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ORIGINAL ARTICLE

Revised Swedish FRAX models and the establishment of age-dependent intervention thresholds

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Abstract

Summary We developed a revised FRAX® model for Sweden, derived from recent incidence data on fractures, mortality, and origin of birth, and defined age-dependent intervention thresholds.

Purpose Since the development of the Swedish FRAX model in 2008, fracture incidence patterns have changed. The primary aim of this study was to develop a revised FRAX model, based on region of birth, and updated incidences for death and fracture for Sweden. A secondary aim was to define age-dependent intervention thresholds.

Methods Based on national registries, all persons from the age of 40 years living in Sweden between 2005 and 2021 were included. Yearly age- and sex-standardized incidences of hip fracture and major osteoporotic fracture (MOF) were calculated and presented per geographic region of birth. Hip fracture and MOF incidences from 2019 to 2021 were used to create a revised FRAX model for Sweden. Two models, one for Swedish/Nordic-born individuals and one for non-Nordic-born, were developed. The revised FRAX models were compared with the previous FRAX model. Age-specific intervention thresholds were calculated and presented.

Results Compared with the previous FRAX model, the revised model yielded lower 10-year probabilities of both hip fracture and MOF in men and women. The non-Nordic models showed substantially lower probabilities across all age groups and sexes. Intervention thresholds for MOF without BMD ranged from a 10-year probability of 4.5% at age 40 years to 21.5% at age 70 years and older.

Conclusion The revised FRAX models provide more accurate fracture prediction in Sweden, with lower risk estimates for older people, but due to the introduction of age-dependent intervention thresholds, it is likely that more younger patients will become eligible for treatment in Sweden.

Keywords Fracture risk predicion model · FRAX · Major osteoporotic fracture · Hip fracture · Age-dependent intervention thresholds

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Introduction

Fractures are associated with significant morbidity, disability, mortality, and substantial health care costs [1]. Therefore, it is crucial to identify individuals at high risk of fracture in order to initiate effective preventive measures, such as treatment with osteoporosis medications [2–4]. The US Preventive Services Task Force recently concluded with moderate certainty that screening for osteoporosis to prevent osteoporotic fractures in postmenopausal women has moderate net benefit [5]. FRAX® is an internationally validated risk tool with nation-specific risk models covering more than 80% of the world population [6]. Community-based screening using FRAX is cost-saving in the UK [7].

The Swedish FRAX model, introduced in 2008, has been used in more than 589,000 calculations. It is based on data from radiologically verified hip, forearm, proximal humerus, and clinical vertebral fractures collected in Malmö in the mid-1990s [8]. Since then, the hip fracture incidence in Sweden has declined for both men and women [9, 10]. Over the past two to three decades, the proportion of residents in Sweden who were born abroad has risen from about 10% in the late 1990 s to 20% in 2022 [11]. This demographic shift has likely influenced fracture incidence rates, as first-generation immigrants in Sweden tend to retain the fracture risk profile of their country of origin, which is often lower than that of individuals born in Sweden [12, 13]. Sweden has suffered from the highest hip fracture incidence in Europe, emphasizing the importance of accurate risk prediction [14]. We hypothesized that recent rapid changes in population demographics have influenced fracture risk probabilities, warranting an update to the Swedish FRAX model.

This update also prompted us to propose revising the age-independent fixed intervention threshold of 20% for 10-year probability of MOF currently used in the Swedish Osteoporosis Society's current national osteoporosis guidelines [15]. The existing approach results in inequitable access to treatment, particularly among younger individuals who are at relatively high risk for their age [16], despite increasing evidence that interventions are effective across a wide range of fracture risk [17–20]. For example, several studies have demonstrated that annual or less frequent administration of zoledronate in postmenopausal women leads to significant reductions in vertebral fracture incidence and improvements in bone mineral density (BMD) compared with placebo controls. Notably, zoledronate treatment was effective regardless of baseline BMD or fracture risk status [21–23]. An alternative approach to setting intervention thresholds, first adopted by the UK National Osteoporosis Guideline Group (NOGG) [3], recommends age-dependent intervention thresholds that reflect the 10-year fracture probability for a woman of the same age with a prior fracture. Thus, probabilities increase with age, but plateau from the age of 70 years upwards [3].

The primary aim of this study was to develop a revised FRAX model for Sweden that accounted for recent changes in demographics and fracture incidence. The secondary aim was to use the revised FRAX model to define age-specific intervention thresholds which could be used for clinical decision-making in Sweden.

Methods

Study design

This nationwide study included all persons 40 years or over from 2005 to 2021 in Sweden and used multiple national registers to collect data on country of birth, deaths, and fractures. Incidences of hip fracture, MOF, and death were calculated for each year stratified by citizenship at birth. The study was approved by the Swedish Ethical Review Authority (2022-00796-01).

Data sources and variable definitions

The cohort was created by Statistics Sweden, and demographic data on citizenship at birth and date of death was retrieved from the Total Population Register. Information regarding fractures was retrieved from The National Patient Register, which includes ICD-10 hospital-based diagnoses from both inpatient and outpatient visits and reports a 95% positive predictive value for hip fracture [24]. Incident hip fracture was defined as fractures of the femoral head, neck, trochanter, or subtrochanteric part of the femur accompanied with a code for surgical procedure. Major osteoporosis fracture was defined as the first fracture of the spine, proximal humerus, wrist, or hip (a complete list of codes is shown in Table S1). In Sweden, all inhabitants are assigned a personal identification number at birth or at the time of immigration, enabling efficient linkage between the registers.

Incidence and time trends of hip fracture, MOF, and death 2005–2021

Incidences of hip fracture, MOF and death were calculated each year (2005–2021) for each person alive and not emigrated on January 1 st with censoring for death, emigration, and end of annual follow-up (December 31 st each year). Time trends in hip and MOF incidences were analyzed for women and men, for all, Swedish/Nordic-born and non-Nordic-born, using an extended Poisson

regression model with current age and current calendar year as piecewise linear functions with breaking points at 55 and 75 years of age and year 2010 and 2015, respectively, thereby allowing different slopes in-between.

Comparison of fracture incidences by region of birth: Swedish/Nordic vs. non-Nordic populations and original FRAX estimates

Due to an observed time trend, the three most recent years 2019–2021 were used as the reference for current incidence rates. As the incidence differed by citizenship at birth, subsequent analyses were stratified into Swedish and other Nordic (Denmark, Iceland, Finland, and Norway) versus non-Nordic citizenship at birth. Due to the known high level of undiagnosed and unreported vertebral fractures [25], the expected number of vertebral fractures was calculated using the known ratio of x-ray-verified vertebral fractures to nonvertebral (hip, wrist, and proximal humerus) fractures in the Malmö cohort [26] and subsequently applied to the number of ICD-10 code identified nonvertebral fractures in the present cohort.

The incidence 2019–2021 of hip and MOF for men and women was calculated by sex and age group for Swedish/Nordic-born and non-Nordic-born citizenship at birth and compared to the incidences used by the original FRAX model. Comparisons between the 2005 fracture incidences and the original FRAX incidences of hip and MOF were also performed.

Development of a revised FRAX model

The hip fracture incidences from 2019 to 2021 were smoothed using a piecewise linear regression model permitting the calculation of the logarithm of hip fracture risk as a continuous function of age yielded breakpoints at 62, 87, and 97 years of age for the Swedish/Nordic model and 57, 87, and 97 years of age for the non-Nordic model. Similarly for MOF, 60, 82, and 92 years of age were used for the Swedish/Nordic model and 57 and 92 years of age for the non-Nordic model. To account for the probability of death, when calculating fracture probabilities, the mortality for Swedish/Nordic and non-Nordic populations during 2019–2021 was used in a piecewise linear Poisson model with breaking points at 55 and 75 years of age. Break points were set at age 55 years, representing the transition to late midlife, and 75 years, representing the transition from "younger old" to "older old," as used for all other FRAX models. These probabilities are used as a foundation for two revised FRAX models, one Swedish/Nordic and one non-Nordic citizenship at birth.

Comparison of the revised Swedish/Nordic FRAX model vs. the original FRAX model

To compare the revised Swedish/Nordic FRAX model with the original model, we calculated the probabilities of MOF (hip, clinical vertebral, forearm, and humerus) and hip fracture alone in men and women aged 50, 60, 70, and 80 years. Calculations were performed for all possible combinations of clinical risk factors across BMD T-scores ranging from 0 to −3.5 SD in 0.5 SD increments, assuming a body mass index (BMI) of 26 kg/m^2. Thus, permutation of all combinations of six risk factors and eight BMD values yielded a total of 512 combinations for each sex and age.

Establishment of age-dependent intervention thresholds

Age-dependent thresholds were calculated and presented using the revised FRAX model. The intervention thresholds (IT) were defined as the age-specific fracture risk equivalent to the 10-year probability of a woman with a previous fracture and a BMI equal to 26 kg/m^2, without knowledge of BMD and without other clinical risk factors. The BMI chosen (26 kg/m^2) was the mean value in 60–79-year-old men and women according to Statistics Sweden [21]. Thresholds were calculated for hip fracture alone and for MOF. Upper and lower assessment thresholds (UAT and LAT) were determined to define a range of probabilities between which a BMD assessment might be warranted as previously described with some modifications [3]. The lower assessment threshold was defined as the age-specific fracture probability equivalent to the 10-year probability of a woman with BMI 26 kg/m^2 without a previous fracture and without clinical risk factors. The upper assessment threshold was defined as 1.2 times the intervention threshold. This choice reflects that when fracture probability exceeds the intervention threshold by 20% or more, the addition of BMD to FRAX rarely results in reclassification from high to low risk [27]. Furthermore, a threshold for very high risk (VHRT) was calculated as 1.6 times the intervention threshold [28]. For those 70 years and older, a fixed threshold was applied and corresponded to the probability of a woman with a previous fracture and no other risk factors at age 70 years, as previously described [29].

Simulation to assess clinical implications of the revised FRAX model and intervention thresholds

Using two subsets of the Swedish population (Swedish/Nordic and non-Nordic, 200,000 each) with a simulated distribution of risk factors [29], the revised FRAX models were used to calculate probabilities, followed by application of

the new age-dependent intervention thresholds. The number of patients eligible for intervention and the number of expected MOF and hip fractures the next 10 years were then compared between the revised and original FRAX models per age group and sex.

Results

Demographic shifts in the Swedish population from 2005 to 2021

The entire Swedish population of women age 40 years or older increased by 16% from 2,402,911 on January 1, 2005, to 2,790,077 on January 1, 2021. During the same period, the non-Nordic-born population of women age 40 years or older increased by 147% from 202,705 in 2005 to 499,726 in 2021, with corresponding proportions from 8.4% to 17.9%, respectively (Fig. 1).

The entire Swedish population of men age 40 years or older increased by 22% from 2,222,584 on January 1, 2005, to 2,721,634 on January 1, 2021. During the same period, the non-Nordic-born population of men age 40 years or older increased by 155% from 201,236 in 2005 to 514,152 in 2021, with corresponding proportions from 9.1% to 18.9%, respectively (Fig. 1).

Hip and MOF incidence by citizenship at birth 2005–2021

Overall hip fracture incidences declined from 461 per 100,000 in 2005 to 345 per 100,000 in 2021 for women and from 234 per 100,000 in 2005 to 189 per 100,000 in 2021 for men, with higher incidences in Swedish/Nordic-born

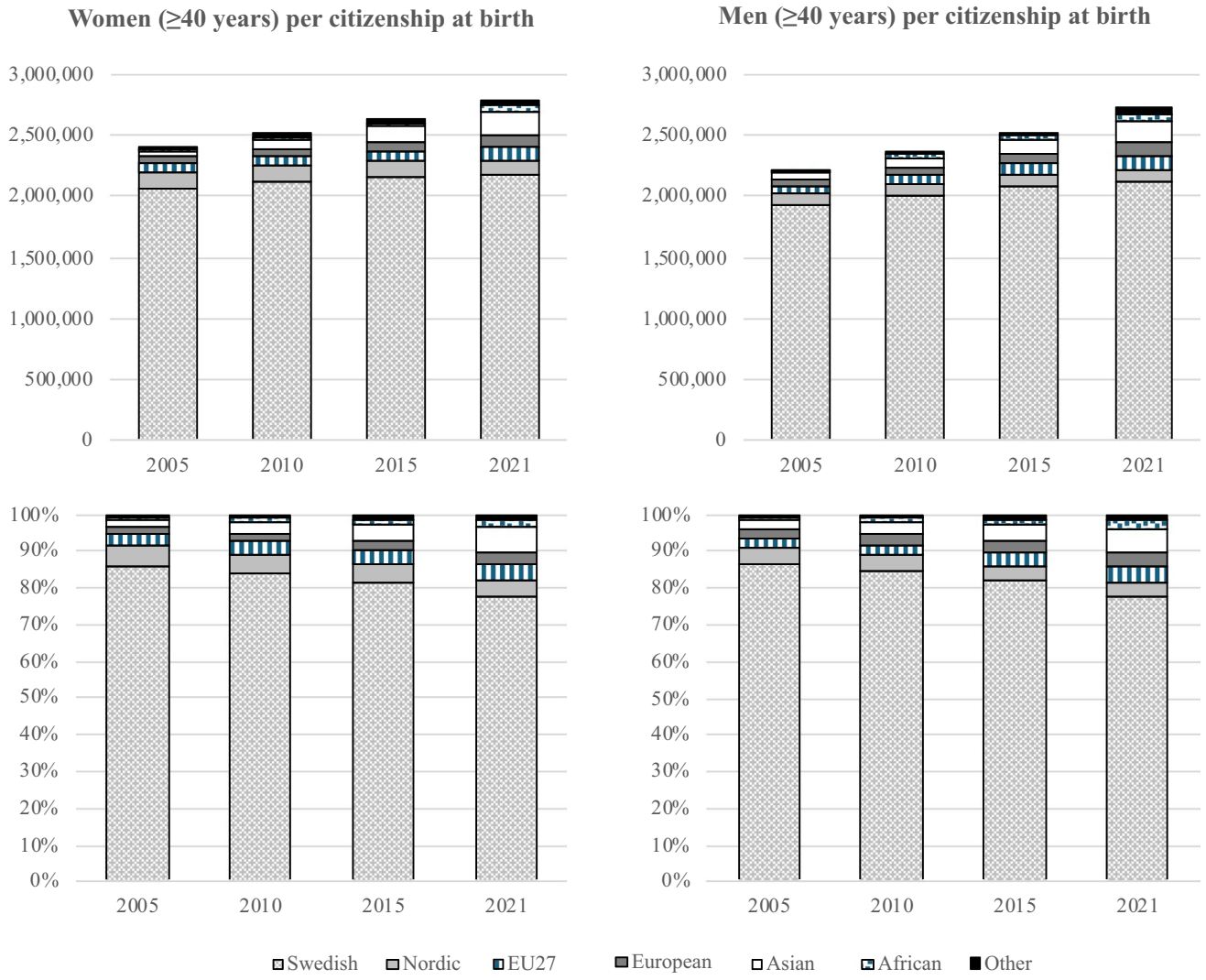

Fig. 1 The Swedish population (40 years and older) 2005–2021 per citizenship at birth. The group "other" consists of South America, North America, Oceania, Soviet Union, unknown, stateless, and missing

compared to non-Nordic-born persons (Fig. 2). All incidences were age-standardized by sex according to the Swedish population 2019 to 2021 (Figure S1). The hip fracture incidence decline of 2–3% per year was statistically significant for all inhabitants and for the Swedish/Nordic-born during 2010–2021 and for the non-Nordic-born during 2015–2021 (Table S2). For MOF, lower incidences in non-Nordic-born persons were seen compared to Swedish/Nordic-born (Fig. 2), and a significant decline of 1–2% per year was observed for both groups during 2010–2021 (Table S3).

Incidences of hip fracture, major osteoporotic fracture, and death

Compared to the original FRAX incidences, the incidences of hip fracture, MOF and death were lower in 2019–2021 for both Swedish/Nordic-born and non-Nordic-born men and women across most age spans (Fig. 3). When the incidences of the original FRAX model were compared to the 2005 incidences of hip and MOF, the differences were of lesser magnitudes (Figure S2). The incidences and the derived probabilities of MOF were higher for men and women using the calculated number of vertebral fractures, applying the ratio of x-ray-verified vertebral fractures to nonvertebral, than when using the register-based vertebral fracture count (Figure S3).

Probabilities of hip and major osteoporotic fracture

Compared to the original FRAX model, the revised FRAX models (Swedish/Nordic and non-Nordic) showed lower 10-year probabilities for hip fracture across all age groups in both men and women. Similarly, the 10-year probabilities for MOF were lower in the revised models, but these differences were restricted to men and women 70 years and older (Fig. 4). Compared to the original FRAX model, the

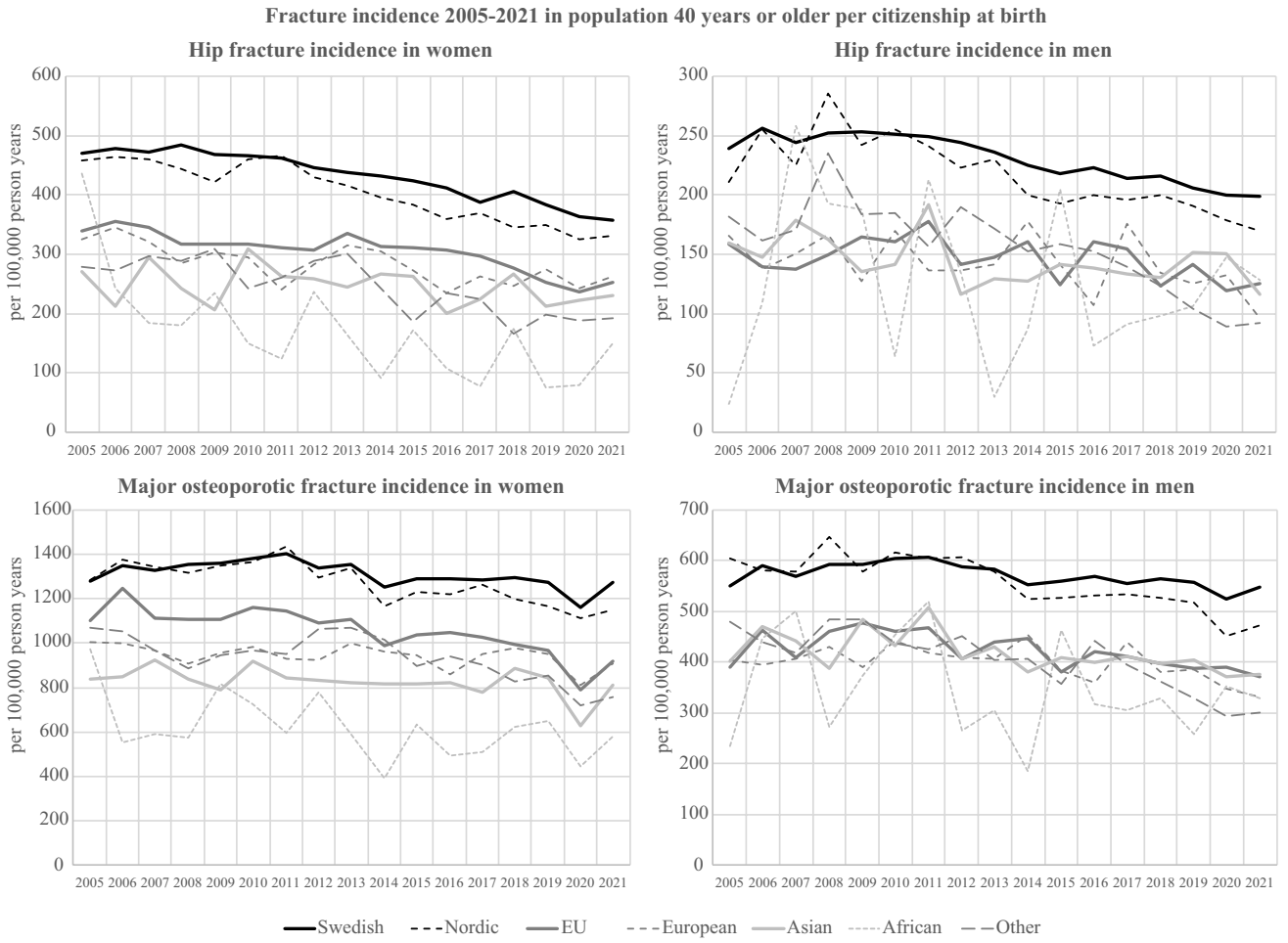

Fig. 2 Incidence of hip and major osteoporotic fracture 2005–2021 per citizenship at birth. MOF includes fractures of the spine, wrist, proximal humerus, and hip (Table S1). The age and sex distribution of the total Swedish population age 40 years and over during 2019–2021 was used as the reference population to achieve comparable numbers over time (Figure S1). The group "other" consists of South America, North America, Oceania, Soviet Union, unknown, stateless, and missing

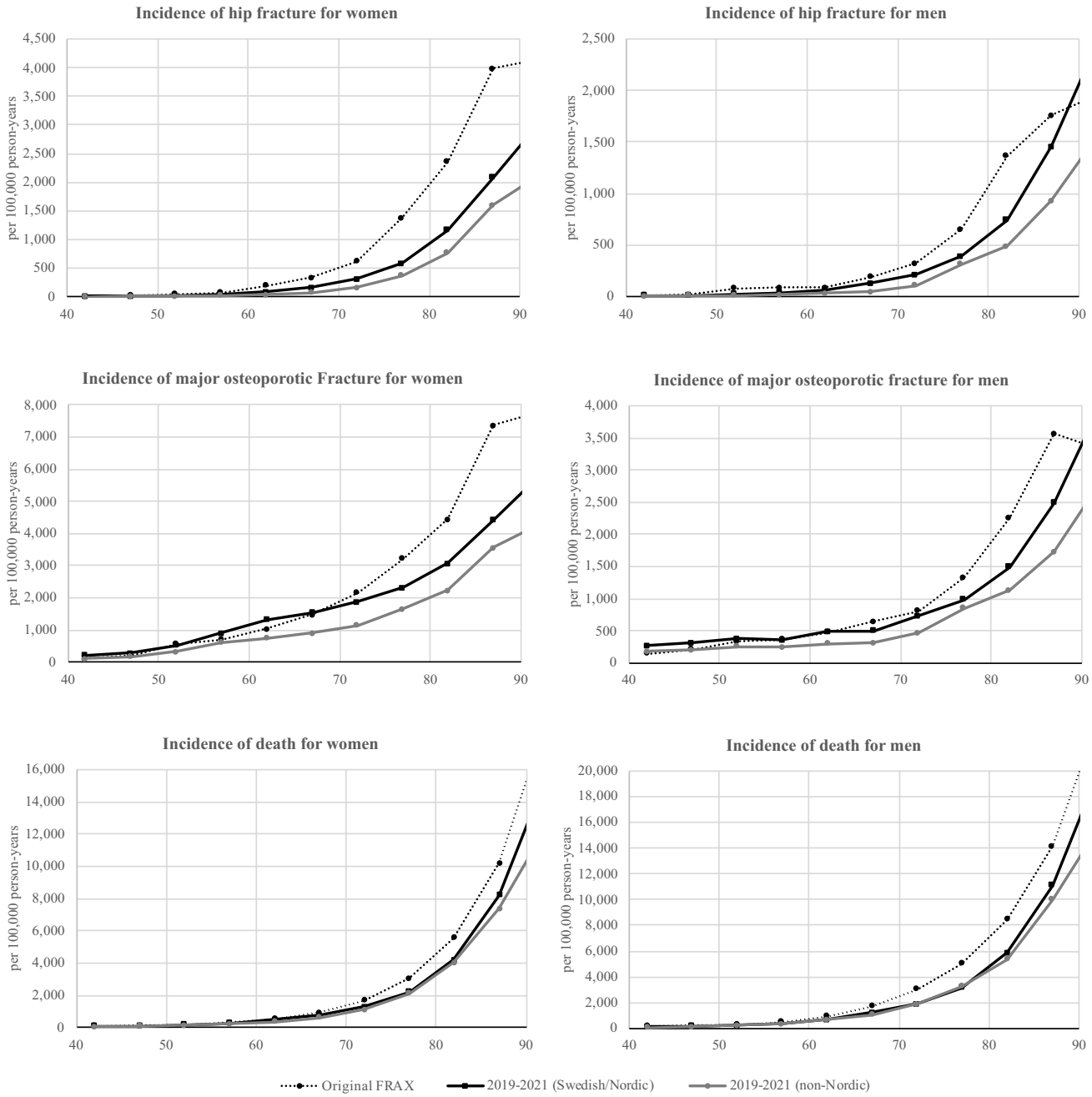

Fig. 3 Incidences of hip fracture, major osteoporotic fracture and death 2019–2021 vs. original FRAX. Incidences of hip fracture, major osteoporotic fracture (MOF), and death for women and men during 2019–2021 for Swedish/Nordic-born and non-Nordic-born compared to the incidences in the original FRAX model. MOF includes vertebral fractures, fracture of wrist, proximal humerus, and hip (Table S1)

revised Swedish/Nordic model probabilities were lower for hip fracture regardless of age and sex (Figure S4A), but for MOF, lower probabilities for the revised model were only observed at higher ages (Figure S4B). Probabilities derived from the original and revised models were highly correlated ($r > 0.98$, Table S4).

Fracture risk probability thresholds

Thresholds for MOF, for assessment without BMD, demonstrated that the intervention threshold ranged from a 10-year probability of 4.5% at age 40 years to 21.5% at age 70 years and older, while intermediate risk, at which a BMD

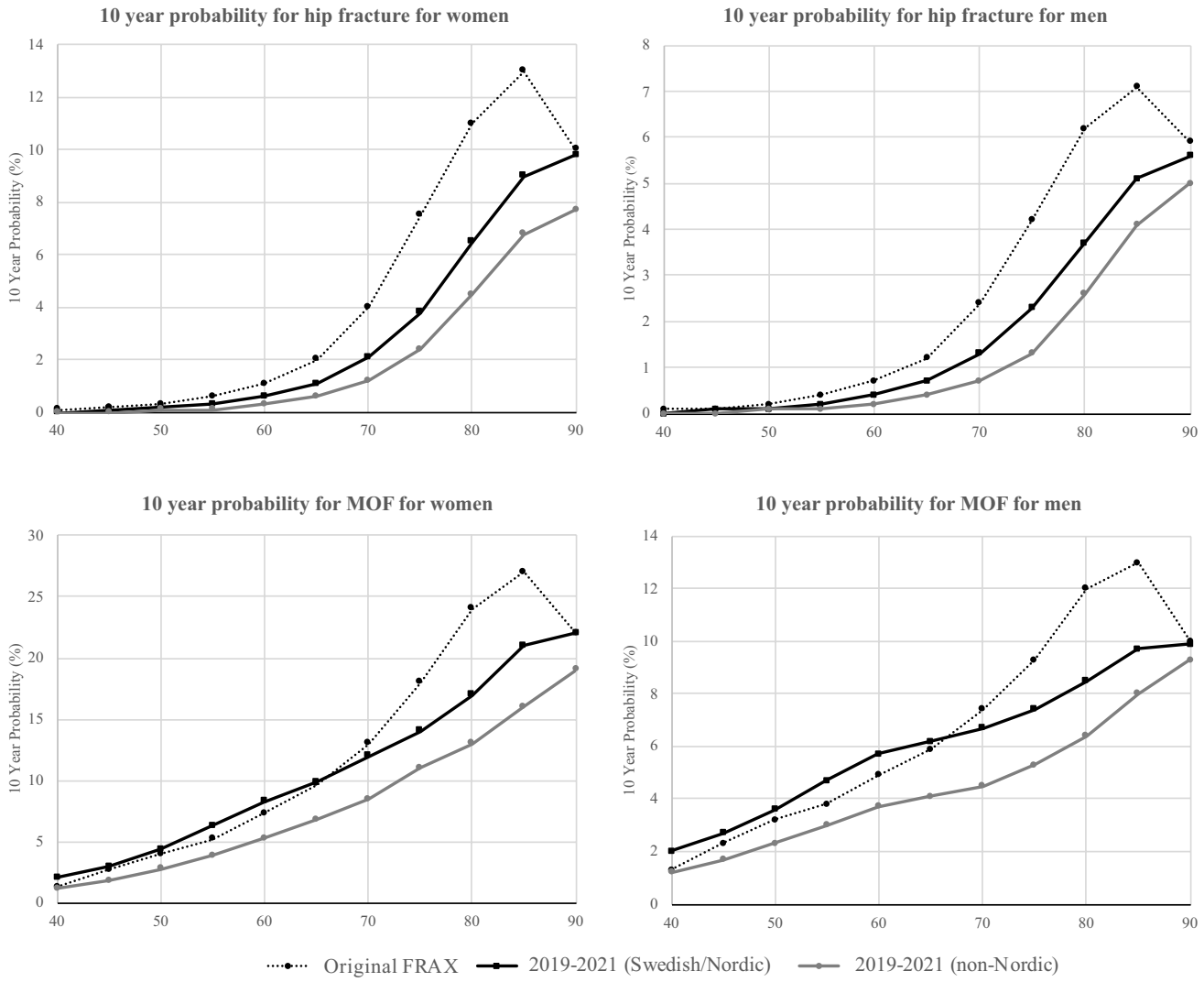

Fig. 4 Probabilities of hip and major osteoporotic fracture using the revised vs. original FRAX model. Ten-year probabilities of hip and major osteoporotic fracture (MOF) for men and women with BMI 26 kg/m^2 and no clinical risk factors are calculated using the incidences and mortality of 2019–2021 for Swedish/Nordic and non-Nordic, respectively, and compared to the probabilities of the original FRAX model. MOF includes spine fractures, fracture of wrist, proximal humerus, and hip (Table S1)

measurement is recommended to more accurately determine risk, ranged from intervals 2.1–5.4% to 11.8–25.8% at the corresponding ages. Low risk, where no BMD measurement is recommended, was defined as a MOF probability ranging from 2.1% at age 40 to 11.8% at age 70 years and older (Fig. 5).

Clinical implications of the revised FRAX model and new intervention thresholds

Using a simulated population cohort to compare the original FRAX MOF model and fixed 20% thresholds to the revised FRAX MOF Swedish/Nordic model with age-dependent intervention thresholds, the proportion of women aged 40–70 years above the intervention threshold increased from 6.8% to 15.8%, and for men aged 40–70 years from 2.1% to 8.3%. In contrast, the proportion of women 70 years and older above the intervention threshold decreased from 57.4% to 36.0%, and for men 70 years and older from 11.7% to 5.9%. When applying both the revised model for hip fracture and MOF, the proportion of women and men, 70 years and older, with probabilities above any of the intervention thresholds, were highly similar to the proportion above the original MOF intervention threshold (Figure S5).

The revised FRAX probabilities in the simulated population were used to estimate the number of MOF and hip fractures occurring over the next 10 years. In the group of Swedish/Nordic women 40–69 years old with high risk identified using the revised FRAX models for MOF or hip fracture, there were more preventable fractures (53,838 MOF

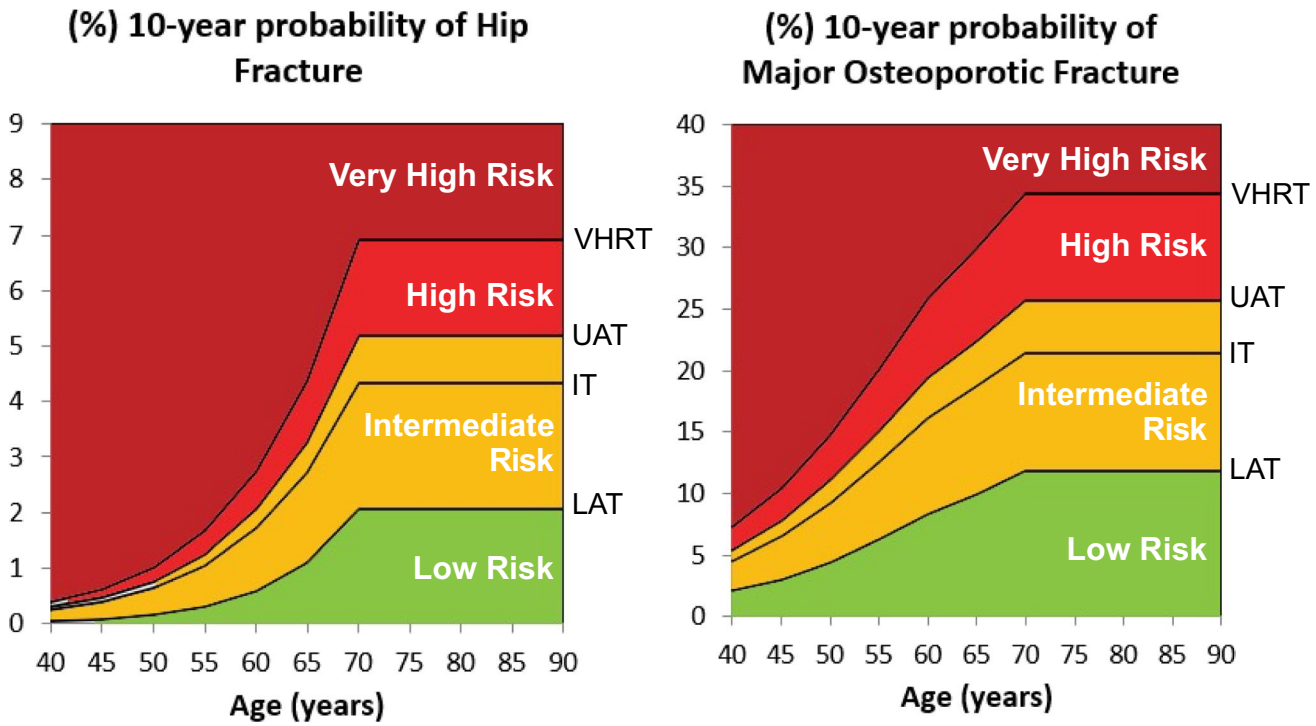

Fig. 5 Thresholds for assessment, intervention, and treatment using the revised FRAX model for Sweden with 10-year probabilities of hip fracture and major osteoporotic fracture (MOF) respectively. The age-dependent probability thresholds are intended for risk stratification. For individuals classified as low risk, lifestyle modification counseling should be considered, with the option of re-evaluation after a period of approximately 2 to 3 years. In case of intermediate risk, BMD measurement should be considered, fracture risk recalculated, and treatment should be considered if above intervention threshold. In case of high risk, treatment to reduce fracture risk should be considered. BMD measurement is recommended to assist in osteoporosis medication choice and provide a baseline for future BMD monitoring. In the cases of very high risk, a referral to an osteoporosis specialist should be considered to assess if the patient is a candidate for osteoanabolic drugs. VHRT, very high risk threshold; UAT, upper assessment threshold; IT, intervention threshold; LAT, lower assessment threshold

and 10,728 hip fractures) compared to using the original FRAX model for MOF (26,553 MOF and 6965 hip fractures). Similarly, there were also more preventable fractures in the group of Swedish/Nordic men 40–69 years old with high risk identified using the revised FRAX models for MOF or hip fracture (27,926 MOF and 5565 hip fractures) compared to the group selected using the original FRAX model for MOF (8183 MOF and 2487 hip fractures). For men and women 70–90 years old, the revised FRAX model for MOF identified a group with fewer future fractures; however, when applying both the revised model for hip fracture and MOF, the number of future fractures was highly similar (Figure S6).

Discussion

This study presents revised FRAX models for Sweden, based on updated and more accurate lower fracture incidences for men and women, and due to differences in fracture risk depending on origin of birth, separate models were developed depending on citizenship at birth. Furthermore, we present age-dependent intervention thresholds, based on the revised FRAX model, with 10-year MOF probabilities ranging from 4.5% at age 40 to 21.5% at age 70 and older. Clinical application of the revised model in Sweden will likely not have a major impact on the number of older individuals classified as high risk, while it will increase the number of younger individuals at high risk for their age and eligible for therapeutic intervention by an estimated 47,000 yearly.

In agreement with previous studies [10, 11, 27], we observed a decline in hip fracture incidence in Sweden. Similar to the hip fracture incidence decline, a decreasing incidence has been found for proximal humerus fractures [30], whereas the incidence of radius fractures has increased, at least between 1999 and 2010 [31]. Thus, any time trends in the incidence of MOF remain uncertain, as data from recent years are limited. Using the entire Swedish population aged 40 years and older, we observed significantly increasing MOF incidences in both women and men between 2005

and 2010, followed by a subsequent decline up to 2021. This pattern was consistent across individuals born in Sweden and the Nordic region, as well as among men and women born elsewhere. Incorporating updated incidences in the revised FRAX model will, as a result, lead to more accurate fracture risk prediction in Sweden.

The present study confirms that immigrants to Sweden from outside the Nordic countries have substantially lower fracture rates [12]. The difference is of sufficient magnitude to be clinically relevant in much the same way that within country models are espoused where large differences in risk are identified on the basis of race/ethnicity [32].

Although fracture incidences in 2019–2021 were substantially lower than those in the original FRAX model, the observed 2005 incidences were also lower than those in the original FRAX model but higher than the fracture incidences in 2019–2021. This discrepancy may reflect a decline over time or differences in methodology, as the original FRAX incidences were derived solely from Malmö, which had approximately 235,000 inhabitants in 1995, whereas the 2005 estimates in this study were calculated using the entire Swedish population aged 40 years and older ($n = 4{,}625{,}495$).

There is considerable scientific evidence demonstrating the effectiveness of osteoporotic medication in reducing fracture risk in osteoporotic postmenopausal women of different ages [33, 34]. In recent years, growing evidence has supported interventions to prevent or reduce bone loss in postmenopausal women with lower absolute fracture risk and BMD values ranging from normal to osteopenic. These include zoledronate every 18 months over 6 years in women, 65 years or older, with osteopenia [22] or every 5 years in early postmenopausal (50–60 years old) women over 10 years, with on average normal BMD [23]. In both studies, zoledronate reduced fracture rates and prevented bone loss, with no serious adverse events noted, which demonstrates that infrequent administration of zoledronate is safe and effective in preventing bone loss and fracture after menopause. Another therapeutic intervention to prevent bone loss and fractures in early postmenopausal women is through menopausal hormone therapy [18], which is now in updated guidelines recommended for short durations in those younger than 60 years and within 10 years of final menses, based on the favorable benefit-to-risk ratio in this group of women [35]. Given the safe and effective available therapeutic interventions for younger postmenopausal women, it can be argued that these interventions should be used in a much larger proportion of women in this category, with normal to osteoporotic BMD, so that the age-dependent deterioration of skeletal microarchitecture and fractures later in life can be avoided [36]. By the introduction of age-dependent thresholds in Sweden using the revised FRAX model, a much wider group of early postmenopausal women with, e.g., previous fracture or other present risk factors, such as heredity or low BMD, will become eligible for earlier interventions compared to the currently used 20% fixed MOF probability [15]. In contrast, applying the revised FRAX model resulted in lower predicted probabilities of hip and major osteoporotic fractures (MOF) among older adults, thereby limiting eligibility for therapeutic intervention to a smaller proportion of this population. However, as shown in the simulated cohort analysis, incorporating an intervention threshold for hip fracture—currently not included in the Swedish guidelines—alongside the MOF threshold would yield highly comparable proportions of men and women eligible for treatment when using the revised versus the previous FRAX models. Also shown in the simulated analysis, the revised FRAX models for MOF or hip with age-dependent thresholds will identify 1.6 to 3.4 times more preventable fractures among men and 40–69 years old than the original FRAX model with fixed a 20% threshold, which if appropriately treated would lead to a substantial reduction in fractures.

Incorporating hip fracture risk assessment with separate hip fracture probability intervention thresholds identifies additional at-risk individuals compared with using MOF probability thresholds alone. Further supporting the use of FRAX hip probability thresholds is their superior discriminatory performance relative to MOF [37, 38]. Moreover, the revised FRAX hip fracture incidence is likely more accurate than the MOF incidence, owing to the higher data quality and completeness of national registry data for hip fractures compared to MOF [24].

Sequential therapy is recommended for patients at very high risk of fracture based on the superior effect in increasing BMD and reducing fracture risk, by using an osteoanabolic drug first, followed by an antiresorptive agent, compared to an antiresorptive only [4, 33]. Head-to-head trials comparing romosozumab to alendronate [39] and teriparatide to risedronate [40] have found that both these osteoanabolic drugs reduce the fracture incidence more than per oral bisphosphonates [4, 33]. The very high fracture risk threshold introduced here in the revised Swedish FRAX model aligns with the NOGG guideline, which defines it as a MOF probability of 1.6 times the intervention threshold—the level of risk at or above which sequential therapy should be considered [3]. Since very high fracture risk has not been defined across different age groups in Sweden previously, the implementation of the revised FRAX model could have a substantial impact on which patients are selected for sequential treatment in Sweden [15, 41].

The presented age-dependent probability thresholds are intended for fracture risk stratification to guide treatment decisions. Up to age 70 years, the age-dependent intervention thresholds represent the risk equivalent to that of a woman of the same age with a prior fracture, consistent with current clinical practice [3]. In case of low risk,

lifestyle advice on physical activity and diet could be offered and possibly reassessment of risk in 2 to 3 years. In case of intermediate risk, BMD measurement should be considered, fracture risk recalculated, and treatment should be considered if above intervention threshold. In case of high risk, treatment interventions to reduce fracture risk should be considered, and BMD should be measured to assist in pharmaceutical intervention choice and provide a baseline for future BMD monitoring. In the cases of very high risk, a referral to an osteoporosis specialist should be considered to assess if the patient might be a candidate for osteoanabolic drugs [3]. High risk or very high risk is considered when either the probability of hip fracture or the probability of MOF is above the respective threshold (Fig. 6). A proposed management algorithm for risk stratification, incorporating the new age-dependent FRAX thresholds into clinical decision-making, is presented in Fig. 7. As fracture probabilities increasingly guide treatment decisions, individuals with low BMD not reaching osteoporosis may still be eligible for therapy if their fracture risk is high—a condition that has been termed *high fracture risk syndrome* [42].

The present study has several strengths. It utilized the entire Swedish population 40 years and older to calculate incidences over a long duration (2005–2021), providing excellent statistical power and ability to analyze trends per calendar year, age group, country of birth, and sex. The revised FRAX model provides age-dependent thresholds and better calibrated risk estimates and is therefore likely to have a large impact if implemented in routine clinical practice in Sweden. It should be acknowledged that the study also has limitations, including the use of registers to capture fracture events. Although hip fractures have been shown to be accurately captured this way [24], other fractures, particularly vertebral fractures [25], are likely not captured as effectively in the diagnostic registers, which could have resulted in an underestimation of fracture risk. To account for the known underreporting of vertebral fractures in registers, the incidence of vertebral fracture was calculated using the known ratio of x-ray-verified vertebral fractures to nonvertebral fractures, derived from the Malmö cohort [26]. As expected, the calculated incidences were higher than the register based. The revised FRAX model was developed based on new incidence numbers but used the same weights for each risk factor as in the original model, under the assumption that the relative importance of these risk factors has remained unchanged, which may not necessarily be true. Due to the declining fracture incidence over calendar year, we used the three most recent years (2019–2021) for development of

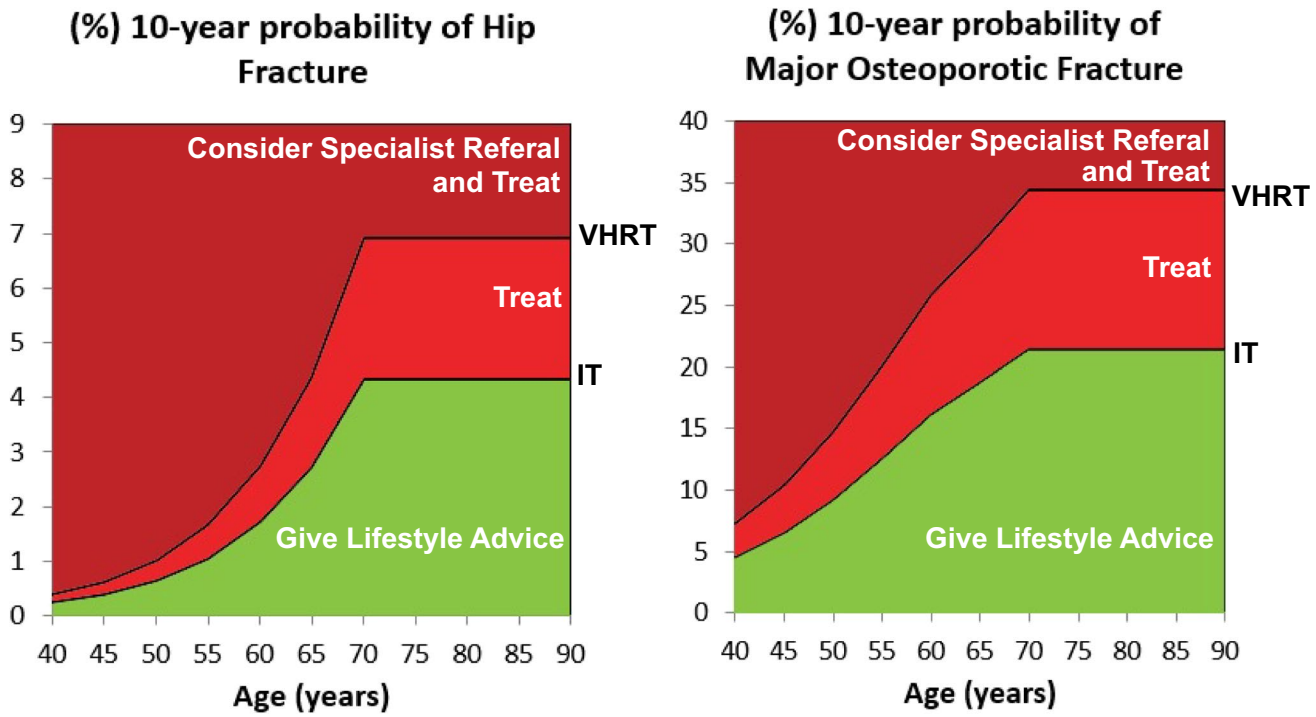

Fig. 6 Thresholds for intervention and treatment after BMD using the revised FRAX model for Sweden. After BMD measurement, FRAX probabilities are recalculated, and the risk is reassessed. In case of high risk (red), treatment to reduce fracture risk should be considered, and in the cases of very high risk (dark red), a referral to an osteoporosis specialist should be considered to assess if the patient is a candidate for osteoanabolic drugs. High risk or very high risk is considered when either the probability of hip fracture or the probability of major osteoporotic fracture is above the respective threshold. VHRT, very high risk threshold; IT, intervention threshold

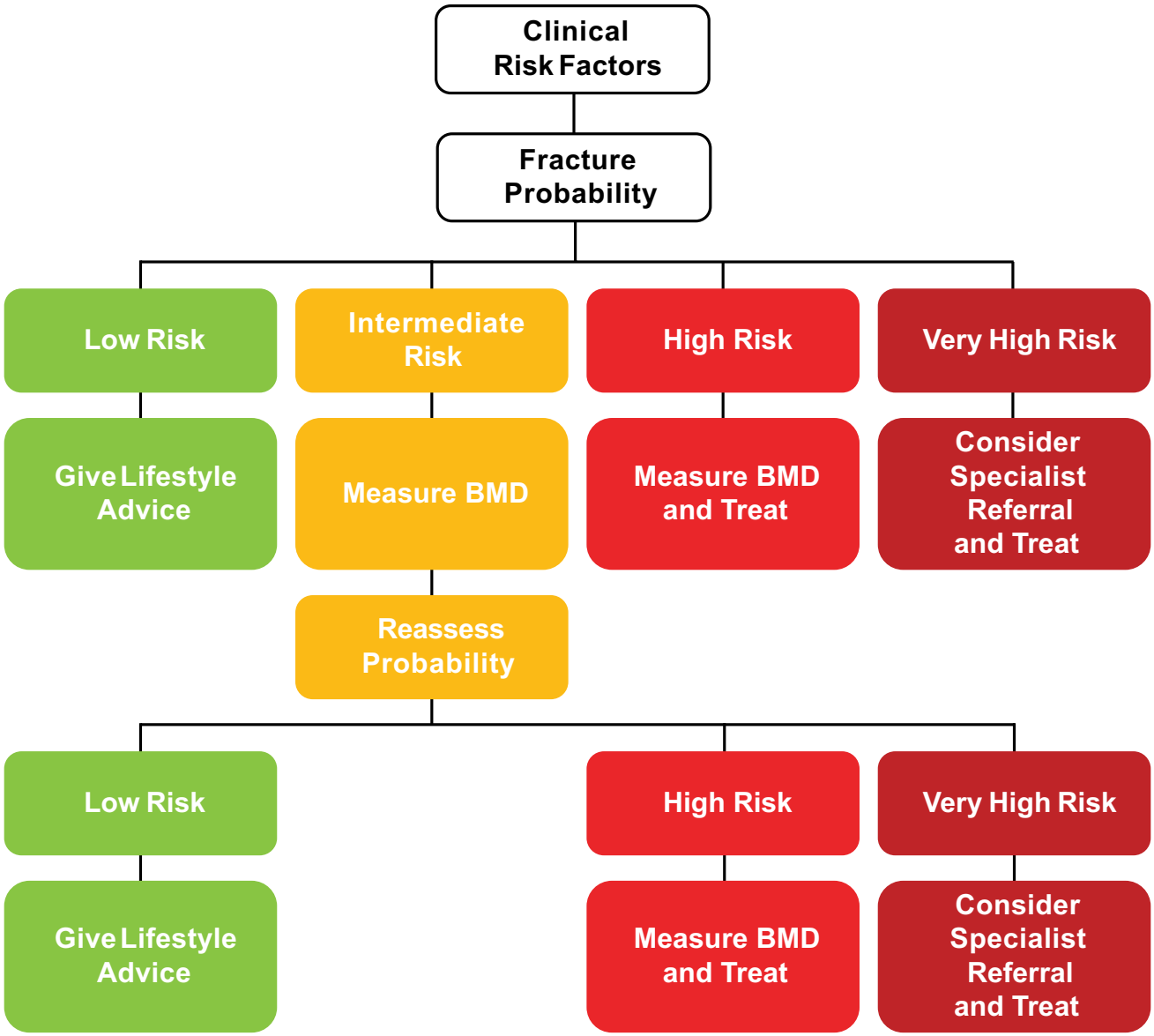

Fig. 7 A proposed management algorithm using the defined revised FRAX model thresholds for Sweden. Management algorithm based on the defined intervention thresholds in the revised FRAX Sweden model for individuals at risk of fracture

the revised FRAX model. However, because the latter two years (2020–2021) coincided with the COVID-19 pandemic, the observed incidence rates may not be fully representative. Notably, a recent review reported that mainly minor fractures, such as forearm fractures, decreased during the pandemic, whereas no significant reduction was observed in major osteoporotic fractures. This finding argues against a meaningful bias in our estimates [43].

In conclusion, the revised Swedish FRAX model offers a more precise quantitative assessment of 10-year fracture probability, to guide both BMD evaluation and intervention, and enables risk estimation by region of birth. Its implementation, incorporating age-dependent thresholds for both MOF and hip fracture risk, is expected to substantially influence the evaluation of fracture risk and the management of osteoporosis in Sweden.

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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

Conflicts of Interest ML has received lecture fees from Astellas, Amgen, UCB Pharma, Medison Pharma, Gedeon Richter, Jansen-Cilag, Medac, and Pharmacosmos and consulting fees from UCB Pharma, Sandoz, Alexion, Gedeon Richter, Medac, Pharmacosmos, Parexel International, and Crinetics, all outside the submitted work. KFA, HL, and HJ have no conflicts of interest. NCH reports personal fees, consultancy, lecture fees, and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Echolight, Theramex, Shire, Consilient Healthcare, UCB, Kyowa Kirin, and Internis Pharma, outside the submitted work. JAK led the team that developed FRAX. He is a director of Osteoporosis Research Ltd which maintains FRAX. He is a member of the Advisory Board of the National Osteoporosis Guideline Group, UK. 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, Pfizer, Radius Health, Redx Oncology, Roche, Sanofi Aventis, UCB, ViiV, Warner Chilcott and I3 Innovus, and is Director of Osteoporosis Research Ltd.

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