FRAX Provides Robust Fracture Prediction Regardless of Socioeconomic Status

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Mini abstract

We investigated FRAX Canada calibration and discrimination according to income quintile in 51,327 Canadian women, with and without a competing mortality framework. Our data show that, under a competing mortality framework, FRAX provides robust fracture prediction and calibration regardless of SES.

Abstract (249 words)

Purpose: FRAX® predicts 10-year fracture risk. Social factors may independently affect fracture risk. We investigated FRAX calibration and discrimination according to socioeconomic status(SES).

Methods: Women aged ≥50yr with baseline femoral neck BMD were identified from the Manitoba Bone Density Program, Canada(n=51,327), 1996-2011. Mean household income, extracted from 2006 census files, was categorized into quintiles. 10-year fracture probabilities were calculated using FRAX Canada. Incident non-traumatic fractures were studied in relation to income quintile in adjusted Cox proportional hazards models. We compared observed versus predicted fractures with and without a competing mortality framework.

Results: During mean 6.2±3.7yr of follow up there were 6,392 deaths, 3,723 women with ≥1 major osteoporotic fracture(MOF) and 1,027 with hip fractures. Lower income was associated with higher risk for death, MOF and hip fracture in adjusted models(all $p<0.005$). More women in income quintile 1(lowest) *vs.* quintile 5 experienced death(19% *vs.* 8%), MOF(10% *vs.* 6%) or hip fracture(3.0% *vs.* 1.3%)(all $p\leq0.001$). Adjustment for competing mortality mitigated the effect of SES on FRAX calibration, and good calibration was observed. FRAX provided good fracture discrimination for MOF and hip fracture within each income quintile(all $p<0.001$). Area under the curve(AUC) was slightly lower for income quintiles 1 *vs.* 5 for FRAX with BMD to predict MOF(0.68, 95%CI 0.66-0.70 *vs.* 0.71, 95%CI 0.69-0.74) and hip fracture(0.79, 95%CI 0.76-0.81 *vs*. 0.87, 95%CI 0.84-0.89).

Conclusion: Increased fracture risk in individuals of lower income is offset by increased mortality. Under a competing mortality framework, FRAX provides robust fracture prediction and calibration regardless of SES.

Keywords: Income, Osteoporosis, FRAX, Fracture prediction, Calibration

Introduction

The World Health Organization (WHO) fracture risk tool (FRAX®) was developed to evaluate the 10-year fracture probabilities based on individual patient models that integrate the risks associated with clinical risk factors, with or without bone mineral density (BMD) measured at the femoral neck (1). Canada FRAX was constructed using national hip fracture and mortality data, and provides robust fracture prediction and calibration for the Canadian population (2, 3).

Clinical risk factors for fracture are known to vary widely according to different levels of socioeconomic status (SES), including body mass index (BMI) (4), smoking (5-8), alcohol consumption (9), and other lifestyle choices including nutrition and physical activity (10-13). Differences across socioeconomic groups have also been observed for BMD (14-17) and mortality (18, 19) in different countries. Given this, it is plausible that social factors may independently affect FRAX risk assessment. Therefore, we investigated the performance of FRAX to determine whether the Canadian tool performs equitably in the clinical setting across different levels of SES.

Materials and methods

Study population

The Province of Manitoba has a population of ~1.25 million according to the Statistics Canada census, virtually all of whom are afforded comprehensive health care coverage (20). 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 51,327 women aged ≥50 years with medical coverage and who had baseline BMD testing at the femoral neck between 1996 and 2011. This study was reviewed and approved by the Health Research Ethics Board for the University of Manitoba, and the Health Information Privacy Committee (HIPC) of Manitoba Health (HIPC File Number 2012/2013-15).

Adverse socioeconomic position

Mean household income, based upon area of residence in the year of the DXA test, for dissemination areas (DAs) was extracted from the public use files of the Statistics Canada Census for 2006. As of 2001 Census, DAs replace enumeration areas as the basic unit for data dissemination, and are the smallest geographic unit for which Census data are released to the public. DAs are composed of one or more neighbouring blocks, and are uniform in population size, ranging from 400 to 700 persons. Mean household income was ranked from the lowest to highest, and then categorized into quintiles, with each quintile containing ~20% of the population, as previously described (14).

Bone mineral density

Prior to 2000, BMD was measured by DXA using a pencil-beam instrument (Lunar DPX, GE Healthcare, Madison, WI, USA), and in later years DXA was performed using fan-beam instruments (Lunar Prodigy, GE Healthcare). All instruments were cross-calibrated using anthropomorphic phantoms and volunteers. DXA scans of the femoral neck were performed and analyzed in accordance with manufacturer recommendations. Osteoporosis was determined as a BMD T-score at the femoral neck of ≥2.5SD below the young adult mean, and calculated using the revised National Health and Nutrition Examination Survey (NHANES) III white female reference values (21).

Fracture ascertainment

Fractures diagnosed before and after BMD testing (1987-2011) 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) (22). 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 (after BMD testing), with the inclusion of a 6 month wash-out period where fractures affected the same site. To enhance diagnostic and temporal specificity, a hip fracture was also required to have a relevant orthopedic procedure code (e.g., open or closed reduction), and a forearm

fracture was required to have a site-specific orthopedic procedure (e.g., cast immobilization or fracture reduction).

Clinical risk factors

Weight and height were recorded at the time of the DXA examination; prior to 2000 this was self-reported, however from 2000 onward height was assessed with a wall-mounted stadiometer and weight was assessed without shoes using a standard floor scale. BMI (kg/m^2) was calculated as weight divided by height squared in kg/m^2. A diagnosis of rheumatoid arthritis was defined from ICD-9-CM/ICD-10-CA codes identified from physician records or hospitalizations in a three-year period prior to BMD testing (22). Chronic obstructive pulmonary disease (COPD) diagnosis was used as a proxy for smoking status, and diagnosis of alcohol or substance abuse was used as a proxy for high alcohol intake. The proxy measures have been shown to give similar prevalence and risk prediction as in other cohorts including the population-based Canadian Multicentre Osteoporosis Study (2, 3). Prolonged corticosteroid use (>90 days dispensed in the year prior to DXA testing) was obtained from the province-wide retail pharmacy system (22). Adjustments were made for incomplete parental hip fracture information, using age- and sex-specific adjustment factors based on 2006-7 parental hip fracture responses, as previously published (3, 23). Osteoporotic drug treatment dispensed in the year prior to DXA testing was used to calculate the medication possession ratio (MPR) (24) and categorised as none <0.5. 0.5-0.8, or >0.8.

Calculation of FRAX probabilities

The 10-year probability of a MOF or hip fracture was calculated for each subject (FRAX Canada, FRAX® Desktop Multi-Patient Entry, version 3.7) using the variables given above, with and without femoral neck BMD.

Statistical analyses

Characteristics of the study population were descriptively analyzed. We determined *a priori* to contrast the extreme ends of the socioeconomic continuum. The lowest income quintile (quintile 1) and the highest income quintile (quintile 5) were compared using a χ^2

test of independence for categorical variables and analysis of variance (ANOVA) for normally distributed continuous variables. We estimated the mean probabilities of MOF and hip fracture, and calculated the crude fracture incidence for the lowest and highest income quintiles. To assess calibration, we used a modified Kaplan-Meier method that accounts for the competing risk of death and compared estimated 10-year fracture probabilities with predicted probabilities for the lowest and highest income quintiles (25). Accounting for competing mortality is imperative, as estimates of 10-year fracture probability may be biased if analyses did not adjust for this effect (25). We have previously shown that our modified Kaplan-Meier method (25) will produce estimates that are consistent with semi-parametric (ie, Cox Proportional Hazards) and non-parametric (two-step procedures for constructing the cumulative incidence function) methods. For comparison, we also examined calibration in a model that did not account for competing mortality risk. Receiver operating characteristics (ROC) curves for income quintiles 1 and 5 were used to assess discriminative performance for each income subgroup. Age-adjusted and multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) were computed for each income quintile (reference: quintile 5). Finally, linear trend as a function of income quintile was assessed using a large-sample chi-squared test. All statistical analyses were performed with Statistica (Version 10.0, StatSoft Inc, Tulsa, OK), with the exception of ROC analyses which were performed with IBM SPSS for Windows (Version 20.0, SPSS Inc., Chicago, IL).

Results

Clinical risk factors for the entire study population (n=51,327) are presented in Table 1. Women in quintile 1 (lowest income) versus women in quintile 5 (highest income) were older (68.7±10.3 *vs*. 63.5±9.3), had greater mean BMI (27.3±5.8 *vs*. 26.5±5.1) and a lower femoral neck T-score (-1.6±1.0 *vs*. -1.3±1.0) (all $p \leq 0.001$). Greater prevalence of all clinical risk factors were observed in women in quintile 1 compared to women in quintile 5 ($p \leq 0.001$) with the exception of parental hip fracture and rheumatoid arthritis.

During mean 6.2 years of follow up incident MOF were observed in 3,723 (7.3%) women (9.5% for income quintile 1 *vs*. 5.6% for income quintile 5, $p<0.001$) among whom 1,027

(2.0%) had incident hip fractures (3.0% for income quintile 1 vs. 1.3% for income quintile 5, $p<0.001$). During the same period 6,392 women died (12.5%), of whom 1,619 (18.6%) were in quintile 1 and 847 (8.2%) in quintile 5 ($p\leq0.001$). Table 2 presents the adjusted HRs for mortality, MOF and hip fracture according to income quintile. A linear dose-response association was observed between lower and higher income quintiles and increased likelihood of all events (all *p*-values for linear trend <0.01). After adjustment for multiple covariates, the HRs and 95% confidence intervals (95%CI) for quintile 1 *vs.* quintile 5 for mortality was 1.43 (95%CI 1.32-1.56), for MOF was 1.28 (95%CI 1.15-1.42) and for hip fracture was 1.30 (95%CI 1.05-1.60).

Accounting for competing mortality, in all women combined the observed 10-year fracture incidence for MOF was 11.0% (predicted 11.6% without BMD, 11.0% with BMD), and for hip fracture was 3.2% (predicted 3.5% without BMD, 2.8% with BMD), indicating good concordance (Figure 1). Mean predicted fracture probabilities were higher for quintile 1 compared to quintile 5 for MOF (13.7% *vs*. 10.1% without BMD, and 12.9% *vs*. 9.6% with BMD) and for hip fracture (4.8% *vs*. 2.7% without BMD, and 3.8% *vs*. 2.1% with BMD). All differences in fracture probabilities for quintiles 1 and 5 were statistically significant ($p\leq0.001$). Observed fracture incidence (accounting for competing mortality) was higher for quintile 1 compared to quintile 5 ($p\leq0.001$) for MOF (14.4% *vs*. 8.7%) and for hip fracture (4.8% *vs*. 2.1%), consistent with the predicted differences. Models that did not account for competing mortality risk gave slightly higher estimates of 10-year fracture incidence, with a larger difference for income quintile 1 (Δ MOF 1.6%, Δ hip fracture 0.6%) compared with income quintile 5 (Δ MOF 0.4%, Δ hip fracture 0.1%).

Figure 1: Mean fracture probability (measured with and without BMD) and observed fracture incidence (estimated with and without adjustment for competing risk of mortality) in the study population for income quintile 1 (lowest income) and quintile 5 (highest income).

Figure 2 shows good concordance between observed and predicted 10-year fracture probabilities for income quintiles 1 and 5 in risk subgroups (low <10%, moderate 10-19%, high ≥20%) after accounting for competing mortality risk. In particular, for the highest risk subgroup, the 95% CI for observed 10-year MOF and hip fracture straddled the line of identity indicating good calibration. Figure 3 presents the agreement between observed and predicted 10-year fracture probabilities without accounting for the effects of competing mortality which gave higher values as expected. For quintile 1, the highest risk subgroup 95% CI for observed 10-year MOF and hip fracture fell above the line of identity indicating miscalibration (underestimation in fracture risk) when competing mortality was omitted from the analysis.

Figure 2: Predicted* *vs.* observed10-year fracture risk (%), with adjustment for competing risk of mortality by risk category (low <10%, moderate 10-19%, high risk ≥20%) for income quintiles 1 and 5, presented for (a) major osteoporotic fracture (MOF), and (b) hip fracture. Error bars represent 95% confidence intervals.

Figure 3: Predicted* *vs.* observed10-year fracture risk (%), without adjustment for competing risk of mortality by risk category (low <10%, moderate 10-19%, high risk ≥20%) for income quintiles 1 and 5, presented for (a) major osteoporotic fracture (MOF), and (b) hip fracture. Error bars represent 95% confidence intervals.

Discrimination for MOF as measured by area under the ROC curve (AUC) was significantly better than chance overall and for each income subgroup (p<0.001), but AUCs were slightly lower for quintile 1 versus quintile 5 for FRAX with BMD (0.68, 95%CI 0.66-0.70 *vs*. 0.71, 95%CI 0.69-0.74, respectively) and without BMD (0.65, 95%CI 0.63-0.67 *vs*. 0.68, 95%CI 0.66-0.70, respectively) (both p=0.04). For hip fracture, AUC was again significantly lower for quintile 1 versus quintile 5 for FRAX with BMD (0.79, 95%CI 0.76-0.81 *vs*. 0.87, 95%CI 0.84-0.89, respectively) and without BMD (0.76, 05%CI 0.73-0.78 *vs*. 0.85, 95%CI 0.82-0.88, respectively) (both $p\leq0.001$). No significant differences in the AUC for the income quintiles were observed for MOF or hip fracture predicted from femoral neck T-score alone (both $p\geq0.4$).

Discussion

We provide the first data to investigate the performance of FRAX according to different levels of SES. We found that adjustment for competing mortality mitigates the effect of SES on FRAX calibration such that good calibration was observed regardless of income level. Our data also suggest that FRAX provides slightly better discrimination for women with the highest income compared to the lowest income.

Little discrepancy in calibration was observed between income quintiles 1 and 5 under a competing mortality framework, however greater discrepancy was seen when not accounting for mortality. It is most likely that the increased fracture risk for women with the lowest income is offset by the increased mortality risk in the same population group. Our women with the lowest income had the greatest proportion of incident fracture, an association that is supported by studies from other developed countries including Sweden (26), the US (27), Denmark (28) and Australia (29, 30). Furthermore, we observed an inverse relationship between mortality and socioeconomic adversity; another association that is well-documented (18, 19). In order to provide accurate 10-year fracture probabilities across different levels of socioeconomic adversity, and to avoid the potential for calibration differences between diverse socioeconomic groups, it is important that a competing mortality framework be employed.

We report better discrimination for FRAX for women with the highest income compared to the lowest income. The underlying mechanisms that may explain the observed differences in discrimination are varied. First, it is plausible that different trauma mechanisms may be involved. For instance, a greater propensity may exist for women from adverse social positions to fall compared to other women (31, 32); reasons may include an over-crowded environment (33), non-involvement in falls prevention clinics when needed (34-36) or sedentary lifestyles that increase the likelihood of reduced muscle strength (37-39). Furthermore, women from lower SES groups are more likely to have co-morbid conditions than other women (9, 40-42). Co-morbid conditions may also increase the likelihood of falling, and include those associated with low lean mass and

poor muscle function such as sarcopenia (43), gait disorders and balance disturbances such as Parkinson's disease (44), or poor sight (32, 45, 46). An alternate explanation for the difference in fracture discrimination between the lowest and highest income quintiles could be related to differences in the dose-response associations of clinical risk factors and fracture risk. It is well-documented that individuals from lower SES groups have less healthy lifestyles than their more advantaged counterparts including a greater likelihood of smoking, lower levels of physical activity, poorer nutritional intake and greater levels of obesity (4, 9, 10, 47). Even though the clinical risk factors included in FRAX tools incorporate some lifestyle behaviours, it is feasible that the dose-response effect of lifestyle behaviours on fracture risk may differ between individuals from different socioeconomic backgrounds. This may be due to a cumulative effect of many factors on bone (48, 49), the duration exposed to various factors, a life-course accumulation of disadvantage or health capital (50), or a combination of factors–issues that add further complexity to efforts aimed at disentangling the inverse associations between income and fracture.

This study has several strengths. These are the first data to investigate whether FRAX performed equally well for individuals from different SES groups. That we observed robust calibration is in part due to FRAX Canada being well calibrated from national hip fracture data (51). Our study size provided significant power to account for the differences in clinical risk factors between women with the lowest and highest income. Our study also has some limitations. Our sample population included women only. For our analyses, we used income quintiles based on the Statistics Canada Census for 2006, however, we have previously shown a strong correlation between area household income from the 2006 Census and household income from the year of DXA (14). Given that we investigated the performance of FRAX Canada, we are unable to comment on the calibration or discrimination of other country-specific FRAX tools according to different levels of socioeconomic status. We report on both the calibration and discrimination of our model, however acknowledge that some limitations to ROC analysis exist (52). For example, the ROC curve retains the full range of sensitivity and specificity values, not all of which may have clinical relevance. Whilst our ROC analysis did not adjust for

differences in follow up time, the mean follow up for income quintiles 1 and 5 were quite similar (6.0 vs 6.3 years). Our sample showed a bias toward greater numbers in the highest income quintile compared to the lowest income quintile; a factor plausibly explained by our population being clinically referred and that individuals from lower SES groups are less likely to utilize DXA (53-56) and more likely to experience geographical or travel-related barriers that limit attendance to testing or treatment (57-60). Furthermore, we were unable to account for ethnicity in these analyses as the study cohort was almost exclusively White (97-98% for each income quintile). Finally, we were unable to verify household income data, and there were no available income data measured at the individual-level. However, a comparison of income measured at the household and area-level showed that risk estimates from area-level income measures are not attenuated relative to estimates obtained from household income (61).

In conclusion, socioeconomic adversity independently modulates risk for death and fracture. Increased fracture risk in individuals of lower income is offset by increased mortality. Our data show that FRAX Canada provides robust fracture prediction and calibration regardless of socioeconomic position when accounting for the competing risk of mortality. Further studies that examine the calibration of other country-specific FRAX tools across socioeconomic groups are warranted to investigate the generalizability of our findings. In view of the importance of competing mortality on fracture probability estimation, country-specific FRAX tools may need to be periodically updated to adjust for any intervening secular changes in mortality and/or fracture rates.

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Disclosures/Conflict of interest

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Table 1: Characteristics of the female study population (n=51,327), presented as mean ± SD or n (%).

	All	Quintile 1 (lowest income)	Quintile 5 (highest income)	*P* value*
N=	51,327	8,699	10,360	
Clinical risk factors				
Age (years)	65.9 ± 9.8	68.7 ± 10.3	63.5 ± 9.3	**<0.001**
BMI (kg/m^2)	27.0 ± 5.4	27.3 ± 5.8	26.5 ± 5.1	**<0.001**
Prior major fragility fracture	6,562 (12.8)	1,399 (16.1)	1,077 (10.4)	**<0.001**
Parental hip fracture†	2848 (12.7)	430 (11.7)	621 (13.5)	**0.002**
COPD (proxy for smoking)	4,232 (8.2)	1,014 (11.7)	594 (5.7)	**<0.001**
Recent glucocorticoid use	2056 (4.0)	446 (5.1)	342 (3.3)	**<0.001**
Rheumatoid arthritis	1,759 (3.4)	332 (3.8)	351 (3.4)	0.11
Substance abuse (proxy for high alcohol consumption)	951 (1.9)	227 (2.6)	162 (1.6)	**<0.001**
Recent osteoporosis treatment	20,605 (40.1)	3,654 (42.0)	4,039 (39.0)	**<0.001**
BMD/Osteoporosis				

Femoral neck T-score	-1.5±1.0	-1.6±1.0	-1.3±1.0	**<0.001**
Osteoporosis (T-score -2.5 SD or lower)	6,936 (13.5)	1,612 (18.5)	1,048 (10.1)	**<0.001**
Fracture probability				
MOF without BMD	11.6±8.0	13.7±9.1	10.1±7.2	**<0.001**
Hip fracture without BMD	3.5±5.2	4.8±6.0	2.7±4.6	**<0.001**
MOF with BMD	11.0±7.3	12.9±8.3	9.6±6.5	**<0.001**
Hip fracture with BMD	2.8±4.4	3.8±5.3	2.1±3.8	**<0.001**

*P value for income quintile 1 *vs*. quintile 5. A bold value indicates a P value that is statistically significant at $\alpha = 0.05$

†Based on 2006-11 parental hip fracture responses

BMI=body mass index, COPD=chronic obstructive pulmonary disease, BMD=bone mineral density, MOF=major osteoporotic fracture

Table 2: Adjusted hazard ratios (HR, 95%CI) for mortality, major osteoporotic fracture (MOF) and hip fracture according to income quintile.

	Mortality		Major osteoporotic fracture			Hip fracture		
Adjustments	Age only	FRAX covariates*	Age only	FRAX, without BMD**	FRAX, with BMD*	Age only	FRAX, without BMD**	FRAX, with BMD*
Income quintile								
1 (lowest)	**1.34 (1.21-1.50)**	**1.43 (1.32-1.56)**	**1.34 (1.21-1.50)**	**1.33 (1.19-1.48)**	**1.28 (1.15-1.42)**	**1.34 (1.09-1.65)**	**1.35 (1.09-1.66)**	**1.30 (1.05-1.60)**
2	**1.13 (1.01-1.25)**	**1.21 (1.11-1.32)**	**1.13 (1.01-1.25)**	**1.12 (1.01-1.25)**	1.08 (0.97-1.2)	**1.25 (1.02-1.54)**	1.23 (1.00-1.51)	1.17 (0.95-1.44)
3	**1.13 (1.01-1.25)**	**1.18 (1.09-1.29)**	**1.13 (1.01-1.25)**	1.11 (1.00-1.24)	1.09 (0.98-1.21)	1.1 (0.89-1.36)	1.07 (0.87-1.33)	1.06 (0.85-1.31)
4	1.11 (0.99-1.24)	**1.12 (1.03-1.23**)	1.11 (0.99-1.24)	1.1 (0.99-1.23)	1.09 (0.98-1.22)	1.07 (0.85-1.34)	1.04 (0.83-1.31)	1.04 (0.83-1.31)
5 (highest)	1 (REFERENT)	1 (REFERENT)	1 (REFERENT)	1 (REFERENT)	1 (REFERENT)	1 (REFERENT)	1 (REFERENT)	1 (REFERENT)
P-trend	<0.001	0.003	<0.001	<0.001	<0.001	0.001	0.001	0.004

* Also adjusted for recent osteoporosis treatment.

** Including adjustment for the FRAX covariates of body mass index, rheumatoid arthritis, chronic obstructive pulmonary disease, alcohol abuse, corticosteroid use, previous fracture, and parental hip fracture, and for recent osteoporosis treatment.

Significant effects ($p \leq 0.05$) in bold. BMD=bone mineral density

Figure 1: **Mean fracture probability (measured with and without BMD) and observed fracture incidence (estimated with and without adjustment for competing risk of mortality) in the study population for income quintile 1 (lowest income) and quintile 5 (highest income).**

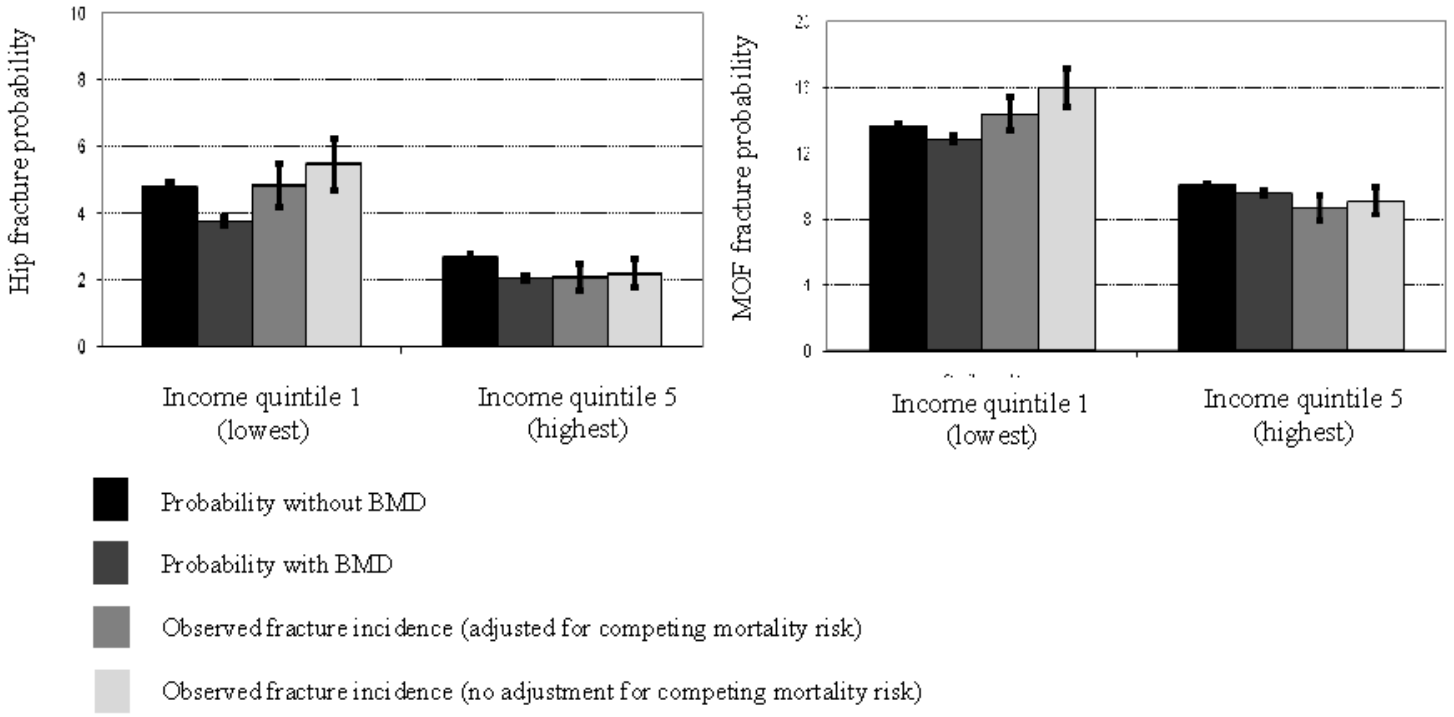


Figure 2: Predicted* *vs.* observed 10-year fracture risk (%), with adjustment for competing risk of mortality by risk category (low <10%, moderate 10-19%, high risk ≥20%) for income quintiles 1 and 5, presented for (a) major osteoporotic fracture (MOF), and (b) hip fracture. Error bars represent 95% confidence intervals.

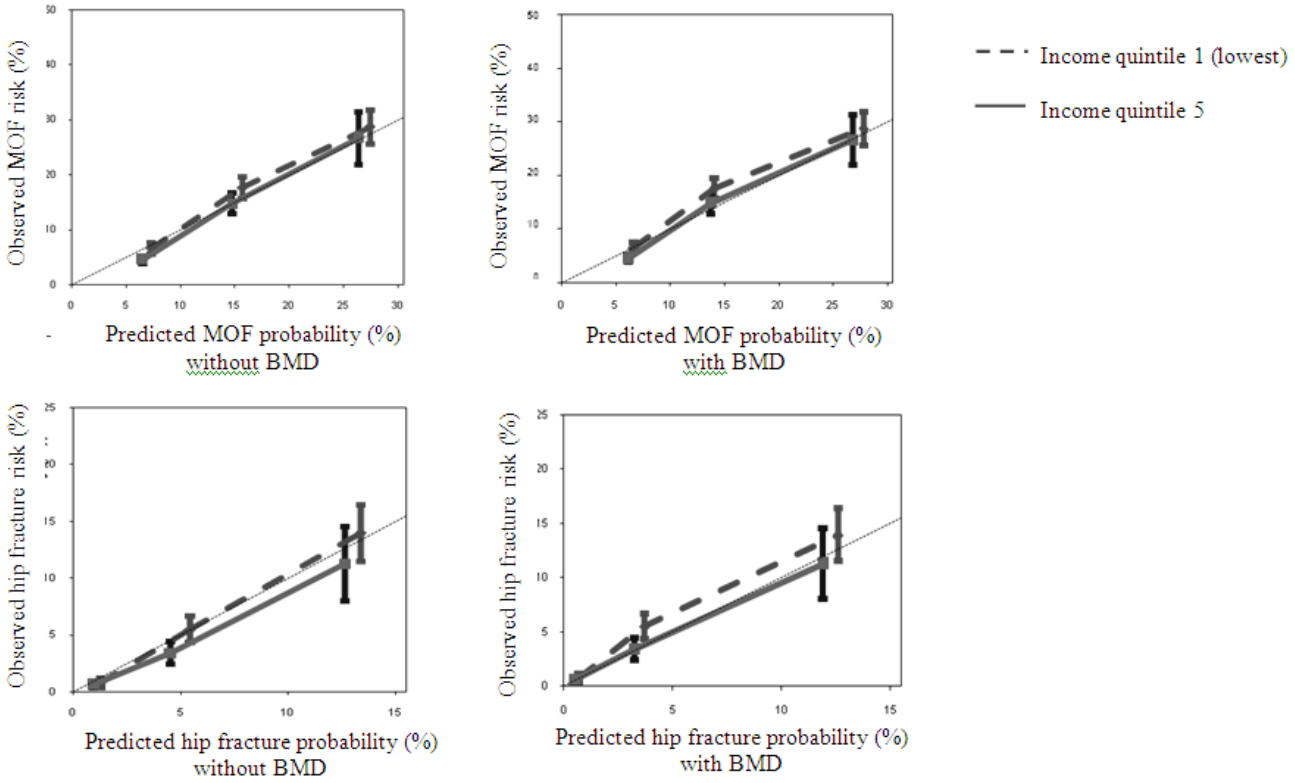
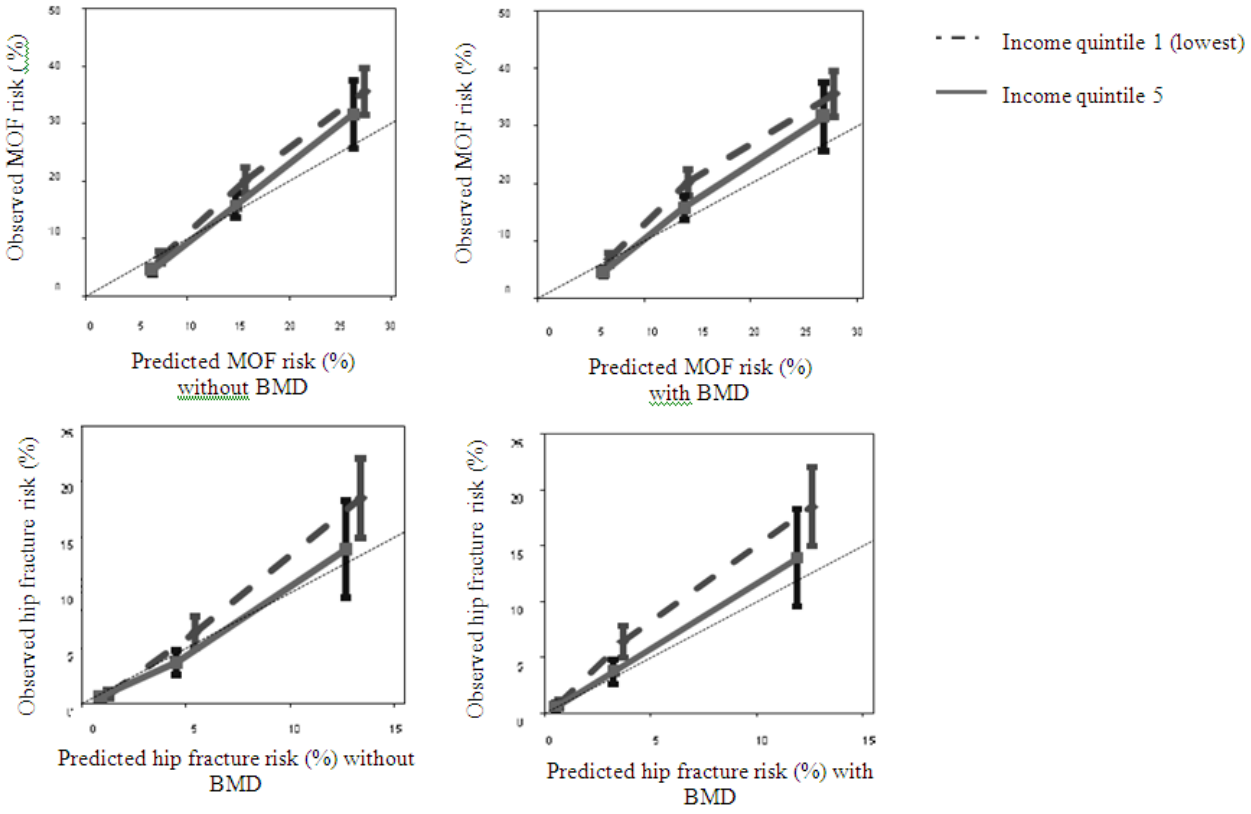


Figure 3: Predicted* *vs.* observed 10-year fracture risk (%), without adjustment for competing risk of mortality by risk category (low <10%, moderate 10-19%, high risk ≥20%) for income quintiles 1 and 5, presented for (a) major osteoporotic fracture (MOF), and (b) hip fracture. Error bars represent 95% confidence intervals.



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