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Impact of changes in mortality on FRAX-derived fracture probabilities

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ABSTRACT

Background: Accurate hip fracture incidence and mortality rates are two essential requirements for FRAX calculators.
Purpose: To investigate the effects of change in mortality on FRAX-derived fracture estimates.
Methods: Lebanese FRAX calculator was updated in 2012 from version 3.00 utilizing WHO mortality data from year 1999, and hip fracture incidence rates from 2007, to version 3.05 utilizing mortality data from 2009, but with identical hip fracture data. FRAX-derived estimates from 679 patients were computed using both FRAX versions and compared. Numbers presented as median [25th–75th] percentiles.
Results: The 10-year FRAX-derived probability of major osteoporotic fracture and hip fracture increased substantially. Changes were most pronounced in high risk sub-groups. The relative increase in probability of major osteoporotic fracture in individuals with a baseline risk of 10–20% was 79% [19%–127%], and in individuals with a baseline risk >20% it was 125% ($N = 3$). The numbers for relative increase in hip fracture probability were 98% [33%–135%], and 129%, respectively. Similarly, individuals older than 70 years had a 125% [89%–150%] relative increase in probability of major osteoporotic fracture and a 122% [95%–145%] relative increase in hip fracture probability. Using the FRAX-based Lebanese guidelines, FRAX 3.05 led to an additional increase in treatment qualification of 3.8 patients per 100 patients, or a relative increase of 24%.
Conclusions: Updates in mortality values increased FRAX-derived estimates, most substantially in older patients, and those at high risk for fracture. The update results in altering individuals' treatment decisions and modifying country wide osteoporosis management. Our results are relevant to the development and update of FRAX models for countries worldwide, and more importantly those with increasing longevity and possible increase in fracture rates.

Introduction

As longevity continues to increase, fractures will contribute to a substantial and greater proportion of morbidity and mortality in our societies. Until recently, bone mineral density (BMD) was the single best test to assess fracture risk, but this single measure is limited by low sensitivity, specificity, variability between measurement tools and site, and its association with relative rather than absolute fracture risk estimates [1–3]. FRAX, a web-based fracture probability calculation tool introduced in 2008, allows the calculation of absolute fracture risk probabilities, based on risk factors, with or without BMD, and facilitates risk stratification and patient tailored therapy. It has since created a paradigm shift in care pathway models and has become the cornerstone for the development of national osteoporosis guidelines [4–6]. Today, there are over 58 FRAX calculators developed in 52 countries accessible online http://www.shef.ac.uk/FRAX/index.aspx?lang=En (accessed December 17, 2013).

The unique features that render the FRAX calculator country specific are the FRAX requirements of availability of country specific hip fracture incidence rates, major osteoporotic fracture incidence rates whenever available, and longevity data. These are all dynamically changing variables that are affected by changes in healthcare and socioeconomic factors [6,7]. Indeed, secular trends in hip fractures have been recently described, with a decline in the West, and a continued rise in the East, with the exception of Hong Kong and Taiwan [8–12]. Concomitantly, while global life expectancy at 60 years of age has only increased by one year from 18 to 19 years in Middle East countries between 2000 and 2011, http://apps.who.int/gho/data/view.main.690?lang, changes in certain countries have been more pronounced and exceeded 20% in certain instances [13].

The possible effects of such changes in epidemiologic data are best exemplified by the recent changes observed in the US population. Age-adjusted fracture incidence and mortality rate have both been on the decline in the US since 1995 [14–16], and revision of the US FRAX version to include an updated data source, the Health Cost and Utilization Project Nationwide Inpatient Sample, as well as a statistical discount in reported fracture rates to accommodate for multiple fractures in the same individuals culminated in lower fracture estimates. Indeed, median probability estimates were lowered by 19% and 24%, for ages 60 and 80 years respectively [17]. The exclusive effect of changes in life expectancy on FRAX derived fracture probabilities have not been

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elucidated. While maintaining the same hip fracture rates, Lebanon's FRAX calculator was updated in early 2012 from the original model that used WHO life expectancy Tables from 1999, to updated WHO 2009 data reflecting improved life expectancy (Table 1).

This study therefore aims at investigating the effects of increasing longevity on FRAX fracture predictions and treatment algorithms, using actual patient information.

Methods

BMD and T-scores

BMD was measured using a Hologic 4500A densitometer, and the NHANES III database was used to derive femoral T-scores. At our institution, same day duplicate scans are usually performed after obtaining permission on different patients, one for each skeletal site, including the femoral neck. The mean ± SD is then calculated monthly. Precision has been stable over the years and is below the International Society of Clinical Densitometry's recommended quality assurance cut-offs, averaging 1.4 ± 0.27% at the femoral neck during the scan acquisition period.

Lebanon FRAX Model

Lebanon FRAX Model was originally launched in 2009, as FRAX version 3.0, based on national hip fracture incidence rates derived from a hip fracture registry maintained by the Lebanese Ministry of Health [18], and WHO life expectancy tables that were available at the time for year 1999. It was since revised and updated to FRAX version 3.05, using WHO life expectancy tables for the country for year 2009. We calculated 1-year survival probability from 1-year mortality data for years 1999 and 2009, as used in FRAX by FRAX Sheffield team, and provided by Dr. Kanis (Table 1).

Study group

We reviewed 805 de-identified bone density hip scans of patients presenting to the bone densitometry unit at the American University of Beirut between February and September 2012; and an additional 202 hip scans of subjects enrolled in a vitamin D supplementation trial in 2011–2012 (http://clinicaltrials.gov/ct2/show/NCT01315366). Scans of non-Lebanese patients, those less than 60 years in age, or those with missing information on risk factors entered into FRAX data were also excluded. Therefore, a total of 679 out of 1007 screened scans were included in the study. Appendix 1 shows patient demographics by source of entry into the study. Risk was estimated for each patient using femoral neck BMD and FRAX 3.0 and FRAX 3.05 software versions.

We classified patients into 3 risk subgroups based on baseline FRAX probability of major osteoporotic fracture, where a probability of fracture <10% was considered to be mild risk, a probability of fracture between 10% and 20% was moderate risk, while a probability ≥20% was considered high risk.

Table 1
1-year survival data and crude hip fracture rates used in original and revised FRAX models.

		Survival 2009[a]	Survival 1999[a]	Absolute increase in survival probability[b]	Relative increase in survival probability (%) [c]	Hip fracture incidence rates[d]
Male	60–64	97.99	97.00	0.99	1	38.7
	65–69	96.84	94.04	2.80	3	78.7
	70–74	95.01	88.18	6.83	8	103.8
	75–79	92.12	79.17	12.95	16	250.2
	80–84	87.39	69.32	18.07	26	838.1[e]
	85–89	80.60	54.8	25.80	47	838.1[e]
Female	60–64	99	97.29	1.71	2	40.4
	65–69	98.36	94.07	4.29	5	113.8
	70–74	97.13	86.99	10.14	12	284.2
	75–79	94.91	76.35	18.56	24	530.8
	80–84	90.79	67.52	23.27	34	1446.7[e]
	85–89	84.33	55.41	28.92	52	1446.7[e]

*Data was provided by Dr. John Kanis (2013).
[a]Probability of 1-year survival derived from data provided by Dr. John Kanis (as used when FRAX Lebanon calculator was revised).
[b]Absolute increase in 1-year survival probability between years 1999 (FRAX 3.00) and 2009 (FRAX 3.05). Calculated as survival probability 2009 − survival probability 1999.
[c]Relative increase in 1-year survival probability between years 1999 (FRAX 3.00) and 2009 (FRAX 3.05). Calculated as (survival probability 2009 − survival probability 1999)/survival probability 1999, rounded to include no decimals
[d]Fracture incidence rates per age group in the entire Lebanese population, expressed as hip fractures/10,0000/year.
[e]Fracture incidence rates for all individuals above 80 years of age.

Treatment allocation by guidelines

Treatment allocation using FRAX was determined for each patient twice by using the most recent Lebanese guidelines in conjunction with FRAX probability estimates obtained from each FRAX version, as detailed below. The Lebanese guidelines recommend the administration of pharmacologic therapy to patients who had a previous fragility fracture of the spine, hip, or two or more other fragility fractures. In the absence of fractures, treatment is recommended in patients with FRAX derived 10 year risk of major osteoporotic fracture ≥10% for patients with age up to 70 years, and according to a moving 10 year FRAX derived moving threshold for major osteoporotic fracture in patients older than 70 years (see Appendix 2). The moving threshold was determined according to the same criteria used in the National Osteoporosis Guidelines Group in the UK, that is the FRAX derived probability of a female patient with the same age, a history of fragility fracture, and a nation specific body mass index (BMI) (30 kg/m^2 in the elderly Lebanese)[19].

Statistical analyses

Analysis of the data was carried out using SPSS for Windows version 20.0 (IBM Corp. Armonk, NY) [20]. For all statistical analysis, we set a-priori a p-value ≤ 0.05 as significant. Because of an obtained skewed distribution of the data, all values are presented as median [25th–75th] percentiles. Independent t-test and ANOVA were used to compare mean values between continuous variables of normally distributed data, while comparisons of non-normally distributed data was done through Wilcoxon signed-rank test for paired distributions, and Mann–Whitney U test for unpaired distributions. Chi-squared analysis was used to assess the differences in the proportions of subjects between two groups, including differences between the proportions of subjects to be treated between the two FRAX versions. Absolute changes in fracture probabilities were calculated as the differences in FRAX derived probabilities FRAX 3.05 − FRAX 3.00.

Results

Patient characteristics

Six hundred seventy nine patients were included in the study. Their median age was 69 [65–74] years, and BMI 28.1 [25.1–31.6] kg/m^2. The median femoral neck BMD T-score was −1.85 [−2.4– −1.2], and less than one in five of the study subjects had a FRAX risk factor other than female gender (personal history of fracture, parent fracture, smoking history, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and daily alcohol use) (Table 2). The average number of FRAX risk factors, including female gender, was therefore 1.47 ± 0.9 risk factors per patient, while the median was 1 [1,2] risk factor, thus representing a low risk group overall. Patient characteristics by sub-study group are shown in Appendix 1.

Table 2
Patient demographics, FRAX defined risk factors[a], and femoral neck bone mineral density T-scores.

	Overall (*N*)	%	Males (*N*)	%	Females (*N*)	%	*P*-value[b]/[c]
Total *N*	679	100	135	20.0	544	80	–
Age (years)	69 [65–74]		72 [67–76]		68 [64–73]		<0.01
BMI[d] (kg/m^2)	28 [25–32]		28 [26–31]		28 [25–32]		0.50
Fragility fracture	99	14.5	14	10.4	85	15.6	0.12
Parental hip fracture	85	12.8	16	11.9	69	12.7	0.91
Smoker	146	21.6	29	21.5	117	21.5	0.93
Glucocorticoid intake	28	4.1	9	6.7	19	3.5	0.10
Rheumatoid arthritis	7	1.0	0 (0.0)	0.0	7	1.3	0.18
Secondary osteoporosis Risk	87	12.8	0 (0.0)	0.0	87	16.0	<0.01
Daily alcohol	0	0.0	0 (0.0)	0.0	0	0.0	–
Femoral neck T-score[e]	−1.9 [−2.4– −1.2]		−1.5 [−2.1– −0.9]		−1.9 [−2.4– −1.3]		<0.01

*Continuous data presented as median [25%–75%].
[a]All risk factors are defined as in FRAX model (http://www.shef.ac.uk/FRAX/tool.jsp).
[b]*P*-value for Mann–Whitney U test.
[c]*P*-value for chi-square test.
[d]Body mass index.
[e]Femoral neck T-scores calculated in reference to NHANES III young female reference data.

Fracture probabilities with FRAX 3.00 and FRAX 3.05

Femoral neck BMD T-score (data not shown) and baseline probabilities of fracture displayed a skewed distribution to the right (Fig. 1). The majority, that is 75% of subjects, had a ten year probability of any osteoporotic fracture less than 5.3% and a probability of hip fracture less than 1.9% when calculated using FRAX 3.00. After update of FRAX to FRAX 3.05, there was a rightward shift in values due to a greater proportion of subjects at high risk of fracture but the majority, that is 75%, still had a probability of any osteoporotic fracture less than 8.9% and a probability of hip fracture less than 3.4% (Fig. 1). Indeed, only 3 female and no male subjects were in the high risk sub-group (see Methods section), and there were 30 women but only 1 man in the moderate risk sub-group.

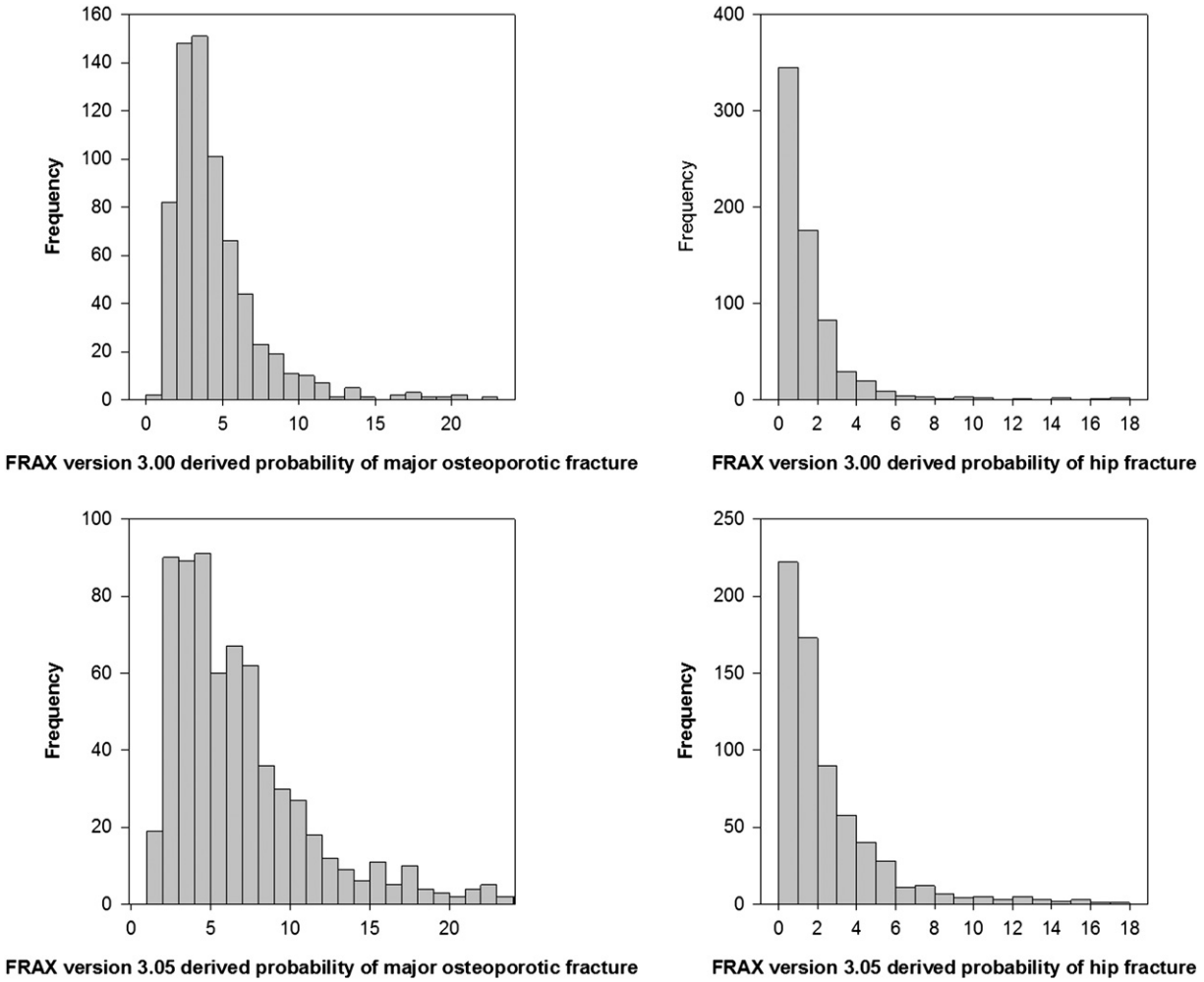

Fig. 1. Number of subjects with FRAX derived probabilities of fracture using FRAX version 3.00 (a and b) and FRAX version 3.05 (c and d). Panels c and d display higher fracture probabilities in the updated model, with redistribution to the right as compared to the original model panels a and b.

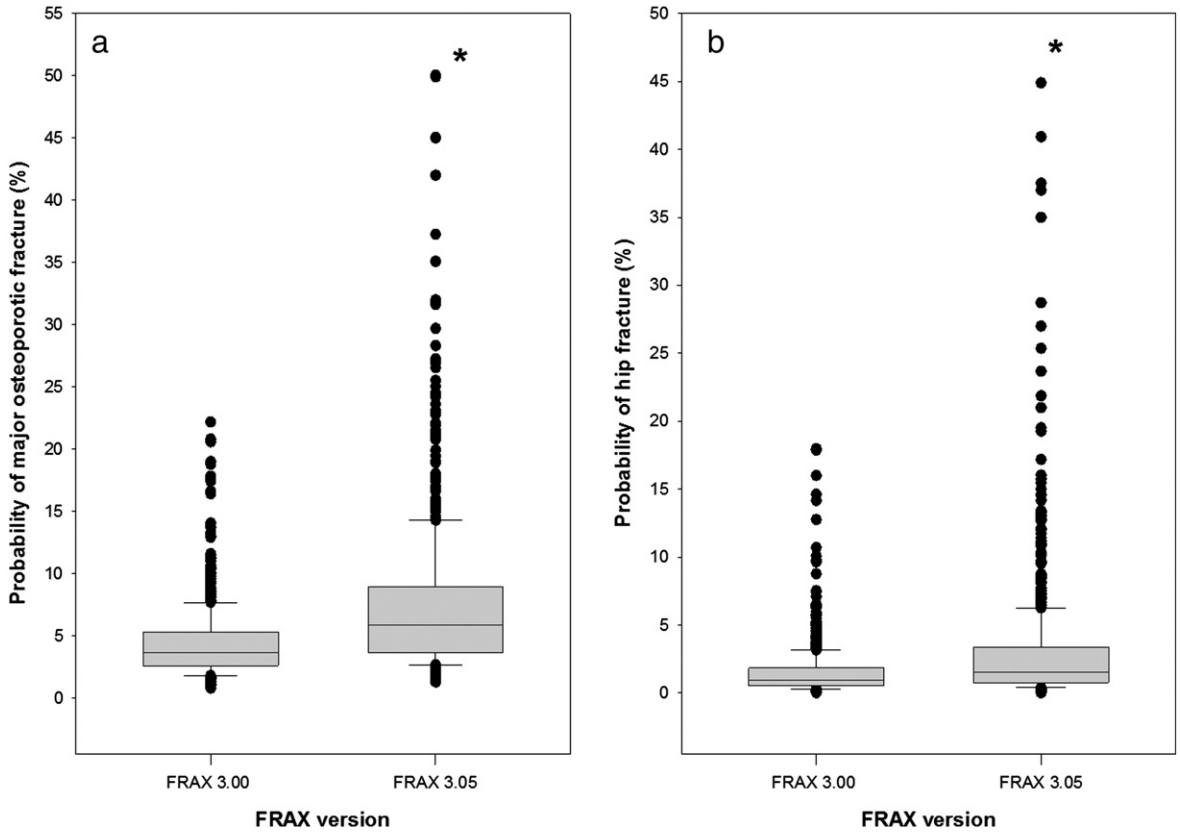

Fig. 2. FRAX derived probability of major osteoporotic fracture (a) and hip fracture (b) by FRAX version (3.00 and 3.05)[a]. Plots represent the median, 10th, 25th, 75th, and 90th percentiles as vertical boxes with error bars, derived with both FRAX versions. The box plots depicted for FRAX 3.05 demonstrate the higher probability estimates than those derived with FRAX 3.00, for all variables of interest. *Significantly higher in FRAX 3.05 compared to 3.00.

The median values in the probability of major osteoporotic fracture increased from 3.7% [2.6–5.3] to 5.9% [3.7–8.9], and in hip fracture increased from 1.0% [0.5–1.9] to 1.5% [0.8–3.4] (Fig. 2). Median absolute increase in the probability of major osteoporotic fracture was 1.8 [0.5–4.0], and the median increase in the probability of hip fracture was 0.6 [0.1–1.5]. Median relative increase was 50% [15%–117%] for major

Table 3
Probability of major osteoporotic fracture as determined using FRAX version 3.00 or FRAX version 3.05 in the overall group and broken down in 2A by risk strata using FRAX version 3.00 and in 2B by age.

			N	FRAX 3.00 10 year probability of major osteoporotic fracture[a] (%)	FRAX 3.05 10 year probability of major osteoporotic fracture[b] (%)	*p*-value[c]	Median absolute change in 10 year probability of major osteoporotic fracture[d] (%)	Median relative change in 10 year probability of major osteoporotic fracture [e]
Overall		Overall	679	3.7 [2.6–5.3]	5.9 [3.7–8.9]	<0.01	1.8 [0.5–4.0]	0.5 [0.2–1.2]
		Males	135	2.0 [1.6–3.3]	4.0 [2.8–6.1]	<0.01	1.9 [0.7–3.0]	0.8 [0.4–1.6]
		Females	544	4.0 [3.0–5.8]	6.3 [4.0–9.7]	<0.01	1.8 [0.5–4.3]	0.4 [0.1–1.0]
A: Risk group[f]	Mild (*N*)	Overall	645	3.5 [2.6–5.0]	5.3 [3.6–8.3]	<0.01	1.7 [0.5–3.7]	0.5 [0.1–1.1]
		Males	134	2.0 [1.6–3.1]	4.0 [2.8–6.1]	<0.01	1.9 [0.7–2.9]	0.8 [0.4–1.6]
		Females	511	3.9 [2.9–5.3]	6.1 [4.0–8.9]	<0.01	1.7 [0.4–4.0]	0.4 [0.1–1.0]
	Moderate (*N*)	Overall	31	11.5 [10.5–14.1]	21.9 [15.7–29.7]	<0.01	10.3 [3.1–16.0]	0.8 [0.2–1.3]
		Males	1	11.6	22.8	–	11.2	1.0
		Females	30	11.4 [10.5–14.1]	21.7 [15.7–29.7]	<0.01	9.5 [3.1–16.1]	0.7 [0.2–1.3]
	High (*N*)	Overall	3	21.0	49.9	0.13	27.7	1.3
		Males	0	–	–	–	–	–
		Females	3	21.0	49.9	0.13	27.7	1.3
B: Age	Less than 70 years	Overall	381	3.6 [2.6–5.1]	4.4 [3.0–6.5]	<0.01	0.6 [0.2–1.5]	0.2 [0.1–0.4]
		Males	56	2.1 [1.6–3.3]	2.8 [2.2–4.5]	<0.01	0.6 [0.5–1.1]	0.3 [0.2–0.5]
		Females	325	3.8 [2.8–5.3]	4.7 [3.2–6.8]	<0.01	0.6 [0.2–1.6]	0.2 [0.1–0.4]
	Above 70 years	Overall	298	3.7 [2.6–5.9]	8.1 [5.2–12.2]	<0.01	4.3 [2.7–6.8]	1.3 [0.9–1.5]
		Males	79	1.9 [1.5–3.1]	4.7 [3.6–7.4]	<0.01	2.7 [2.0–4.1]	1.5 [1.1–1.7]
		Females	219	4.3 [3.3–6.8]	9.7 [6.7–14.4]	<0.01	4.9 [3.3–7.7]	1.2 [0.9–1.4]

*Continuous data presented as median [25%–75%].
[a]FRAX probability of fracture using the original Lebanese FRAX calculator version 3.00 that utilizes mortality data from 1999.
[b]FRAX probability of using the updated Lebanese FRAX calculator version 3.05 that utilizes mortality data from 2009.
[c]*P*-value for Mann–Whitney U test
[d]Absolute change in probability of having a fracture after updating the Lebanese FRAX calculator from version 3.00 to version 3.05: Change in FRAX = FRAX 3.05 Probability − FRAX 3.00 Probability.
[e]Relative change in probability of fracture calculated as (Probability of fracture in FRAX 3.05 − Probability of fracture in FRAX 3.00)/Probability of fracture in FRAX 3.00, numbers expressed as fractions rounded to the closest decimal.
[f]Risk groups defined by FRAX 3.00 probability of any osteoporotic fracture: Mild risk: probability <10%; Moderate risk: 10–20%; High risk group: >20%.

osteoporotic fracture and 62% [20%–120%] for hip fracture (Tables 3, 4). Some subgroups registered higher relative increments as detailed below.

Major predictors of change in FRAX derived estimates

There was a significant correlation between age and change in fracture probability (Pearson correlation = 0.63 for major osteoporotic fracture, and 0.48 for hip fracture with p-value < 0.01 for both). Subjects over 70 had a significantly greater change in the probability of major osteoporotic fracture than did their younger counterparts (Table 3). The median probability of major osteoporotic fracture increased by just 0.8 from 3.6 [2.6–5.1] to 4.4 [3.0–6.5] in those younger than age 70; however, it increased by 4.4 from 3.7 [2.6–5.9] to 8.1 [5.2–12.2] in those older than age 70. The median relative increase in the probability of major osteoporotic fracture was just 18 [7–38]% in those younger than 70 years and 125 [90–150]% in those older than 70 years of age (Table 3). The increase in hip fracture probability also had a 25 [10–48]% relative increase in those younger than 70 compared to a 122 [95–145]% relative increase in patients older than 70 years of age (Table 4).

There was also a significant correlation between change in fracture probability and baseline fracture probability (Pearson correlation = 0.67 for major osteoporotic fracture and 0.91 for hip fracture with p-value < 0.01 for both). This correlation remained significant even after accounting for the effects of age, in a multi-linear regression analysis. Patients belonging to the moderate risk group (FRAX 3.00 probability of major osteoporotic fracture = 10–20%) had a more than doubling in the median estimated probability of major osteoporotic fracture from 11.5 [10.5–14.1] to 21.9 [15.7–29.7], while patients in the high risk group (FRAX 3.00 probability of major osteoporotic fracture >20%) also showed a prominent increase, all be-it limited by the small sample size (Table 3). Similarly, the median probability of hip fracture also almost doubled, increasing from 5.7 [4.2–9.8] to 11.4 [5.2–19.5] in the moderate risk group and showing prominent increases in the 3 patients who qualified as high risk (Table 4). The median relative change in the ten-year probability of major osteoporotic fracture and of hip fracture also tended to increase with increasing baseline risk of fracture. These were again most substantial in the high and moderate risk groups (Appendix Fig. 3), and lowest in the low risk sub-group (Tables 3 and 4). Indeed, the moderate risk had a 79 [19–127] % increase (Appendix 3), whereas the mild risk group only a 48 [14–113] % increase in the probability of major osteoporotic fracture (Table 4). Similarly, the median relative increase in 10 year probability of hip fracture was 98 [33–135]% for the moderate risk group, and 59 [19–116]% for the mild risk groups respectively (Table 3).

We also note that females, individuals with a personal fracture, and individuals with a parental history of fracture all also had a significantly greater change in probability of hip and osteoporotic fracture (both for mean and median changes) than did their male counterparts, and those with no history of fracture (data not shown).

Changes in treatment allocation

Using the Lebanese guidelines as detailed in the Methods section, 105 individuals qualified for treatment in FRAX 3.00, and 131 qualified for treatment in FRAX 3.05 p-value (0.06). This translates to a 24% relative increase equivalent to a 3.8% absolute increase in the number of patients fulfilling national guidelines for osteoporosis treatment.

Select case demonstrations

Patient 146

76 year old female with BMI = 21 kg/m^2, a parental history of fracture, and a femoral neck BMD T-score = −4.02. 10-year survival increased from 2.6% in FRAX 3.00 to 42.2% in FRAX version 3.05. FRAX 3.00 gave a 21% 10 year probability of major osteoporotic fracture prediction, as well as an 18% probability of hip fracture. Estimates using FRAX version 3.05 were 50% and 45% respectively, therefore more than doubling the estimated risk of fracture derived from older version.

Table 4
Probability of hip fracture as determined using FRAX version 3.00 or FRAX version 3.05 in the overall group and broken down in 2A by risk strata using FRAX version 3.00 and in 2B by age.

			N	FRAX 3.00 10 year probability of hip fracture[a] (%)	FRAX 3.05 10 year probability of hip fracture[b] (%)	p-value[c]	Median absolute change in 10 year probability of hip fracture[d] (%)	Median relative change in 10 year probability of hip fracture[e]
Overall		Overall	679	1.0 [0.5–1.9]	1.5 [0.8–3.4]	<0.01	0.6 [0.1–1.5]	0.6 [0.2–1.2]
		Males	135	0.7 [0.5–1.4]	1.4 [0.8–2.8]	<0.01	0.7 [0.3–1.3]	1.0 [0.5–1.5]
		Females	544	1.1 [0.6–2.0]	1.6 [0.8–3.5]	<0.01	0.5 [0.1–1.5]	0.5 [0.2–1.1]
A: Risk group[f]	Mild (*N*)	Overall	645	0.9 [0.5–1.6]	1.5 [0.7–3.0]	<0.01	0.5 [0.1–1.3]	0.6 [0.2–1.2]
		Males	134	0.7 [0.5–1.3]	1.4 [0.8–2.8]	<0.01	0.7 [0.3–1.3]	1.0 [0.5–1.5]
		Females	511	1.0 [0.5–1.7]	1.5 [0.7–3.0]	<0.01	0.4 [0.1–1.3]	0.5 [0.1–1.0]
	Moderate (*N*)	Overall	31	5.7 [4.2–9.8]	11.4 [5.2–19.5]		6.4 [1.4–10.5]	1.0 [0.3–1.4]
		Males	1	9.7	19.5	–	9.9	1.0
		Females	30	5.3 [4.2–9.8]	11.3 [5.2–19.3]		5.6 [1.4–10.5]	1.0 [0.3–1.4]
	High (*N*)	Overall	3	17.9	40.9	0.15	23.0	1.3
		Males	0	–	–	–	–	–
		Females	3	17.9	40.9	0.15	23.0	1.3
B: Age (years)	Less than 70 years	Overall	381	0.8 [0.4–1.4]	1.0 [0.5–2.0]	<0.01	0.2 [0.1–0.5]	0.3 [0.1–0.5]
		Males	56	0.6 [0.3–0.9]	0.9 [0.5–1.2]	<0.01	0.2 [0.1–0.5]	0.4 [0.2–0.7]
		Females	325	0.9 [0.4–1.5]	1.1 [0.5–2.1]	<0.01	0.2 [0.1–0.5]	0.2 [0.1–0.4]
	Above 70 years	Overall	298	1.3 [0.7–2.3]	2.8 [1.5–5.2]	<0.01	1.5 [0.8–3.0]	1.2 [1.0–1.5]
		Males	79	0.8 [0.5–1.6]	2.0 [1.2–4.0]	<0.01	1.1 [0.7–2.1]	1.4 [1.0–1.7]
		Females	219	1.5 [0.8–2.7]	3.2 [1.6–5.9]	<0.01	1.6 [0.8–3.5]	1.2 [0.9–1.4]

*Continuous data presented as median [25%–75%].
[a]FRAX probability of fracture using the original Lebanese FRAX calculator version 3.00 that utilizes mortality data from 1999.
[b]FRAX probability of using the updated Lebanese FRAX calculator version 3.05 that utilizes mortality data from 2009.
[c] P-value for Mann–Whitney U test.
[d]Absolute change in probability of having a fracture after updating the Lebanese FRAX calculator from version 3.00 to version 3.05: Change in FRAX = FRAX 3.05 Probability − FRAX 3.00 Probability.
[e]Relative change in probability of fracture calculated as (Probability of fracture in FRAX 3.05 − Probability of fracture in FRAX 3.00)/Probability of fracture in FRAX 3.00. Numbers expressed as fractions rounded to closest decimals.
[f]Risk groups defined by FRAX 3.00 probability of any osteoporotic fracture: Mild risk: probability <10%; Moderate risk: 10–20%; High risk group: >20%.

Patient 31

79 year old female with BMI = 32 kg/m^2, glucocorticoid use, secondary osteoporosis, and femoral neck BMD T-score = −2.32. Modeled 10-year survival probability increased from 1.0% in FRAX 3.00 to 29.6% in FRAX 3.05. FRAX version 3.00 predicted a 6% and 3% probability of major osteoporotic and hip fracture, respectively. FRAX version 3.05 leads to an increase in major osteoporotic and hip fracture risk to 18% and 8% respectively. The patient, not needing treatment on FRAX 3.00 probability estimates, was thus reclassified after the update as qualifying for treatment in accordance with the Lebanese guidelines highlighted above.

Discussion

Updates of FRAX

Our analysis showed how a relative increase in 1-year survival ranging between 1 and 52% may lead to a significant 68% and 71% relative increase in predicted probability of major osteoporotic fracture or hip fracture respectively, in the overall study group, and a 120–130% increase in a susceptible population of individuals older than 70 years. In a population with an overall low baseline fracture risk, there was an absolute increase in the number of subjects assigned to receive treatment of 3.8 out of 100 subjects, that is a relative increase of 24%. Indeed, our case-demonstration highlighted an individual whose calculated probability of fracture more than doubled, and another for whom there was a change in treatment allocation from no treatment using FRAX 3.00 to treatment using FRAX 3.05. The changes would have been even more substantial in a higher risk population. Despite this, the observed changes upon updating the Lebanese model are more pronounced than those seen in any other model updates we are aware of. Updating epidemiologic data in the Italian and American models culminated in a maximum 20% change in the Italian model, and 19 and 24% decrease in major osteoporotic fracture probabilities for ages 60 and 80 in the American model [14,21]. The lesser changes observed in other western model updates may be partly explained by the fact that these FRAX revisions had competing updates of increased longevity and decreased fracture rates, whereas the Lebanese model is unique in having only updated the former, while fracture incidence rates remained essentially unchanged from 2007 till present date (MOH registry data, Ballane G, El-Hajj Fuleihan, submitted for publication).

It is notable in our study that the large changes in probability of fracture translated into smaller changes in treatment allocation by comparison. This is because of the non-uniformity of the change in fracture probability observed with mortality update. The change in fracture probability was most pronounced in older individuals and in those at high baseline risk for osteoporotic fracture who therefore had greater likelihood of having already been assigned to receive treatment using FRAX 3.00. Conversely, individuals with low risk of fracture, those likely not to have been recommended treatment, had only smaller changes in FRAX. Secondly, fracture probability distribution was skewed towards the lower risk categories, meaning that most subjects' probabilities were at a distance from treatment thresholds, so that even large relative changes in probability of fracture were not enough to result in a change in treatment allocation. Still the update significantly affected the case finding strategy allowed in the FRAX model. Indeed, there was a 24% relative increase in treatment allocation that is likely to have a significant effect on individual patient care and public health level intervention and thus spending in the country.

Mortality and fracture prediction

A big advantage of using FRAX over other calculators of fracture risk is that it accounts for competing mortality. Accounting for competing mortality has already been shown to decrease estimates of fracture risk by 17–35% in high mortality groups such as individuals older than 80, individuals with high FRAX probability, diabetics, and men [22]. Indeed, patients living today are likely to have a lower risk of mortality at old age 10 years from now, than their current older counterparts do. Incorporating even conservative projections of mortality improvement during the years of risk estimation was shown to significantly increase the estimated fracture rates [23]. To our knowledge, this is the first study to evaluate changes in FRAX model predictions in response to changes exclusively limited to the mortality data used by that model. The changes observed were more pronounced than those seen in the study of Leslie et al. that utilized real patient fracture incidence and mortality data, for construction of a modified Kaplan–Meier method to estimate 10 year fracture probability [22]. The reasons for this difference may be explained only through understanding the mechanisms by which mortality is accounted for in FRAX, which is not clear yet.

Qualitatively, decreasing mortality may be expected to increase fracture incidence via two potential pathways, that is simultaneously increasing the duration of risk exposure as well as the average risk the patient is exposed to. The latter results from the fact that age is itself a risk factor for fracture, and it also compounds the effects of other risk factors like smoking, so that the risk for fracture is progressively increasing as patients survive into older ages [1,24]. Older individuals have the greatest increase in modeled survival due to the greater decrease in absolute mortality (Table 1) and will therefore incur major changes in fracture probability after the update. Concomitantly, patients with a higher baseline risk of fracture will also have a greater risk of fracture during the extra survived years modeled into the FRAX algorithm, again contributing towards greater changes in FRAX. The fact that individuals at high risk of fracture and those older than 70 were most impacted after the update in our study is consistent with these expectations.

Significance for other countries

The low risk of fracture in the Lebanese population, 163/100 000 [18], is likely to underestimate the changes that may be observed in countries with a greater risk of fracture. Our data therefore stresses the importance of using up-to-date country specific mortality data when developing or updating a FRAX calculator [7]. Eastern populations with concomitantly rising fracture incidences are expected to have two compounding effects and may thus experience the most pronounced increments in FRAX derived estimates [9]. Our study findings further underscore the ISCD-IOF recommendations that countries without a FRAX calculator must also take special care in choosing a calculator from a surrogate country with very similar mortality rates and life expectancy to its own [6]. Clinicians may also be advised to factor in patient-specific life expectancy during treatment decision making for individuals at higher or lower risk of death than the general population as these factors may profoundly affect fracture probability estimates derived using population based mortality that FRAX uses.

Limitations of our study include the fact that it used FRAX calculated probabilities and not actual fracture incidence data, the inclusion of a population from a country with low fracture incidence, and a study group with a relatively young age, and low risk profile, having had only 3 individuals in the high risk category. Because it is not clear how the age function is entered into the FRAX calculator, our ability to adjust for age during correlations and regressions was limited. Our study remains, however, the only study to our knowledge, investigating changes in FRAX probability estimates in response to an exclusive increase in life expectancy while fracture incidence rates remained unchanged. As opposed to theoretical or modeled studies, our analysis was carried out on real cases who are strongly representative of everyday clinic patients.

FRAX predicted fracture risks are very sensitive to changes in mortality and life expectancy, especially for older individuals at high risk of fracture. This Lebanese case study therefore illustrates not only the need to use accurate and updated mortality data when building or revising FRAX, but also the underestimation of fracture risk if one does

not do so. This may result in under-treatment and thus accentuate the care gap in osteoporosis management.

Conflict of interest

No disclosures.

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Appendix A

Appendix 1
Patient demographics, FRAX risk factors, and femoral neck bone mineral density T-scores detailed by sub-study group.

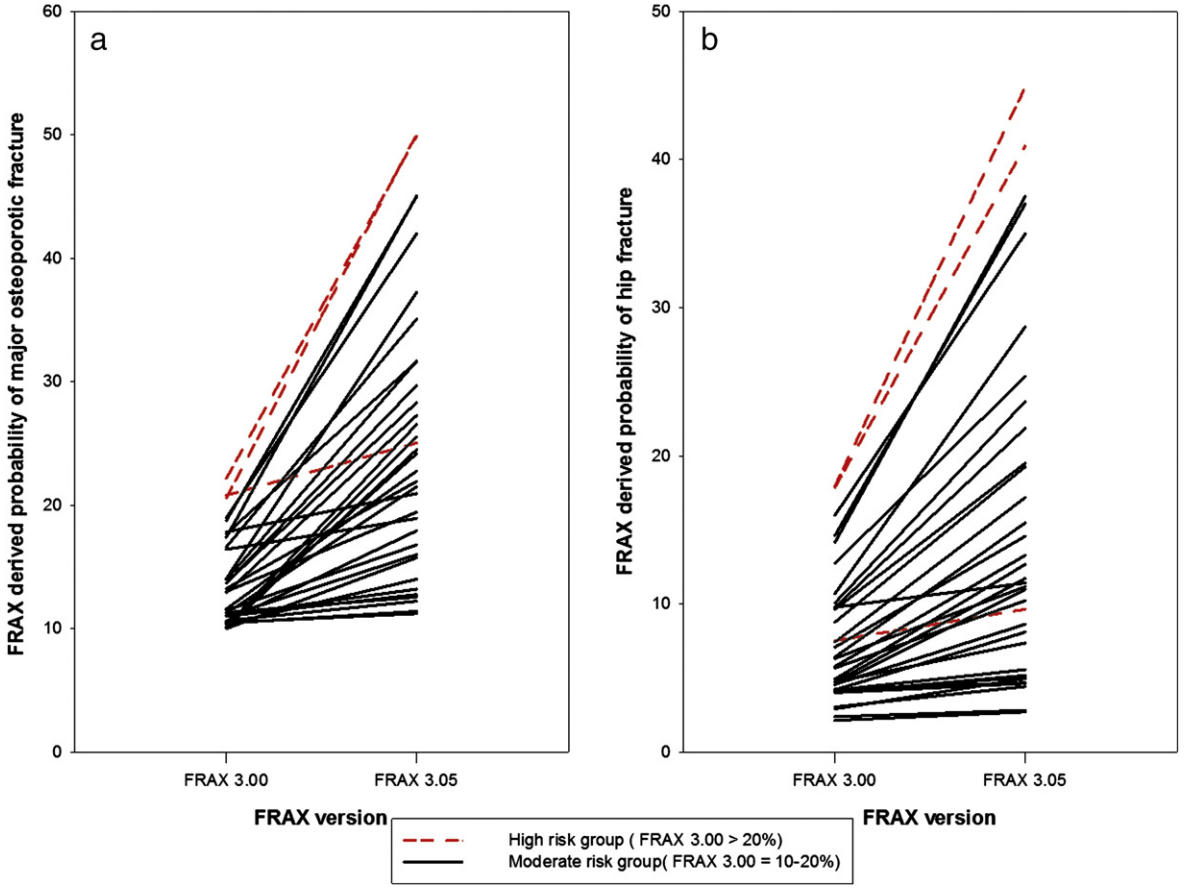
		Overall	Males	Females	P-value[d/e]
Clinical sub-study	Total *N* (%)	479 (100)	55 (11.5)	424 (88.5)	–
	Age (years)	68 [63–74]	73 [67–77]	68.4 ± 6.4	0.00
	Fragility fracture[a] *N* (%)	98 (20.5)	13 (23.6)	85 (20.0)	0.54
	Parent fracture[a] *N* (%)	69 (14.4)	10 (18.2)	59 (13.9)	0.40
	Smoker[a] *N* (%)	96 (20.0)	9 (16.4)	87 (20.5)	0.47
	Glucocorticoid intake[a] *N* (%)	28 (5.8)	9 (16.4)	19 (4.5)	0.00
	Rheumatoid arthritis[a] *N* (%)	7 (1.5)	0 (0.0)	7 (1.7)	0.34
	Secondary osteoporosis[a] *N* (%)	70 (14.6)	0 (0.0)	70 (16.5)	0.00
	Daily alcohol[a] *N* (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
	Femoral neck T-score[b]	−1.9 [−2.4– −1.3]	−1.8 [−1.2–2.2]	−1.9 [−2.4–1.3]	0.12
	BMI[c](kg/m^2)	27.6 [24.5–31.4]	27.8 [25.3–30.9]	27.6 [24.4–31.4]	0.76
Vitamin-D sub-study	Total *N*	200 (100)	80 (40.0)	120 (60.0)	–
	Age (years)	70 [68–74]	71.7 ± 5.0[d]	71.1 ± 4.5[d]	0.39
	Fragility fracture[a] *N* (%)	1 (0.5)	1 (1.2)	0 (0.0)	0.22
	Parent fracture[a] *N* (%)	16 (9.0)	6 (6.5)	10 (8.3)	0.91
	Smoker[a] *N* (%)	50 (25.0)	20 (24.7)	30 (25.0)	0.88
	Glucocorticoid intake[a] *N* (%)	0 (0.0)	0.0 (0.0)	0 (0.0)	–
	Rheumatoid arthritis[a] *N* (%)	0 (0.0)	0.0 (0.0)	0 (0.0)	–
	Secondary osteoporosis[a] *N* (%)	17 (8.4)	0.0 (0.0)	17 (14.0)	0.00
	Daily alcohol[a] *N* (%)	0 (0.0)	0.0 (0.0)	0 (0.0)	–
	Femoral neck T-score[b]	−1.6 [−1.1–2.3]	−1.3 [−1.8–0.9]	−1.9 [−1.3–2.4]	0.00
	BMI[c] (kg/m^2)	29.1 [26.5– 32.1]	27.6 [25.6–30.4]	29.8 [27.7–33.1]	0.00

*Continuous data presented as median [25%–75%].
[a]All risk factors are defined as in FRAX model (http://www.shef.ac.uk/FRAX/tool.jsp).
[b]T-scores calculated using NHANES female database.
[c]Body mass index.
[d]*P*-value for Mann–Whitney U test.
[e]*P*-value for chi-square test.

Appendix 2
Treatment threshold categories adapted from FRAX based Lebanese treatment guidelines[a].

Age range (years)	FRAX major osteoporotic fracture probability intervention threshold used (%)
60–70	10
70–72	10
72–75	12
75–77	15
77–80	17
80–82	21
82–85	23
85–87	27
87–90	28
>90	30

[a] Presented at the 4th Annual meeting of the Lebanese Society of Osteoporosis and Metabolic Bone Disorders, December 2012; manuscript in preparation.



Appendix Fig. 3. Change in probability of major osteoporotic fracture (a) and hip fracture (b) in individuals belonging to the moderate and high risk fracture groups.

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