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ORIGINAL ARTICLE

Effect of FRAXplus adjustments on fracture risk reclassification in older Swedish women—results from the SUPERB-study

M. Zoulakis[1,2] · H. Johansson[1] · N. C. Harvey[3,4] · K. F. Axelsson[1] · H. Litsne[1] · L. Johansson[1,5] · M. Schini[6] · L. Vandenput[1] · E. V. McCloskey[7,8] · J. A. Kanis[8] · Mattias Lorentzon[1,2]

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Abstract

Summary FRAXplus® facilitates adjustment of FRAX® fracture probabilities for additional clinical risk factors. This study examined how FRAXplus adjustments affect the proportion of older Swedish women eligible for treatment at a major osteoporotic fracture (MOF) probability intervention threshold (IT) ≥ 26%.

Background FRAXplus enables adjustments based on additional clinical information, such as recency of osteoporotic fractures, high-dose oral glucocorticoids, T2DM duration, lumbar spine (LS) bone mineral density (BMD), trabecular bone score (TBS), falls in the previous year, and hip axis length. We aimed to determine how these adjustments alter treatment eligibility in older Swedish women.

Methods Ten-year fracture probabilities with femoral neck BMD were calculated using FRAX and adjusted by FRAXplus in the SUPERB cohort of 3028 Swedish women aged 75 to 80 years. Clinical risk factors (CRFs) and outcomes were collected via questionnaires and national registers over 8 years, with incident X-ray-verified MOFs. FRAXplus adjustments were applied one factor at a time; if multiple were available, the most influential factor was used. Net reclassification improvement (NRI) was calculated.

Results Overall, 90% ($n = 2723$) had their 10-year MOF probability adjusted upwards, with a mean (± SD) change of 4.25% (5.12%). Common adjustments included HAL (31%), TBS (23%), falls (20%), LS BMD (8%), and recent fracture (5%). Similar patterns were observed for hip fracture probabilities. Among those below the IT using FRAX alone, 1785 remained below, with 365 (20.4%) experiencing incident MOFs. Of 339 women uplifted above the IT using FRAXplus, 119 (35.1%) sustained incident MOFs. Among 904 above the IT with both FRAX and FRAXplus, 324 (35.8%) experienced incident MOFs. The NRI was 4.82% (95% CI: 1.87–7.77%; $p < 0.01$).

Conclusions FRAXplus improved risk stratification, with a significant proportion of older Swedish women having their fracture probabilities uplifted above the IT, more accurately reflecting their elevated fracture risk, thereby enhancing the utility of risk assessment tools and improving patient management.

Keywords Fracture risk prediction · FRAXplus · Hip fracture · Major osteoporotic fracture (MOF) · Osteoporosis · Swedish woman

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and fracture risk [1]. Fractures are associated with significant morbidity, mortality, and healthcare costs [2]. Therefore, identifying individuals at high risk of fractures and initiating appropriate preventive measures is a key public health goal [3].

The FRAX® tool is a widely used clinical algorithm that estimates the 10-year probability of major osteoporotic fractures (MOFs), defined as fractures of the hip, spine, forearm, or humerus, in individuals based on their age, sex, body mass index (BMI), and several clinical risk factors [4]. The FRAX tool can be used to guide treatment decisions by comparing the estimated fracture probabilities with intervention thresholds (ITs), which are the levels

Extended author information available on the last page of the article

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of fracture risk above which pharmacological intervention is recommended [5].

The FRAX tool was designed to be simple and practical, using a limited number of risk factors that are easily measured or self-reported, and that have a strong and independent association with fracture risk. Furthermore, the risk factors included in FRAX were selected to reflect modifiable aspects of fracture risk that could benefit from pharmacological or non-pharmacological interventions.

However, FRAX has some limitations [6–8], as it does not capture the full range and diversity of fracture risk and does not integrate other well-established risk factors for fractures [8]. For instance, FRAX does not account for some key additional risk factors such as a history of falls or for the dose–response relationship between some of the included risk factors and fracture risk, such as exposure to glucocorticoids.

To address some of the limitations, FRAXplus® was recently developed. FRAXplus allows for univariable adjustment of the FRAX probabilities by using additional clinical information, such as the number, type, and recency of previous fractures [9], differences in BMD between lumbar spine and femoral neck [10], or the dose of glucocorticoids [11]. The FRAXplus adjustments are based on empirical data from cohort studies and are applied as multipliers to the original FRAX probabilities.

In this study, we aimed to examine the impact of using FRAXplus adjustments on the proportion of older Swedish women eligible for treatment. We utilized a MOF probability intervention threshold of ≥ 26% and for hip fracture ≥ 9.8%, representing the risk in a 70-year-old Swedish woman with a previous fractur, threshold derivations recommended by the National Osteoporosis Guideline Group (NOGG) in the UK [5].

Methods

Study subjects

This study utilized data from the Sahlgrenska University Hospital Prospective Evaluation of Risk of Bone Fractures (SUPERB) study, a population-based cohort conducted in the greater Gothenburg area of Sweden. The primary aim was to identify predictors of fragility fractures. Between March 2013 and May 2016, 3028 women aged 75 to 80 years were randomly selected from the Swedish national population register. Detailed characteristics of the cohort have been previously reported [12, 13].

Out of 6832 women who received formal invitations via letter followed by telephone contact, 436 women (6.4%) met exclusion criteria, which included bilateral hip replacement, non-ambulatory status (aided or unaided), and inability to communicate in Swedish. An additional 3368 women (52.6%) declined participation. Consequently, 3028 women were enrolled in the SUPERB study, yielding an inclusion rate of 47.4%. The study protocol was approved by the Regional Ethical Review Board in Gothenburg, and all participants provided informed consent prior to participation. Examinations were conducted at the Department of Geriatrics, Sahlgrenska University Hospital in Mölndal, Sweden. Standardized equipment was used to measure participants' height and weight.

Questionnaires

Participants completed a standardized questionnaire to collect information on medical history, medication use, and FRAX clinical risk factors (CRFs). The FRAX CRFs included previous fractures (sustained after age 50 years at any location except the skull and face), parental history of hip fracture, current smoking status, oral glucocorticoid use, rheumatoid arthritis, secondary osteoporosis (conditions such as type 1 diabetes mellitus, hyperthyroidism, chronic liver disease, inflammatory bowel disease, or premature menopause), and excessive alcohol consumption (three or more units per day).

Medical register data

Data on oral glucocorticoid and diabetes prescription medications were obtained from the Swedish Prescribed Drug Register. Diagnosis of type 1 diabetes related to secondary osteoporosis was acquired using ICD codes from the Swedish National Patient Register.

Dual-energy X-ray absorptiometry (DXA)

Areal bone mineral density (aBMD), body composition, and vertebral fracture status were evaluated using dual-energy X-ray absorptiometry (DXA). The majority of participants ($n = 2995$) were scanned using a Hologic Discovery A device, with data analyzed using the manufacturer's software. A subset ($n = 33$) was scanned using a Hologic QDR 4500/A Delphi DXA device, with cross-calibration performed to ensure consistency [14]. Scans were conducted at the femoral neck, total hip, and lumbar spine (L1–L4), yielding coefficients of variation of 1.3%, 0.8%, and 0.7%, respectively. The average of L1 to L4, excluding any vertebrae with fractures, was used to compute the trabecular bone score (TBS).

Incident fractures

Participants were followed from baseline for fracture incidence until March 2023, with all fracture events occurring after the baseline DXA scan documented. Information was obtained

from the regional X-ray archives of the Västra Götaland region, encompassing 49 municipalities around Gothenburg. Research nurses reviewed radiology reports up to March 2023, and any radiographs with uncertain fracture diagnoses were examined by an experienced orthopedic surgeon. Fractures were categorized into two groups: (1) MOF, including hip, clinical spine, wrist, and humerus fractures; (2) hip fractures.

FRAX

The 10-year fracture probability for hip fracture and MOF was calculated using the FRAX tool with Sweden as the reference country, incorporating standard FRAX adjustments for age, weight, height, CRFs, and femoral neck BMD. The CRFs included history of previous fractures, parental history of hip fracture, current smoking status, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and daily alcohol consumption of three or more units.

FRAXplus model

FRAXplus allows the integration of additional risk factors not accounted for in the initial tool. The current FRAXplus model accommodates univariable adjustments, allowing adjustment for one additional risk factor, for variables such as recency and site of fractures, fall history within the past year, dosage of corticosteroid, hip axis length (HAL), duration of type 2 diabetes mellitus (T2DM), TBS, and discrepancies in lumbar spine–hip T-score (ΔLS-FN). The input of these variables provides a multiplication factor to adjust the 10-year probabilities of MOF and hip fractures.

In general, FRAXplus allows for the selection of any risk factor and can both increase and decrease the probability of fracture risk. However, in this study (SUPERB), we chose to apply only the most impactful risk factor per individual and focused solely on increasing the probability. For example, if a participant had a recent spine fracture (0–1 months) and two falls in the previous year, the FRAX scores would be adjusted based solely on fracture recency, as it carries the highest multiplication factor of 1.60 versus 1.23 for two falls (with BMD in the model). This approach was taken because we believed it aligns with clinical practice, where the goal is to determine how high the risk could become when adding FRAXplus variables.

Recency and site of fracture

In cases of prior fractures, "recency" refers to the time elapsed since the last fracture, and "site" refers to the anatomical location of the previous fracture. The fracture probabilities for different scenarios of prior fracture were calculated using data from the Reykjavik study as previously described [9]. An adjustment ratio for each scenario was derived to modify the FRAX probabilities. For brevity, a fracture within the previous two years is termed a "recent fracture" unless otherwise noted. The ratio used for multiplication also depends on the time elapsed since the "recent fracture," categorized as 0–1 month, 1–6 months, 6–12 months, and 12–24 months. Five categories of sentinel fractures were defined: clinical vertebral fractures, humeral fractures, forearm fractures, hip fractures, and other osteoporotic fractures.

Exposure to oral glucocorticoids

To assess the impact of oral glucocorticoid use on fracture risk, we calculated the average daily dose each patient received during their treatment period. The total amount of prednisolone (or equivalent glucocorticoid) prescribed to each patient in milligrams was divided by the number of days treated. Patients were classified into three groups based on their average daily dose: low dose (<2.5 mg/day), medium dose (2.5–7.5 mg/day), and high dose (>7.5 mg/day). We modified the FRAX probabilities according to the average daily glucocorticoid dose, assuming that the medium dose (2.5–7.5 mg/day) provided the probabilities as seen in FRAX. The FRAX hazard ratios were adjusted upward for the high dose and downward for the low dose, using the complex age-adjusted approach described in a previous publication [15].

Duration of type 2 diabetes (T2DM)

The influence of T2DM on fracture risk was assessed by categorizing diabetes duration into none (reference), less than 5 years, 5–10 years, and more than 10 years. For FRAX without BMD, secondary osteoporosis should be ticked; otherwise, no adjustment was made. For FRAX with BMD, the ratios from Leslie et al. [16] were used.

TBS, falls, and hip axis length (HAL)

Adjustments to the FRAX probabilities were applied based on TBS values, the number of falls (none, 1 fall, 2 falls, ≥ 3 falls), and HAL, using correction factors derived from the Manitoba cohort [11, 17, 18]. The HAL adjustment was based on the deviation of individual HAL measurements from the mean value.

BMD discordance

The difference in BMD T-score between the lumbar spine (LS) and femoral neck (FN; ΔFN-LS) was calculated

by subtracting the LS T-score from the FN T-score. The impact of this discordance on FRAX probabilities was determined by a previous analysis in the Manitoba cohort, resulting in a multiplier of $1.12^{\Delta \text{FN-LS}}$ used to adjust the FRAX probability with BMD [19].

Net reclassification improvement (NRI)

We examined reclassification rates and categorical net reclassification improvement (NRI) by applying FRAXplus adjustments to FRAX-based probabilities for MOF, using fixed intervention thresholds (IT) above 70 years, as recommended by the National Osteoporosis Guideline Group (NOGG) [5]. An IT for MOF of ≥ 26% represents the risk in a 70-year-old Swedish woman with a previous fracture. NRI was computed separately for individuals with and without incident fractures, as well as for overall reclassification improvement [20, 21]. For participants who experienced a fracture during follow-up (events), correct reclassification was defined as moving to a higher FRAX risk category and incorrect reclassification as moving to a lower category. Conversely, for those without a fracture (nonevents), correct reclassification was defined as moving to a lower risk category and incorrect reclassification as moving to a higher category. Positive values of NRI indicate improved risk classification, while negative values suggest inferior prediction. An asymptotic test of significance for the null hypothesis of NRI = 0 was conducted based on the multinomial distribution.

Other statistical analysis

Descriptive statistics were employed to summarize baseline characteristics and fracture incidence within the study population. Continuous variables are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution assessed by the Shapiro–Wilk test. Categorical variables are summarized as counts and percentages. Group differences between participants with and without incident MOF or hip fractures were evaluated. For continuous variables, independent samples *t*-tests were used for normally distributed data, while the Mann–Whitney *U* test was applied for non-normal distributions. Categorical variables were compared using the chi-square test or Fisher's exact test when expected frequencies < 5.

Receiver operating characteristics (ROC) curve analysis was performed to evaluate and compare the discriminative ability of the original FRAX model and the FRAXplus model in predicting incident MOF and hip fractures. The area under the ROC curve (AUC) was calculated for each model, with 95% confidence intervals (95% CIs) obtained using the DeLong method. Comparisons between AUCs were conducted using the method described by DeLong et al., allowing for statistical assessment of differences in model performance. Calibration was evaluated visually using decile-based plots comparing observed and predicted risks for both MOF and hip fractures. Predicted probabilities from FRAX and FRAXplus were grouped into deciles, and observed event rates were plotted against the mean predicted risk per decile, with 95% Wilson score confidence intervals and a dashed line for perfect calibration.

Missing data for variables included in the FRAXplus such as HAL, TBS, fall history, diabetes duration, and recency/site of fracture were handled by including all study subjects in the calculations, but missing data on individual variables did not contribute to the models. For information on the number of missing observations, see Table 1. All statistical tests were two-tailed, and a *p*-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 29 and R version 2024.04.02.

Results

Baseline characteristics

The analysis revealed that participants who experienced incident MOF were generally older and had lower body mass index (BMI) compared to those without fractures. They had a higher prevalence of previous fractures, including recent and vertebral fractures (Table 1 and Supplemental Table 1). Smoking and self-reported falls were more common among those with incident MOF, with a notable increase in the number of falls reported. BMD T-scores at the femoral neck and lumbar spine were lower in participants with incident MOF, and their trabecular bone scores were lower (Table 1). Similarly, participants who experienced incident hip fractures were older and had lower BMI than those without hip fractures. They exhibited a higher prevalence of previous fractures, particularly vertebral fractures, and reported more falls. Smoking was also more prevalent in this group. These participants had lower femoral neck BMD T-scores and differences in HAL (Table 1).

Overall, higher FRAX probabilities, both with and without BMD, were observed in participants who experienced incident fractures (Supplemental Table 2).

Analyses of the FRAXplus model

The FRAXplus model (which raises the FRAX 10-year probability for the most influential FRAXplus risk factor) significantly modified the 10-year fracture probabilities for the majority of women by incorporating additional clinical risk factors not accounted for in the original FRAX model. Out of 3028 women, 2723 (90%) had their

Table 1 Baseline characteristics

Baseline characteristics	All ($n=3028$)	Incident MOF ($n=808$)	No incident MOF ($n=2220$)	p	Incident HIP ($n=238$)	No incident HIP ($n=2790$)	p
Age (years)	77.8 ± 1.6	78.0(1.6)	77.7 (1.6)	< 0.001	78.1 (1.6)	77.8 (1.6)	0.002
BMI (kg/m^2)	26.3 ± 4.4	26.2 (4.4)	26.3 (4.5)	< 0.001	25.4 (4.1)	26.3 (4.4)	0.002
Previous fracture	1117 (36.9)	379 (46.9)	738 (33.2)	< 0.001	115 (48.3)	1002 (35.9)	< 0.001
Recent fractures*	193 (6.4)	73 (9.0)	120 (5.4)	< 0.001	21 (8.8)	172 (6.2)	0.11
Glucocorticoid[1]	103 (3.4)	31 (3.8)	72 (3.2)	0.43	5 (2.1)	98 (3.5)	0.25
Dose				0.59			0.17
Low dosage	7 (0.2)	3 (0.4)	4 (0.2)		0 (0)	7 (0.2)	
Medium dosage	41 (1.4)	13 (1.6)	28 (1.3)		2 (0.9)	39 (1.4)	
High dosage	40 (1.3)	11 (1.4)	29 (1.3)		1 (0.4)	39 (1.4)	
Rheumatoid arthritis	120 (4.0)	40 (5.0)	80 (3.6)	0.09	11 (4.6)	109 (3.9)	0.59
Secondary osteoporosis[2]	787 (26.0)	204 (25.2)	583 (26.3)	0.57	62 (26.1)	725 (26.0)	0.98
Parental history	533 (17.6)	155 (19.2)	378 (17.0)	0.17	50 (21.0)	483 (17.3)	0.15
Smoking	158 (5.2)	49 (6.1)	109 (4.9)	0.21	24 (10.1)	134 (4.8)	< 0.001
Alcohol[3]	17 (0.6)	4 (0.5)	13 (0.6)	0.77	1 (0.4)	16 (0.4)	076
Self-reported falls	896 (29.6)	284 (35.1)	612 (27.6)	< 0.001	90 (37.8)	806 (28.9)	< 0.01
Number of falls				< 0.001			0.07
0	2132 (70.4)	524 (64.9)	1608 (72.4)		148 (62.2)	1984 (71.1)	
1	470 (16.0)	135 (16.7)	335 (15.1)		40 (16.8)	430 (15.4)	
2	343 (11.6)	117 (14.5)	226 (10.2)		35 (14.7)	308 (11.0)	
3+	83	32 (4.0)	51 (2.3)		15 (6.3)	68 (2.4)	
FN BMD T-score	− 1.64 ± 0.89	− 1.90 ± 0.78	− 1.54 ± 0.90	< 0.001	− 2.10 ± 0.78	− 1.60 ± 0.89	< 0.001
LS BMD T-score[a]	− 0.94 ± 1.54	− 1.20 ± 1.40	− 0.85 ± 1.60	< 0.001	− 1.07 ± 1.40	− 0.93 ± 1.55	0.20
Trabecular bone score[b]	1.21 ± 0.11	1.19 ± 0.11	1.22 ± 0.11	< 0.001	1.20 ± 0.11	1.21 ± 0.11	0.08
Hip axis length[c]	104.5 ± 5.9	104.9 ± 6.0	104.8 ± 5.8	0.50	106.0 ± 6.0	104.7 ± 5.9	< 0.001
Type 2 diabetes	294 (9.8)	81 (10.0)	213 (9.6)	0.72	24 (8.2)	214 (7.8)	0.84
Diabetes duration[d]				0.47			1
0–5 years	90 (3.0)	22 (2.7)	68 (3.1)		7 (2.9)	83 (3)	
5–10 years	143 (4.7)	45 (5.6)	98 (4.4)		11 (4.6)	132 (4.7)	
10+years	12 (0.4)	2 (0.2)	10 (0.5)		1 (0.4)	11 (0.4)	

Baseline characteristics are presented as mean ± standard deviation (SD) for continuous variables and as the number of subjects with group percentages in parentheses for categorical variables

FX fracture, l, *FN and LS BMD* femoral neck and lumbar spine bone mineral density

Missing values $a=19$, $b=28$, $c=13$, $d=49$

[a]Current glucocorticoid usage

[b]Secondary osteoporosis includes: type 1 diabetes mellitus, hyperthyroidism, malnutrition, osteogenesis imperfecta, chronic liver disease, premature menopause, and hyperparathyroidism

[c]Alcohol intake more than 3 units/day

*Number of recent fractures (< 2 years) and locations are presented in Supplementary Table 1

10-year probability of MOF uplifted by the FRAXplus model; a similar pattern was observed for the 10-year hip fracture probabilities. The most common risk factors that increased fracture probabilities were HAL, TBS, fall history, LS BMD discordances, and recent fractures when the highest probability was chosen. These factors elevated the probability in 31%, 23%, 20%, 8%, and 5% of the women, respectively (Fig. 1). A comparison of the original FRAX and FRAXplus models with and without BMD adjustments is shown in (Fig. 2).

MOF

The study population was divided into three groups based on the 10-year MOF probabilities using FRAX and FRAXplus: those who were reclassified from below to above the

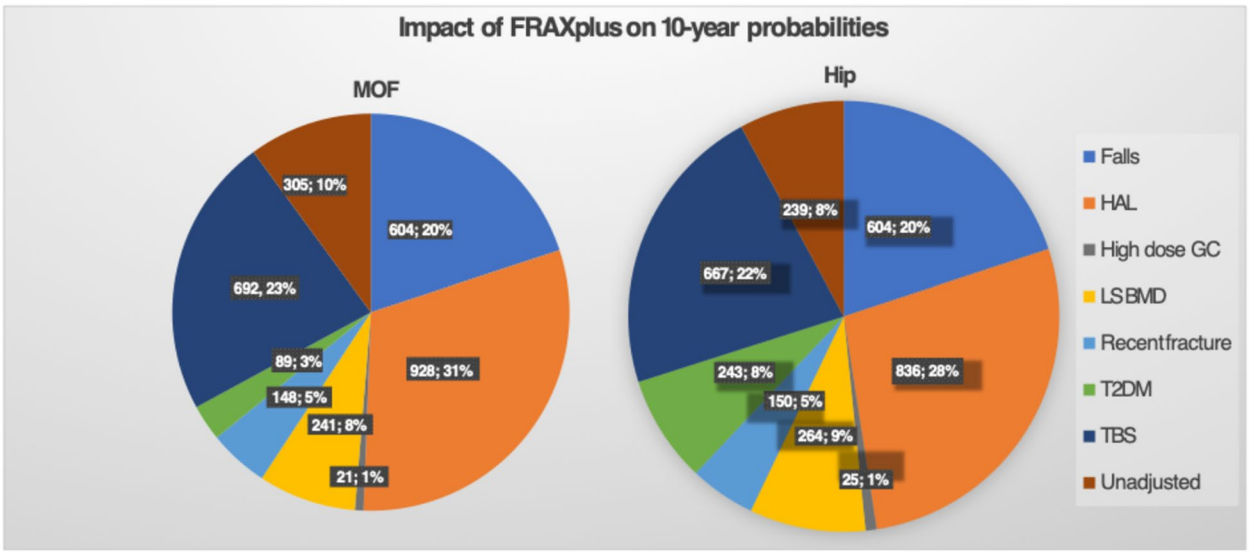

Fig. 1 The impact of FRAXplus on 10-year MOF (left) and hip fracture (right) probabilities in older Swedish women in the SUPERB-cohort

IT ("uplifted above IT"), those who remained below and those above the IT even after FRAXplus adjustment. A total of 339 women (11.2%) had their 10-year MOF probability reclassified from below to above the IT using FRAXplus. Within this group, 119 women (35.1%) experienced an incident MOF during follow-up. The incidence of MOF was higher in this group compared to those who remained below the IT. Out of the 2124 women who were below the IT using FRAX alone, 1785 remained below the IT after FRAXplus adjustment. Among these women, 365 (20.4%) experienced an incident MOF. There were 904 women who were above the IT using FRAX alone and remained above the IT after FRAXplus. Within this group, 324 women (35.8%) experienced an incident MOF. The incidence of MOF was similar between the FRAX and FRAXplus models for these women. The three groups, along with the entire cohort population, are presented in (Fig. 3).

The NRI was 4.82% (95% confidence interval CI: 1.87–7.77; $p < 0.01$), with an NRI of + 14.73% for events and − 9.91% for nonevents, demonstrating a significant improvement in risk stratification with the FRAXplus model (Fig. 4).

Hip fracture

The study population was similarly categorized based on a 10-year hip fracture threshold of 9.8%. A total of 216 women (7.1%) were reclassified from below to above the threshold using FRAXplus, of whom 24 (11.1%) experienced a hip fracture. Among the 1703 women who remained below the threshold, 73 (4.3%) sustained a hip fracture, while 1109

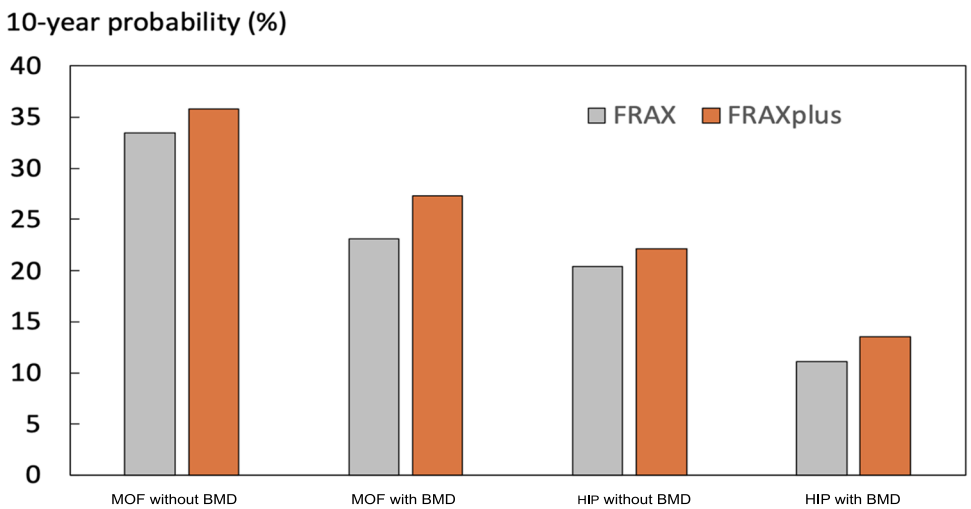

Fig. 2 10-year probabilities according to FRAX (grey) and FRAXplus (orange) for MOF and hip fracture with and without femoral neck BMD adjustments in older Swedish women in the SUPERB-cohort

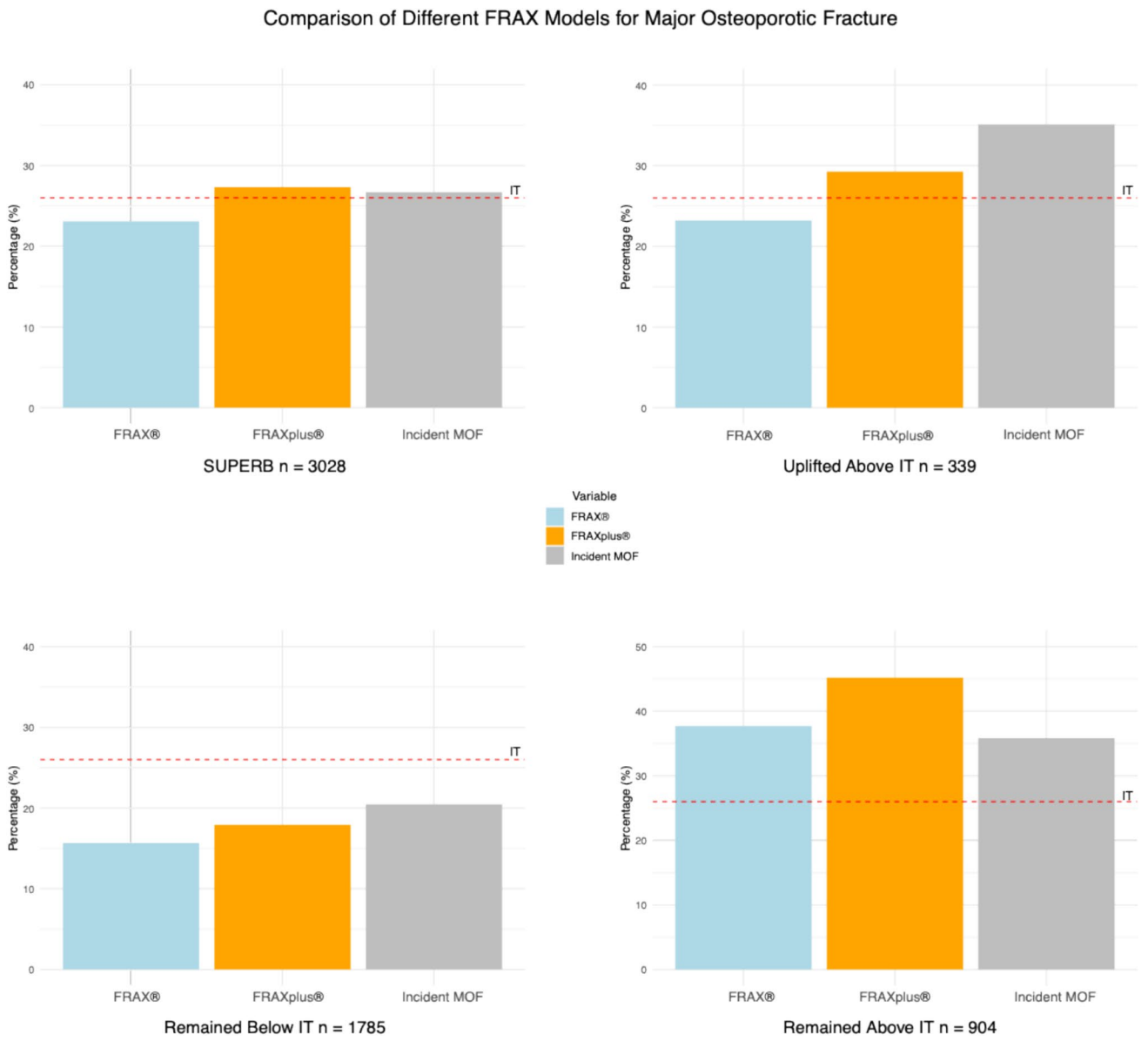

Fig. 3 Comparison of FRAX models (original FRAX and FRAXplus) for predicting major osteoporotic fracture (MOF) across groups reclassified by risk category: uplifted, remained below IT, remained above IT, and all adjusted with FRAXplus model. The red dashed line indicates the intervention threshold (IT)

women were above the threshold under both FRAX and FRAXplus, with 141 (12.7%) experiencing a hip fracture. The NRI for hip fractures was 3.2% (95% CI: − 0.9 to 7.4; $p = 0.13$), reflecting + 10.1% for events and − 6.9% for non-events, indicating a modest improvement in reclassification using FRAXplus.

ROC analysis

For both MOF and hip fractures, the FRAXplus models showed improved AUC values compared to the original FRAX probabilities. For MOF with BMD included, the AUC increased from 0.625 (95% CI: 0.603–0.647) for the original FRAX model to 0.631 (95% CI: 0.609–0.653) for the FRAXplus model ($\chi 2 = 2.07$, $p = 0.038$). For models without BMD, the AUC increased from 0.570 (95% CI: 0.547–0.593) for the original FRAX to 0.577 (95% CI: 0.554–0.600) for the FRAXplus model ($\chi 2 = 2.35$, $p = 0.019$). For hip fractures, a significant improvement was observed only in models without BMD, with the AUC increasing from 0.591 (95% CI: 0.554–0.628) for the original FRAX to 0.601 (95% CI: 0.564–0.637) for the FRAXplus ($\chi 2 = 2.24$, $p = 0.025$). In contrast, the increase for hip fracture prediction with BMD, from 0.659 (95% CI: 0.625–0.693) to 0.664 (95%

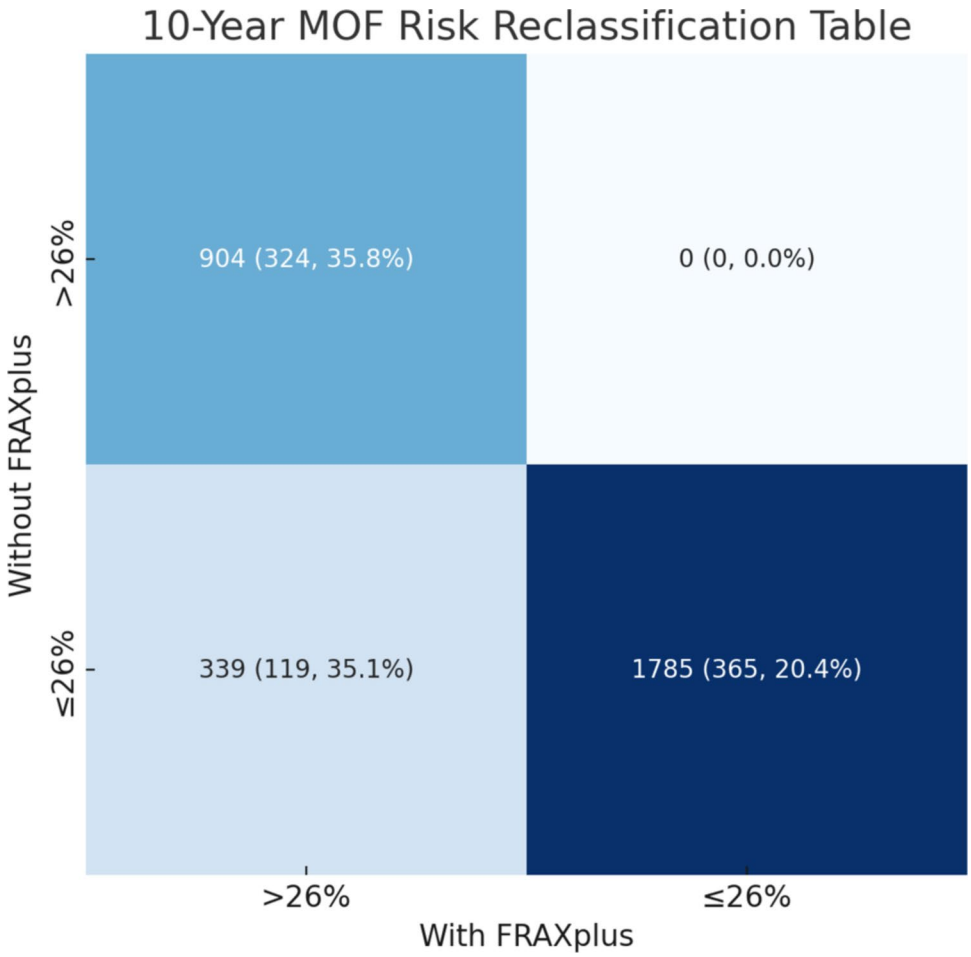

Fig. 4 The reclassification of women based on 10-year probabilities of major osteoporotic fracture (MOF) with and without FRAXplus adjustments. Values in the table represent total counts, number of fractures (cases) in parentheses, and percentages of fractures

CI: 0.631–0.698), was not statistically significant ($\chi 2 = 1.39$, $p = 0.165$) (Supplemental Table 3).

Calibration

Calibration plots for hip and major osteoporotic fracture risk are provided in Supplementary Fig. 1, showing overall agreement between predicted and observed risk across most deciles for both Original FRAX and FRAXplus models, with some overestimation by both models at higher predicted probabilities (e.g., decile 10). The plots include 95% confidence intervals, highlighting greater uncertainty in lower deciles for hip fractures due to fewer events.

Discussion

This study evaluated the efficacy of the FRAXplus prediction tool in reclassifying individuals from below to above the intervention threshold by incorporating additional risk factors not available in the original FRAX model in older Swedish women. Using an intervention threshold of 26% for major osteoporotic fractures (MOF), equivalent to a woman aged 70 years with a prior fragility fracture as recommended by the National Osteoporosis Guideline Group (NOGG), we assessed the tool's ability to improve treatment decisions by considering additional clinical risk factors often overlooked in the standard fracture risk assessments.

Our principal findings indicate that the application of the FRAXplus model resulted in an upward adjustment of 10-year major osteoporotic fracture probabilities for 90% of women in the cohort. Notably, FRAXplus reclassified 339 women (11.2%) from below to above the intervention threshold, more accurately reflecting their elevated fracture risk, compared to the original FRAX probabilities. The calculated FRAXplus probabilities closely matched the actual observed incidence of MOF (Fig. 3), and the NRI was 4.8%, demonstrating a meaningful enhancement in risk stratification.

The inclusion of additional risk factors in FRAXplus enhances fracture risk prediction by capturing nuances not considered in the original FRAX model. By identifying more women who could benefit from pharmacological or preventive interventions, FRAXplus has the potential to ameliorate the treatment gap in osteoporosis management. The tool's ability to reclassify women previously considered low risk underscores its value in refining treatment decisions

and potentially influencing the choice of pharmacological treatments. Specifically, women with severe osteoporosis or poor bone microarchitecture—who may not respond optimally to antiresorptive therapies—could be identified for osteoanabolic treatments like teriparatide, abaloparatide, or romosozumab [3]. Osteoanabolic therapies have shown greater efficacy [22, 23] in reducing fracture risk but come with higher costs. Therefore, FRAXplus could aid in selecting appropriate candidates, optimizing both treatment efficacy and cost-effectiveness.

As illustrated in Fig. 1, the predominant upwards adjustments in the FRAXplus model were attributed to TBS, HAL, and self-reported falls. These three factors collectively accounted for approximately 80% of all FRAXplus adjustments. The prominence of these factors is noteworthy because they are readily obtainable through medical history and DXA scans, enhancing the practicality of FRAXplus in clinical settings.

Several limitations of this study should be acknowledged. First, the level of evidence for FRAXplus is lower than that of the original extensively validated FRAX model. The adjustments for each additional risk factor are based on limited cohorts, such as the Reykjavik and Manitoba studies, which have not been extensively validated across the numerous cohorts included in the original FRAX except for TBS adjustments [24]. This highlights the need for additional research and external validation to confirm the generalizability of FRAXplus across diverse age groups, settings, and populations before its risk factors can be considered for incorporation in future iterations of FRAX, currently being developed [6]. Second, the relatively modest AUC performance observed in this study is likely a consequence of the restricted age range (75–80 years) that limits variability and prediction due to age [25]. Although FRAXplus achieved a statistically significant increase in AUC, the improvement was modest. In a cohort of relatively narrow heterogeneity, such small changes in AUC may not fully capture clinically meaningful reclassifications around treatment thresholds [21]. Accordingly, the net reclassification improvement (NRI) provides complementary insights, reflecting how individuals are more accurately shifted into clinically relevant risk categories. Calibration plots indicated general agreement between predicted and observed risks across most deciles, with some overestimation observed at higher predicted probabilities. These patterns are not unexpected in a relatively homogeneous older population and do not detract from the improved reclassification performance observed with FRAXplus.

Third, the follow-up duration was approximately 8 years, shorter than the 10-year probability estimate provided by FRAX, which may affect the accuracy of long-term risk predictions. Fourth, while the sensitivity of fracture risk prediction might be improved by utilizing FRAXplus, the specificity may be limited. This study is designed to assign a higher score to those with an additional risk factor, which could lead to overestimation of risk in some cases. While the unidirectional adjustment aligns with the goal of identifying high-risk individuals, it may bias reclassification metrics such as the NRI by omitting protective effects from variables like TBS, HAL, and the absence of falls. Future work should explore bidirectional adjustment models and multivariable adjustments to more accurately assess both discrimination and reclassification performance. Finally, the clinical utility and cost-effectiveness of FRAXplus were not assessed in this study. The inclusion of additional risk factors, although enhancing prediction accuracy, may necessitate extra equipment, time, and cost. For instance, measuring HAL requires specialized software for hip DXA scans, and assessing TBS necessitates software for spine DXA image analysis. These requirements could hinder the widespread adoption of FRAXplus, especially in primary care settings where resources may be limited.

The study also has strengths. A key strength is the inclusion of a large, population-based cohort of older Swedish women, providing a robust foundation for our findings. The substantial number of incident fractures observed provides sufficient statistical power of the study. Additionally, the verification of fractures through X-ray imaging adds a reliable layer of accuracy to the outcomes. Detailed information on all FRAX and FRAXplus clinical risk factors further strengthens the comprehensiveness of our analysis.

In conclusion, this study demonstrates that FRAXplus significantly improves fracture risk prediction in older women by incorporating additional risk factors absent from the standard FRAX model. These findings suggest that FRAXplus could play a crucial role in narrowing the treatment gap in osteoporosis management by identifying more women who may benefit from preventive interventions or advanced pharmacological treatments.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-025-07588-w

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Data availability Data cannot be made publicly available for ethical and legal reasons. Such information is subject to legal restrictions according to national legislation. Specifically, in Sweden, confidentiality regarding personal information in studies is regulated in the Public Access to Information and Secrecy Act (SFS 2009:400). The data underlying the results of this study might be made available upon request, after an assessment of confidentiality. There is thus a possibility to apply to get access to certain public documents that an authority holds. In this case, the University of Gothenburg is the specific authority that is responsible for the integrity of the documents with research data. Questions regarding such issues can be directed to the head of the

Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. Contact information can be obtained from medicin@gu.se.

Declarations

Conflict of interest JA Kanis led the team that developed FRAX as director of the WHO Collaborating Centre for Metabolic Bone Diseases; he is a director of Osteoporosis Research Ltd that maintains FRAX. EV McCloskey, WD Leslie, M Lorentzon, NC Harvey, M Schini, E Liu, L Vandenput, and H Johansson are members of the FRAX team. JA Kanis, NC Harvey, and EV McCloskey are members of the advisory body to the National Osteoporosis Guideline Group. M Schini received funding for her fellowship from the Medical Research Council Centre of Excellence for Musculoskeletal Ageing, from the Osteoporosis 2000 support group, and from Roche Diagnostics and honoraria from MA Health care and Kyowa Kirin—all unrelated to this work.
Dr. Johansson received lecture fees from UCB Pharma outside the scope of this work. Dr. Axelsson received personal fees from Amgen, Meda/Mylan, and Lilly, also outside the scope of this work.EV McCloskey has received consultancy/lecture fees/grant funding/honoraria from AgNovos, Amgen, AstraZeneca, Consilient Healthcare, Fresenius Kabi, Gilead, GSK, Hologic, Internis, Lilly, Merck, Novartis, ObsEva, Pfizer, Radius Health, Redx Oncology, Roche, Sanofi Aventis, UCB, ViiV, Warner Chilcott and I3 Innovus. M. Lorentzon has received lecture fees from Amgen, Astellas, Meda, Jansen-Cilag, Medison Pharma, Gedeon Richter, UCB Pharma, and consulting fees from Amgen, UCB Pharma, Medac, Gedeon Richter, Pharmacosmos, and Parexel International, all outside the presented research. NC Harvey has received consultancy/lecture fees/honoraria/grant funding from Alliance for Better Bone Health, Amgen, MSD, Eli Lilly, Ra- dius Health, Servier, Shire, UCB, Kyowa Kirin, Consilient Healthcare, Theramex, and Internis Pharma. No other conflicts of interest were reported.

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Drs Zoulakis and Lorentzon had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Authors and Affiliations

M. Zoulakis[1,2] · H. Johansson[1] · N. C. Harvey[3,4] · K. F. Axelsson[1] · H. Litsne[1] · L. Johansson[1,5] · M. Schini[6] · L. Vandenput[1] · E. V. McCloskey[7,8] · J. A. Kanis[8] · Mattias Lorentzon[1,2]

✉ Mattias Lorentzon
mattias.lorentzon@medic.gu.se

[1] Sahlgrenska Osteoporosis Centre, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[2] Region Västra Götaland, Geriatric Medicine Clinic, Sahlgrenska University Hospital, Mölndal, Sweden

[3] MRC Lifecourse Epidemiology Centre, University of Southampton, Southampton, UK

[4] NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK

[5] Department of Orthopedics, Sahlgrenska University Hospital, Mölndal, Sweden

[6] Mellanby Centre for Musculoskeletal Research, Division of Clinical Medicine, School of Medicine & Population Health, University of Sheffield, University of Sheffield, Sheffield, UK

[7] MRC and Arthritis Research UK Centre for Integrated Research in Musculoskeletal Ageing, Mellanby Centre for Musculoskeletal Research, Sheffield, UK

[8] Centre for Metabolic Bone Diseases, University of Sheffield, Sheffield, UK