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Direct comparison of eight national FRAX® tools for fracture prediction and treatment qualification in Canadian women

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Abstract
Summary We compared the calibration of FRAX tools from Canada, the US (white), UK, Sweden, France, Australia, New Zealand, and China when used to assess fracture risk in 36,730 Canadian women. Our data underscores the importance of applying country-specific FRAX tools that are based upon high-quality national fracture epidemiology.
Purpose A FRAX® model for Canada was constructed for prediction of hip fracture and major osteoporotic fracture (MOF) using national hip fracture and mortality data. We examined the calibration of this model in Canadian women and compared it with seven other FRAX tools.
Methods In women aged ≥50 years with baseline bone mineral density (BMD) measures identified from the Manitoba Bone Density Program, Canada (n=36,730), 10-year fracture probabilities were calculated with and without BMD using selected country-specific FRAX tools. FRAX risk estimates were compared with observed fractures ≤10 years (506 hip, 2,380 MOF). Ten-year fracture risk was compared with predicted probabilities, and proportions exceeding specific treatment thresholds contrasted.
Results For hip fracture prediction, good calibration was observed for FRAX Canada and most other country-specific FRAX tools, excepting Sweden (risk overestimated) and China (risk underestimated). For MOF prediction, greater between-country differences were seen; FRAX Sweden and FRAX China showed the largest over- and underestimation in this Canadian population. Relative to treatment qualification based upon FRAX Canada, treatment of high-hip fracture probability (≥3 %) was greater by FRAX Sweden (ratio 1.41 without and 1.55 with BMD), and markedly less by FRAX China (ratio 0.09 without and 0.11 with BMD). Greater between-country differences were observed for treat4ment of high MOF (≥20 %); FRAX Sweden again greatly increased (ratio 1.76 without and 1.83 with BMD), and FRAX China severely reduced treatment qualification (ratio 0.00 without and 0.01 with BMD).
Conclusions The use of country-specific FRAX tools, accurately calibrated to the target population, is essential. Relatively small calibration differences can have large effects on high-risk categorization and treatment qualification.

Keywords Bone mineral density · Dual energy x-ray absorptiometry · Osteoporosis · Fracture prediction models · FRAX

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Introduction

The World Health Organization (WHO) fracture risk tool (FRAX®) was developed to evaluate 10-year fracture probability based on individual patient models that integrate the risks associated with clinical risk factors, with or without BMD measured at the femoral neck [1]. Given that fracture and mortality rates are known to vary widely between countries [2], country-specific FRAX tools have been developed

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and customized to the fracture and mortality epidemiology in specific regions [1]. Furthermore, calibration is a fundamental performance aspect of predictive tools [3], whereby incorrect calibration could affect performance of the model in clinical practice. The changing rate of fracture and mortality across time necessitates the periodic review and updating of FRAX tools [4]. Accordingly, a FRAX model for Canada was constructed using national hip fracture data from 2005 and mortality data from 2004. The Canada FRAX has been shown to have good calibration and discrimination for fracture specific to the Canadian population [5].

Although the point of FRAX is to customize fracture risk assessment to the fracture epidemiology of the target population, there is curiosity on this point given cultural and ethnic similarities and differences between Canada, the US, and other countries. We examined differences in predicted fracture probability between different countries reflecting a broad range in underlying risk by comparing the performance of the Canadian FRAX tool with those from the US (white), UK, Sweden, France, Australia, New Zealand, and China. Furthermore, given the potential to under- or overtreat due to incorrect determination of fracture probability, we examined the categorization of women meeting a fixed-treatment threshold under these country-specific models. Women with a hip fracture probability of ≥3 % and major osteoporotic fracture (MOF) probability of ≥20 % were categorized as falling above the treatment threshold: a threshold determined by the National Osteoporosis Foundation (NOF), in conjunction with low bone mineral density (BMD), to require intervention [6–8].

Methods

Study population

The Province of Manitoba has a population of 1.25 million, virtually all of whom are afforded comprehensive health care coverage [9]. From the Manitoba BMD Program database, which captures all clinical dual energy x-ray absorptiometry (DXA) results for the Province of Manitoba, Canada, we identified 36,730 women aged ≥50 years with medical coverage and who had baseline BMD testing (femoral neck) between January 1990 and March 2007.

Fracture ascertainment

Fractures diagnosed before and after BMD testing up to March 2008 were ascertained through the combined use of hospital discharge records (diagnoses and procedures coded using the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] prior to 2004, and ICD Tenth Revision, Canada [ICD-10-CA] after 2004) and physician billing claims (coded using ICD-9-CM) [10]. To code a prior fracture for FRAX calculation, we included MOFs of the hip, clinical vertebra, forearm or humerus that had been diagnosed before BMD testing and were not associated with a code for high trauma. A similar definition was used for incident fractures, except that a 6-month wash-out period affecting the same site was also included. The mean period of observation was 5.6 years with 1,698 women still under observation at 10 years.

Clinical risk factors

Rheumatoid arthritis was defined from compatible ICD-9-CM/ICD-10-CA codes identified from physician records or hospitalizations in a 3-year period prior to BMD testing. Chronic obstructive pulmonary disease (COPD) was used as a proxy for smoking status and diagnosis of alcohol or substance abuse was used as a proxy for high alcohol intake. Prolonged corticosteroid use (>90 days dispensed in the year prior to DXA testing) was obtained from the provincial pharmacy system [11]. Adjustments were made for incomplete parental hip fracture information, using age- and sex-specific adjustment factors based on 2006–2007 parental hip fracture responses, as previously published [12, 13]. Weight and height were recorded at the time of the DXA examination (prior to 2000 this was by self-report and starting in 2000, height was assessed with a wall-mounted stadiometer and weight was assessed without shoes using a standard floor scale). BMI (in kilograms per square meter) was calculated as [weight (in kilograms)/divided by height (in square meter)].

Calculation of FRAX probabilities

DXA scans of the femoral neck were performed and analyzed in accordance with manufacturer recommendations, and T scores were calculated from the revised National Health and Nutrition Examination Survey (NHANES) III white female reference values (Prodigy version 8.8) [14, 15]. Ten-year probability of a hip fracture or MOF was calculated for each subject by the WHO Collaborating Centre (FRAX v3.7) using the previously defined variables and femoral neck BMD without knowledge of the fracture outcomes.

Statistical analyses

We calculated, and graphically present, the mean values of probability for hip fractures and MOF for the eight countries, including Canada. We examined the age effects (5-year age strata) on the outputs from country-specific FRAX tools. Ten-year fracture risk was estimated using a modified Kaplan–Meier method. To assess calibration, we compared fracture

rates at 10 years, adjusted for competing mortality and duration of follow-up [16], with predicted probabilities using FRAX in subgroups defined by risk quintiles of fracture probability. Receiver operating characteristics (ROC) curve for different models were compared to examine the accuracy of discrimination. Finally, proportions exceeding treatment thresholds of 3 % for hip fracture and 20 % for MOF for each FRAX tool were compared to treatment rates determined from the Canada FRAX (referent). All statistical analyses were performed with Statistica (Version 10.0, StatSoft Inc, Tulsa, OK) except for ROC analysis which was performed with IBM SPSS for Windows (Version 20, SPSS Inc., Chicago, IL).

Results

The study population comprised 36,730 adult women; during follow-up, 2,420 women died and only 1,143 were lost to follow-up from migration out of province. Clinical risk factors for the study population are presented in Table 1. The mean age was 65.7±9.8 years, and mean BMI was 26.8±5.2 kg/m^2. Of our study population, 14.3 % had femoral neck T scores in the osteoporotic range.

Mean probability of fracture using country-specific FRAX tools are provided in Table 2 assessed with and without BMD. Average fracture probabilities without BMD from FRAX Canada were 11.6 % for MOF and 3.6 % for the hip. The probability of MOF estimated without BMD ranged from 14.9 % (Sweden) to 3.0 % (China). For hip fracture, mean probabilities estimated without BMD were similar for most of the country-specific tools (all 3–4 %), while much greater mean probability was seen for FRAX Sweden (6.2 %) and much lower probability for FRAX China (0.9 %).

Table 1 Clinical risk factors for the female Canadian (Manitoba) study population (n=36,730), presented as mean ± SD or n (%)

Variable	Value
Age (years)	65.7±9.8
Body mass index (BMI) (kg/m^2)	26.8±5.2
Prior major fragility fracture	4,984 (13.6 %)
Parental hip fracture*	1,110 (13.2 %)
Rheumatoid arthritis	1,311 (3.6 %)
Current/recent glucocorticoid use	1,542 (4.2 %)
COPD (proxy for smoking)	2,928 (8.0 %)
Substance abuse (proxy for high alcohol consumption)	874 (2.4 %)
Femoral neck T score$^{\infty}$	−1.5±1.0
Osteoporotic (femoral neck T score ≤ −2.5) $^{\infty}$	5,258 (14.3 %)

COPD chronic obstructive pulmonary disease

*Adjustments made for incomplete parental hip fracture data, by use of 2005–2007 data for n=8,349 women

$^{\infty}$ Based on the NHANES III White female reference range [15]

Table 2 Mean probability of fracture risk in the study population using country-specific FRAX tools (in descending order)

Country	FRAX without BMD	FRAX with BMD
Major osteoporotic fracture (MOF) probability (%)		
Sweden	14.9	14.1
US (white)	12.9	12.4
Canada	11.6	11.1
UK	11.4	10.9
France	8.7	8.0
New Zealand	8.0	7.4
Australia	6.9	6.3
China	3.0	3.0
Hip fracture probability (%)		
Sweden	6.2	5.1
US (white)	3.9	3.1
Canada	3.6	2.8
UK	3.8	3.0
France	3.8	3.0
New Zealand	3.5	2.7
Australia	3.1	2.4
China	0.9	0.8

Figure 1 presents the effect of age on predicted 10-year fracture risk by 5-year age strata for country-specific FRAX tools determined with the inclusion of BMD in the calculation. Large discordance in both MOF and hip fracture was seen for the Swedish and Chinese tools compared to Canada and the other country-specific tools. After an age of 80 years, there was less discordance in probabilities of MOF and hip fracture between the Swedish FRAX and non-Chinese tools. Of note, there was little increase in MOF or hip fracture probability with advancing age in the China tool.

We observed 2,380 incident MOF and 506 incident hip fractures. Figure 2 presents agreement between predicted 10-year fracture probabilities (determined with BMD) versus 10-year fracture rates by risk quintile. The overall ratios of observed versus expected fracture risk using the Canadian FRAX tool were 0.97 for hip fracture and 1.08 for MOF; results from the UK tool were similar (0.90 and 1.11, respectively) and the US tool was only slightly lower (0.88 and 0.97, respectively), with the calibration curves contained within the 95 % confidence intervals for FRAX Canada. The observed versus expected ratios were consistently much lower with the Swedish tool (0.54 and 0.85, respectively) and consistently much higher with the Chinese tool (3.37 and 3.99, respectively). For the other FRAX tools, there was a good concordance for hip fracture prediction (ratios 0.92 France, 1.13 Australia, 1.00 New Zealand) but underestimation

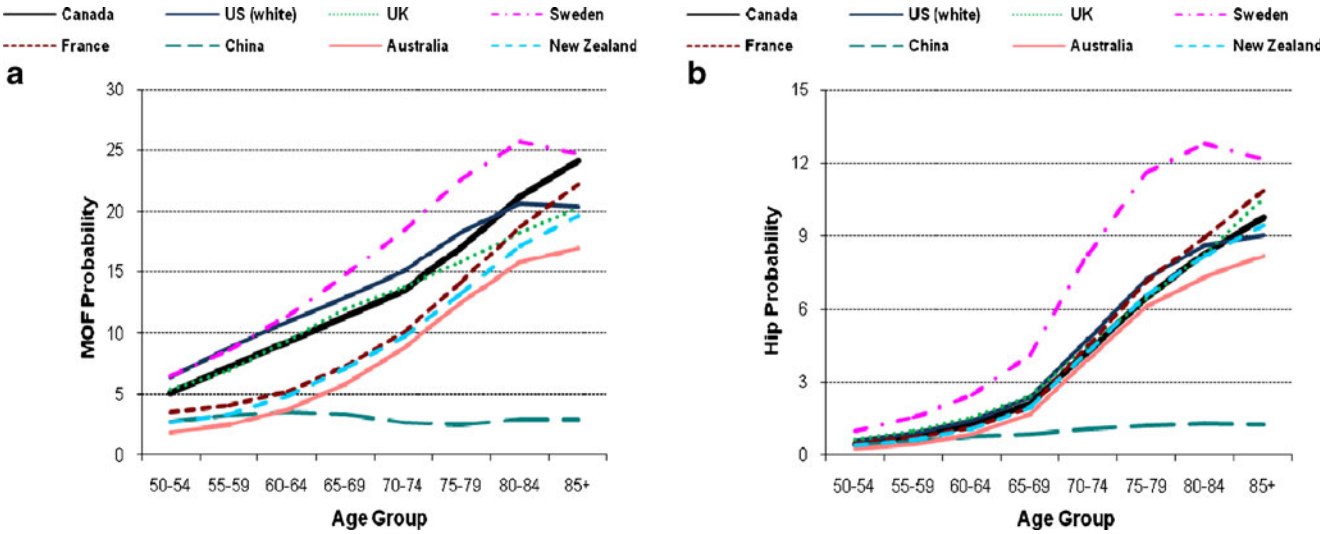

Fig. 1 Age effects (by 5-year age strata) on **a** major osteoporotic fracture (MOF) probability and **b** hip fracture probability according to country-specific FRAX tools, defined with the inclusion of BMD

in MOF prediction (ratios 1.51 France, 1.91 Australia, 1.64 New Zealand).

Discrimination for MOF fracture as measured by ROC showed few differences in the area under the curve (AUC) for most country-specific FRAX tools determined with BMD compared to Canada (AUC 0.70, 95 % CI 0.69–0.71); for UK, US, Sweden, and France, the AUC was identical to FRAX Canada; and for Australia and New Zealand was 0.69 (95 % CI 0.68–0.70). The only exception was a significantly lower AUC for FRAX China which was 0.64 (95 % CI 0.62–0.65). For hip fracture, with the exception of the FRAX tool for China (AUC 0.81, 95 % CI 0.79–0.82), the AUC for all country-specific FRAX tools determined with BMD were identical to Canada at 0.83 (95 % CI 0.82–0.85).

Using the Canadian FRAX tool with inclusion of BMD, 28.0 % of women had hip fracture probability that exceeded 3 % while 11.3 % had MOF probability that exceeded 20 %. Relative to the proportion of individuals meeting treatment thresholds using FRAX Canada, qualification for treatment of hip fracture probability ≥3 % was identified in a higher proportion when using the FRAX Sweden (ratio 1.41 without and 1.55 with inclusion of BMD), and markedly less by FRAX China (ratio 0.09 without and 0.11 with inclusion of BMD). Even greater between-country differences were observed in the proportion of individuals qualifying for treatment based upon MOF ≥20 %, with the largest proportion observed for FRAX Sweden (ratio 1.76 without and 1.83 with inclusion of BMD), and the smallest proportion observed for FRAX China (ratio 0.00 without and 0.01 with

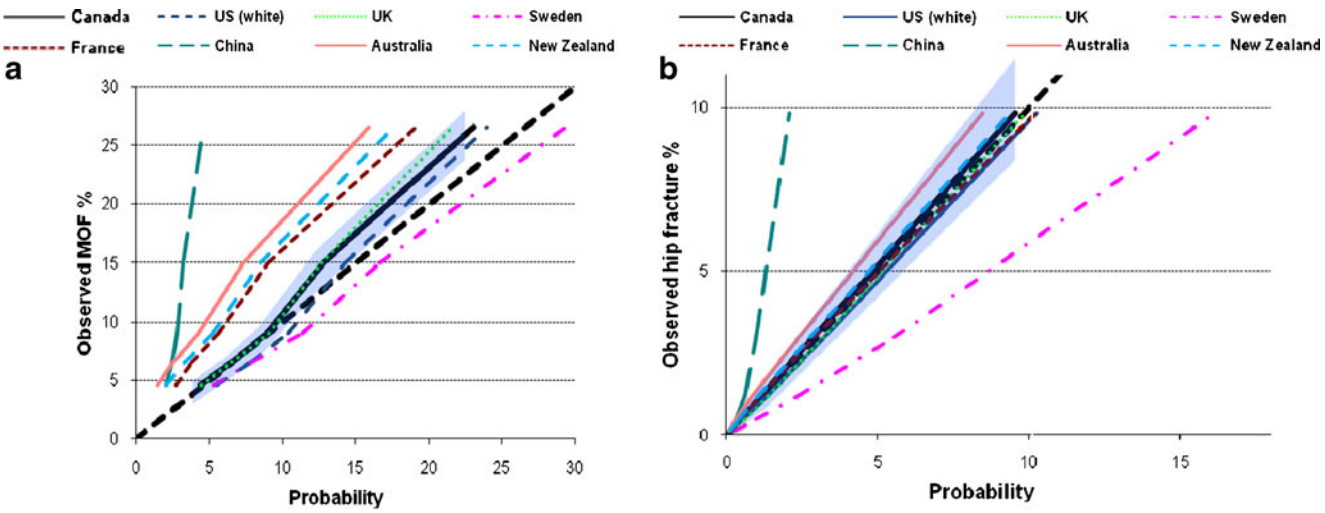

Fig. 2 Predicted 10-year fracture probability for the study population (using country-specific FRAX tools defined with BMD) versus 10-year fracture rates by risk quintile, presented for **a** major osteoporotic fracture, and **b** hip fracture. The *shaded area* indicates the calibration curves contained within the 95 % confidence intervals for FRAX Canada

inclusion of BMD). There was a positive correlation between relative change in FRAX calibration and the proportion of individuals that qualified for treatment (expressed relative to the Canadian FRAX tool): slopes 1.7 for MOF 1.0 for hip fracture.

Discussion

We compared the performance of the Canadian FRAX tool with tools from the US (white), UK, Sweden, France, Australia, New Zealand, and China, and examined the categorization of Canadian women above the treatment thresholds using country-specific models. Our data suggest that, with the exception of Sweden and China, the other countries evaluated have similar hip fracture probability (reflecting the competing effects of death and fracture hazards) to our Canadian population as reflected in their FRAX calibration. However, greater between-country discrepancies were observed for MOF, with the exception of the US and UK FRAX tools which showed good agreement with the Canadian FRAX tool. Significant discordance was observed in applying treatment thresholds for hip fracture (≥3 %) and MOF (≥20 %), whereby the proportion of individuals qualifying for treatment were significantly greater when estimated by FRAX Sweden and severely lower when estimated by FRAX China.

The greater discrepancies observed for 10-year MOF probability between countries may reflect different approaches to FRAX calibration. The FRAX tools from France, NZ, and Australia all employ the Swedish hip/non-hip ratios for imputing fractures of the spine, forearm and humerus. The US and UK employ Swedish ratios for vertebral fracture, but use their own country-specific data for forearm and humerus fractures. China also employs Swedish ratios for vertebral fractures, but uses country-specific hip fracture data. Furthermore, there was little increase in MOF or hip fracture probability with advancing age in the China tool may be explained by a smaller age-related increase in the fracture hazard relative to the competing mortality hazard. Finally, the Canadian FRAX tool employs US ratios [4, 17]. Given that greater agreement was observed between the Canadian FRAX tool and those of US and UK, compared to other countries, it is plausible that Swedish vertebral fracture data may be applicable to most countries while forearm and humerus fracture data may be more variable or more difficult to ascertain.

Given that cost-effective osteoporosis therapy such as bisphosphonates, can reduce fracture risk by as much as 50 % [18–20], it is imperative that those at high risk are appropriately identified using an accurate risk calculator in order to provide efficacious treatment. However, it is equally important to ensure that unnecessary treatment is avoided. We found the FRAX Sweden would result in an overestimate of Canadian women with a 10-year hip fracture probability of ≥3 %, a level considered by the NOF for intervention when the individual has low bone mass [6–8, 21]. In contrast, the Chinese FRAX tool would severely underestimate 10-year hip fracture probability and the need for treatment intervention in Canadian women. Similar results were seen when both the FRAX Sweden and China calculations were defined with and without BMD. Similarly, the intervention rate for MOF ≥20 % would also have been overestimated by the Swedish tool, and underestimated by the Chinese tool, suggesting that employing either the Swedish or Chinese FRAX tool for Canadian women could result in either unnecessary pharmacotherapy or significant under-treatment, respectively. However, it could be argued that if individuals falling into the top 10 % of risk were targeted for treatment, then it is likely that the same group of individuals would be identified, regardless of the model used. Given this, the use of FRAX should be encouraged even in countries where no country-specific model exists, The steep gradient in the relationship between FRAX calibration and treatment qualification is consistent with a previous simulation study which found that for every 1 % change in MOF calibration there was a 2.5 % change in intervention rates for women, with a hip fracture calibration slope close to unity [22]. While this current study showed concordance between the Canadian and US FRAX tools, it should be noted that our study population was a clinical referral population. A previous study that used national hip fracture statistics from Canada showed US women to have higher hip fracture rates than Canadian women [23], data that supported the need for a Canada-specific FRAX, thus we suggest caution in interpreting the concordance shown in this current study between FRAX Canada and US. Our data demonstrates the potential for individuals to be incorrectly categorized as high or low risk when applying a country-specific FRAX tool to a different population.

This study has several strengths. We employed a large cohort of women for our analyses and thus had sufficient numbers of fractures for analyses. FRAX calibration for hip fracture was robust as expected, given that calibration is based on national (Canadian) hip fracture data [23]. This study also has some limitations. Although we ascertained incident fractures from administrative data records, which may be prone to misclassification, we employed definitions of incident fracture that agree with CaMos population-based fracture rates [24]. Furthermore, we have previously reported high agreement between the observed and predicted fracture risk overall, within subgroups, and with regards to individual risk factors [12]. Our methodology employed proxies for current smoking status and high alcohol intake. Diagnosed COPD and alcohol and/or substance abuse are likely to reflect the most extreme forms of smoking and alcohol

consumption, but are also likely to have the largest effects on fracture risk which would mitigate the potential underestimation in fracture risk. In addition, we have previously reported that both proxy variables gave hazard ratios for fracture that are comparable to the weight given in FRAX [12]. Furthermore, this was a clinical referral population with universal health coverage rather than a randomly selected population. Related to this, is that 14.3 % of our study population were defined as osteoporotic at the femoral neck, a figure slightly in excess of the general Canadian female population (11.1 %) [17].

In conclusion, these data shows the importance of applying country-specific FRAX tools that are based upon high-quality national fracture epidemiology. Furthermore, it is essential to use country-specific FRAX tools that have been accurately calibrated to the target population. Even relatively small calibration differences can have large effects on high-risk categorization and eligibility for treatment.

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