Inverse weight (100/weight, kg)	0.5233	43	^a	0.4111	43	^a	0.3443	47	^a	0.3701	34	^a
4. Past fracture, same type	2.8367	27	^a	2.1910	37	^a	1.3492	27	^a	0.6852	220	2.0 (1.8–2.2)
5. Past fracture, different type	0.4173	53	1.5 (1.4–1.7)	0.2932	38	1.3 (1.2–1.5)	NA	NA	NA	0.3432	49	1.4 (1.3–1.6)
6. Single fall	0.185 5	28	1.2 (1.1–1.4)	0.1841	64	1.2 (1.1–1.3)	0.2364	142	1.3 (1.2–1.4)	0.1760	56	1.2 (1.1–1.3)
Two or more falls	0.3580		1.4 (1.3–1.6)	0.4114		1.5 (1.4–1.7)	0.4748		1.6 (1.5–1.7)	0.3824		1.5 (1.3–1.6)
7. Maternal hip fracture	0.2729	16	1.3 (1.2–1.5)	0.1847	12	1.2 (1.1–1.3)	0.1955	22	1.2 (1.1–1.3)	0.1805	12	1.2 (1.1–1.3)
8. Parkinson's disease	0.6788	12	2.0 (1.4–2.9)	0.5204	9	1.7 (1.2–2.4)	0.3380	5	1.4 (1.0–1.9)	NA	NA	NA
9. Decreased moderate activity	0.1999	20	1.2 (1.1–1.3)	0.1687	23	1.2 (1.1–1.3)	0.1185	18	1.1 (1.1–1.2)	NA	NA	NA
10. Lost 10 lb in a year	0.2370	10	1.3 (1.1–1.5)	0.2076	12	1.2 (1.1–1.4)	0.1598	10	1.2 (1.1–1.3)	0.1637	7	1.2 (1.0–1.3)
11. Decreased usual activity	2.4357	44	^a	1.5764	30	^a	0.8217	13	^a	1.040	13	^a
12. Interaction of 1 and 4	–0.2607	13	^a	–0.1772	13	^a	–0.1014	8	^a	NA	NA	NA
13. Interaction of 1 and 11	–0.3030	38	^a	–0.2048	28	^a	–0.0960	9	^a	–0.1195	10	^a
14. Osteoarthritis	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.0921	5	1.1 (1.0–1.2)
15. Reduced general health	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.1351	33	1.1 (1.1–1.2)

Abbreviations: β -hat, model estimate; CI, confidence interval for HR; F5, any 5-year fracture of hip, pelvis, upper leg, clavicle, or spine; F7, any 5-year fracture of hip, pelvis, upper leg, clavicle, spine, UAS, or rib; F10, any 5-year fracture of any of the 10 bones in Table 2; Major, any 5-year fracture of hip, spine, UAS, or wrist (FRAX major osteoporotic fracture); HR, hazard ratio, which is $\exp(\beta\text{-hat})$, except for interactions; NA, not applicable; χ^2 , model χ -square, an indication of relative strength of a risk factor in a given model (each χ^2 has 1 degree of freedom, except for falls (2 degrees of freedom)).

^a See Figure 2 for clarification of F5 model's nonlinear terms; other models have nonlinear effects that are similar but less pronounced than in F5.

ability increases nearly 8-fold from 1.1% at age 55 y to 8.4% at age 85 y) than for those with prior F5 fracture (a less than 4-fold increase from 4.4% at age 55 y to 15% at age 85 y). A 55-year-old woman with a prior F5 fracture has a similar expected F5 fracture risk to a 75-year-old with no prior F5 fracture (4.4% and 4.3%). The association of reduced ability to perform usual activities such as work, study, and housework with F5 fracture is strongest for younger women (estimated risk increases from age 55 y to 85 y from 1.1% if no problems to 5% if unable to perform usual activities), becoming irrelevant somewhere between age 75 and 85 years (no increased risk with reduced performance). Similar age interaction effects appear in the other composite models but are less dramatic (model estimates, β -hats, are smaller).

All four composite models were improved by using inverse, instead of linear, weight (Table 3 and Figure 2). The most pronounced asymmetry appears in the F5 model, whose estimated 5-year cumulative fracture rates drop from 4.2% to 2.4% for 40- and 70-kg women, respectively, to 1.9% for a 100-kg woman. A similar but smaller asymmetry exists in the other composite models.

All four composite fracture models passed the goodness-of-fit test ($P > .05$), indicating observed and model-expected fractures are similar across the range of fracture risk. Harrell's c index is highest for F5 and F7 ($c = 0.75$

and $c = 0.71$), lowest for F10 and major fracture models ($c = 0.65$ and $c = 0.67$). Refitting the models using logistic instead of Cox regression yields c statistics (areas under receiver operator curve) nearly identical to Harrell's c indices. If wrist fracture is removed from the major fracture model, the number of fractures (hip, spine, or forearm) drops to 1557, whereas the c index increases to 0.72 (data not shown).

Results adjusting for bone medication use were similar to those reported above (data not shown), as were results using multiple imputation for missing data (data not shown).

Discussion

Existing composite fracture models, although clinically appealing, have not exhibited strong model discrimination. The FRAX-New Zealand risk tool reported c statistics of 0.62–0.64 for FRAX osteoporotic fracture and 0.64 for Garvan osteoporotic fracture (14); among nine population-based FRAX validation studies, all but three c statistics for other osteoporotic fractures without BMD were less than 0.60 and all but one less than 0.63 for other osteoporotic fractures with BMD (5); Study of Osteoporotic Fractures has reported c statistics from 0.63 to 0.70

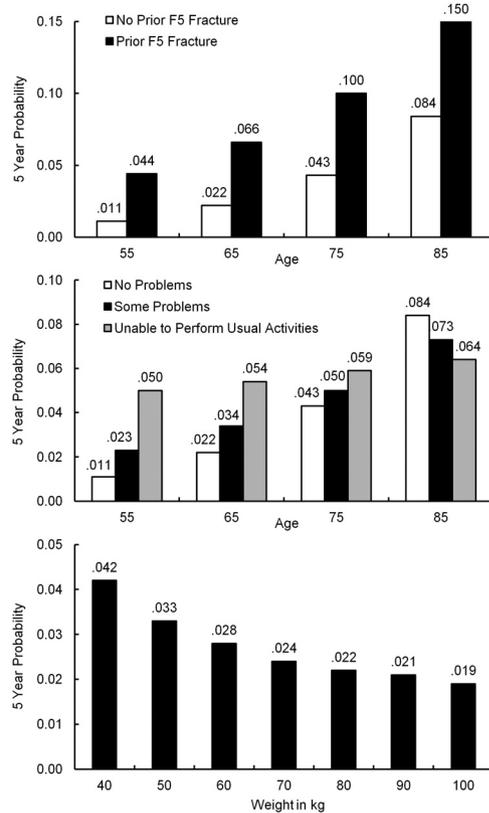


Figure 2. Estimated 5-year cumulative probability of F5 fracture (hip, pelvis, upper leg, spine, or clavicle fracture) for nonlinear model terms.

for FRAX osteoporotic fracture with and without BMD for all women and among obese and nonobese subgroups (4, 15). Such composite models may accumulate large numbers of fractures, but the risk profiles for the individual fracture sites differ enough that, when sites are combined, the models fail to discriminate well. In the GLOW data, the c index of 0.75 for the F5 model drops to 0.71 when UAS and rib are added and to 0.65 when lower leg, wrist, and ankle are added. The FRAX major osteoporotic fracture model's c index of 0.67 increases to 0.72 when wrist fractures are removed because women who fracture a wrist tend to be younger.

A tool with a c statistic or c index less than 0.70, in which the possible range is from 0.50 to 1.0, has limited model predictive ability. On the other hand, a model with impressive discrimination may not appear clinically useful or may have accumulated too few fractures to be useful.

The F5 composite fracture model features a new approach to combining fractures. It has an empirical, objective basis, and natural interpretation. No determination as to which fracture sites are osteoporotic or major is needed. Because the F5 model's component fractures are all strongly associated with advanced age, the model has better discrimination, as measured by its c index, than a composite model whose individual patient risk profiles are less compatible.

In clinical practice, however, the utility of a composite fracture model depends on the effectiveness of intervention in reducing the risk of the fractures included in the model. All of the approved pharmacological interventions have been shown to reduce vertebral fracture, and most also reduce hip fracture. However, pelvic, clavicle, and upper leg fractures are usually combined into a general nonvertebral fracture category, and data for the efficacy of treatment against these fractures have not been separately reported. Reduction in the risk of falling is likely to be important in decreasing the risk of hip, pelvis, upper leg, and clavicle fracture, although less so in the risk of vertebral fracture. The similarity in individual patient risk profile between fractures in the F5 model suggests that treatment should be similarly effective across the range of included fractures, although this remains to be formally tested.

Other possible fracture combinations may be posited based on similarity of patient risk profiles, but it is difficult to see a unifying thread with the strength of age. Most individual fractures have some unadjusted association with age, weight, falling, adverse health, reduced activity, and prior fracture, but ankle, wrist, and lower leg fractures are especially difficult to characterize, with the exception that lower leg and ankle fractures are similarly associated with higher weight (16, 17).

Limitations

Data are self-reported. Outcomes and risk factors are therefore, to some extent, misclassified. To that extent, model associations are underestimated. We did not have information on BMD. Other risk factors that GLOW did not collect may exist, but they may be idiosyncratic or difficult to collect in a survey.

We could not directly assess the impact of study deaths on fracture rate estimates because deaths were not uniformly reported.

We did not choose to consider the possible effect of bone medication because women at high fracture risk are those most likely to take medication. An F5 model controlling for the use of baseline bone medication showed little change from the reported F5 risk factor estimates (data not shown).

We also elected not to include glucocorticoids associated with bone loss in the modeling. Unlike risk factors inherent in a woman, medications can be started and stopped, thus changing risk. If the current use of glucocorticoids at baseline were added to the F5 model, discrimination would not change appreciably (c index increases from 0.753 to 0.754).

Data were missing for about 15% of model F5 observations. Results using imputation were similar to those

shown (data not shown), but we cannot be certain that the missing data had no influence on model estimates. It seems unlikely the risk factor associations would differ for women who failed to answer a question from those who answered, but it is possible.

Similarly, about 10% of women contributed no information after study baseline. Because women without complete follow-up tended to be older and in poorer health, our absolute fracture rates are likely to be underestimated.

Model discrimination (c index) is not impressive for any of the composite fracture models, although greater than 0.7 for F5 and F7 models. It may not be possible to form a composite outcome from different fractures and expect excellent discrimination because risk factor profiles vary to some extent by individual fracture type. Any model with more than one fracture site will be, to some extent, a compromise between individual site-specific models; F5 is a compromise between individual hip, pelvis, upper leg, clavicle, and spine models.

If some F5 model risk factors are unavailable, model discrimination will be reduced to some extent. A model containing age, prior fracture, weight, falls, and some measures of health, physical function, and vitality would be expected to perform nearly as well as the full F5 model (factors with relatively large χ^2 values contribute most to discrimination).

Finally, our results are from a single, although large and multinational, study. External validation from independent sources is desirable. Average fracture rates in different regions and even sites within a region may be lower or higher than those observed in GLOW, but estimates of risk factor effects (HRs) and relative model performance among the four described models are expected to be reasonably universal.

Strengths

The F5 model is simple and does not require BMD. Five-year fracture risk is clinically relevant compared with the longer duration of the 10-year FRAX assessment. The findings are multinational and practice based, thus more generalizable than prediction tools not so based. The model incorporates risk associated with prior falls, general health and activity, weight loss, and disease, factors that are not commonly considered in other risk tools.

Conclusions

Several possible individual fracture sites may be combined to form a fracture outcome. Rather than a priori define a composite fracture outcome and then create a best-fit model for this outcome, we present an alternate approach. After examining results for 10 individual sites, we found advanced age to be the single best possibility for

uniting several different fracture sites, and formed the F5 composite of hip, pelvis, upper leg, spine, or clavicle fracture. Results from the F5 model may be used to predict an individual woman's 5-year F5 fracture risk, if aged 55 years or older, with an expected mean 5-year probability of about 4%. Such a model may be particularly pertinent for fractures associated with involutional osteoporosis. It is hoped that, in addition to its possible clinical utility, the F5 model may stimulate curiosity and investigation into why different fractures have distinctive risk profiles.

Technical note on how to convert Table 2 results into estimates of an individual's 5-year cumulative fracture probability

To estimate a particular woman's 5-year cumulative composite fracture risk using Table 2 results, one may use the following formula: $1 - [\hat{S}_{o(5)}^{\exp(\mathbf{X}\hat{\beta})}](8)$.

$\hat{S}_{o(5)}$ is baseline survival at 5 years. $\mathbf{X}\hat{\beta}$ is the combination of a woman's observed covariate value (such as age), and the estimate associated with the observed covariate value (labeled β -hat in Table 2).

Baseline survivals (where all covariates have a value of zero) at 5 years are 0.999 990 37, 0.999 813 85, 0.996 531 35, and 0.999 467 29 for F5, F7, F10, and major fracture models, respectively.

For a woman aged 78 years, vitality index 25, weight 57 kg, prior F5 fracture, prior fracture of a different bone, two or more falls at baseline, maternal hip fracture, no Parkinson's disease, limited a lot in moderate activity, did not lose 10 lb unintentionally in the past year, and no problems performing usual activities, the F5 model's $\mathbf{X}\hat{\beta} = \{((78/10) \times 0.9939) + ((100 - 25)/20 \times 0.1159) + ((100/57) \times 0.5233) + (1 \times 2.8367) + (1 \times 0.4173) + (1 \times 0.3580) + (1 \times 0.2729) + (0 \times 0.6788) + (-1 \times 0.1999) + (0 \times 0.2370) + (1 \times 2.4357) + ((78/10) \times 1 \times -0.2607) + ((78/10) \times 1 \times -0.3030)\} = 10.829$.

Her expected risk of suffering a fracture of one or more of the five bones within 5 years of baseline is $1 - [0.99999037 \times \exp(10.829)] = 0.385$, much higher than the 4% average risk.

Dedication

We dedicate this work to Dr Steven Boonen, who was helpful and encouraging in our various fracture risk model efforts and approved an early version of this paper.

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