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REVIEW

An overview of the use of the fracture risk assessment tool (FRAX) in osteoporosis

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Abstract

FRAX®, a simple-to-use fracture risk calculator, was first released in 2008 and since then has been used increasingly world-wide. By calculating the 10-year probabilities of a major osteoporotic fracture and hip fracture, it assists clinicians when deciding whether further investigation, for example a bone mineral density measurement (BMD), and/or treatment is needed to prevent future fractures. In this review, we explore the literature around osteoporosis and how FRAX has changed its management. We present the characteristics of this tool and describe the use of thresholds (diagnostic and therapeutic). We also present arguments as to why screening with FRAX should be considered. FRAX has several limitations which are described in this review. This review coincides with the release of a version, FRAXplus, which addresses some of these limitations.

Keywords FRAX · Fractures · Calculator · Osteoporosis · Fracture risk · Epidemiology

Introduction

In this review, we explore the literature around osteoporosis and how FRAX has changed its management.

Osteoporosis: definition and diagnosis

Osteoporosis, although first used to characterise post-mortem bones with hollow spaces in 1820, was first defined from a consensus group in 1993 as 'a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture'. Dual-energy X-ray absorptiometry (DXA) was approved for the measurement of bone mineral density (BMD) by the Food and Drug Administration (FDA) in 1988 [1]. A few years later, osteoporosis was defined by a WHO Working Group in densitometric terms as a BMD that was 2.5 standard deviations (SD) or more below the mean value of young healthy women, i.e., a T-score $<-$ 2.5 SD [2]. This threshold would classify 30% of all postmenopausal women as having osteoporosis [3]. Osteopenia was defined as a T-score between $-$ 1.0 and $-$ 2.5. The recommended reference range is the Third National Health and Nutrition Examination Survey (NHANES III) database for femoral neck in white women aged 20–29 years [4, 5]. As per its definition, osteoporosis increases the risk for fractures. Major osteoporotic fractures were defined as those at the hip, clinical spine, forearm, and proximal humerus as they account for about 80% of the fractures and the majority of the economic burden. Moreover, these fractures are strongly associated with low BMD, are predictive of future fractures, and display an age-dependent pattern [6].

The BMD-based threshold for osteoporosis, while serving a critical role in clinical diagnosis and management of osteoporosis, has several limitations which compromise its utility in identifying patients who go on to experience an

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incident fracture. The most important one is that although BMD has a high specificity, its sensitivity is low [2] and the majority of fractures (60–70%) occur in individuals without osteoporosis [7]. BMD might not be available or not reliable, either due to limited access to facilities or due to individual patient issues (degenerative changes at the spine, hip replacements etc.). Moreover, the significance of any given T-score threshold differs by age (Fig. 1). A T-score of − 2.5 in a woman age 65 years denotes a modest increase in the probability of fracture when compared to a woman with no clinical risk factors whose BMD is not available. With increasing age, the difference in the probability between those with T-score of − 2.5 and the general population decreases, and at older ages, for example from the age of 78 years upwards in the United States (Fig. 1), the fracture probability progressively decreases compared to the age- and sex-matched general population and a T-score of − 2.5 becomes a protective factor [8]. Furthermore, many clinical risk factors do not act solely via BMD, and thus may provide further independent contribution to risk stratification [9]. Finally, fracture rates differ between countries, and the variations cannot be explained by BMD alone. For example, the T-score corresponding to a 10-year major osteoporotic fracture probability of 20% varies from − 4.6 in Venezuela to − 2.0 in Iceland [8].

In summary, it is apparent that BMD does not capture the likelihood of fracture completely. This has led to the adverse consequence that patients at high fracture risk for non-BMD reasons have been denied appropriate treatment, because the threshold for densitometric osteoporosis has not been reached. There have been discussions whether the definition of osteoporosis should be reconsidered to include fractures [10, 11]. However, there are problems with including
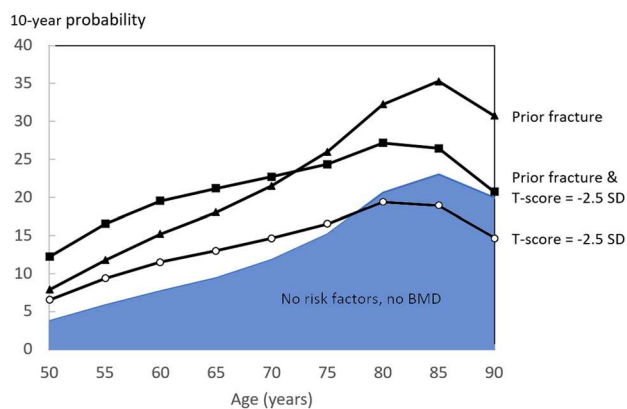
outcomes in multifactorial diseases. There are parallels with other multifactorial diseases like stroke. Blood pressure, a known risk factor for stroke, is a continuous variable like BMD, but not all patients with stroke have hypertension. It would be inappropriate to define hypertension on the basis of stroke. The same applies to myocardial infarction and hypercholesterolaemia [12]. A change in the BMD definition might not be widely adopted so it was recently proposed that it be retained for now and a distinction be made between diagnostic and intervention thresholds [12]. In an effort to address the insensitivity of BMD for the identification of individuals who go on to experience a fracture, risk calculators have been developed which use clinical risk factors plus/minus BMD to generate a risk of fracture over a defined period. Of these, FRAX is the most widely used, validated, and best established worldwide.

FRAX: development and characteristics

FRAX is a computer-based algorithm that calculates the 10-year probability of a major osteoporotic fracture and a hip fracture. It was developed in 2008 by the then World Health Organization (WHO) Collaborating Centre at the University of Sheffield in the United Kingdom (UK) (http://frax.shef.ac.uk/FRAX). Through a series of extensive meta-analyses [from 12 prospective population-based studies from North America, Europe, Asia, and Australia: Rotterdam, EVOS/EPOS, CaMos, Rochester, Sheffield, Dubbo, EPIDOS, OFELY, Kuopio, Hiroshima, and two cohorts from Gothenburg, with a total of 60,000 men and women (75%) and a total follow-up of over 250,000 person years [13–18]], several risk factors for fractures were identified and incorporated into the tool. One of the main aims for the tool was for it to be easily accessible and simple-to-use in primary care. Thus, FRAX uses seven readily available dichotomous clinical risk factors (inserted as yes or no into the calculator): prior fragility fracture, parental hip fracture, smoking, systemic glucocorticoid use, excess alcohol intake, rheumatoid arthritis, and other causes of secondary osteoporosis. Other factors included in FRAX are age, sex, and body mass index (BMI). FRAX can calculate fracture probability with or without femoral neck BMD so accommodating situations where densitometric assessment is not available.

There are other well-validated assessment tools available, including the Garvan fracture calculator and QFracture. The latter (https://qfracture.org/) is a UK model [19, 20]. Similar to FRAX, it takes into account the history of smoking, alcohol, previous fracture, parental history, and glucocorticoid use. It asks specifically about several causes of secondary osteoporosis and also includes a history of falls and whether oestrogen or hormone replacement therapy (HRT) is used. BMD is not included in this tool, and it is only applicable in the UK. The Garvan tool (https://www.garvan.org.

Fig. 1 Comparison of 10-year probabilities of a major osteoporotic fracture (%) derived for a Caucasian woman in the US with a T-score of − 2.5 alone at different ages and those with a prior fracture alone, with no risk factors and unknown BMD or a combination of prior fracture and a T-score of − 2.5. From [8] by kind permission of RightsLink

au/bone-fracture-risk) includes sex, age, weight, number of fractures since age 50 (0, 1, 2, 3, or more), and falls over the last 12 months.

A big difference of FRAX from these other tools is that FRAX calculates the probability of fracture by also considering the competing risk of mortality. This is because some risk factors (female sex, age, BMI, BMD, glucocorticoids, and smoking) affect both these outcomes. Based on that, the model integrates the hazard ratios of fracture and death [6]. The other risk engines, QFracture and Garvan, effectively report cumulative fracture incidence [21].

The impact of combining clinical risk factors and BMD can be examined using the gradient of risk, defined as the hazard ratio (HR) per SD unit change in the examined variable in the direction of increased risk (e.g., for BMD this would be a 1 SD decrease in BMD). The gradients of risk for the use of the clinical risk factors alone, femoral neck BMD alone, and the combination are shown in Table 1 [21]. Both the CRFs alone and BMD alone result in significant gradients of risk, but estimates increase when both BMD and CRFs are used, reflecting a statistically significant but relatively weak correlation between CRFs and BMD ($r = 0.25$) [21]. This correlation is, however, important to acknowledge, since it results in high FRAX probability, on average, tending to identify patients with low BMD where BMD is not included [22, 23]. FRAX has been validated using 11 independent cohorts that did not participate in the model synthesis. In all of the validation cohorts, the gradients of risk using CRFs alone or with BMD were comparable to the original ones presented in Table 1 [24].

To develop a country-specific model, which is necessary because age-specific rates of fracture and death differ, data on the number of hip fractures from national sources and mortality rates from United Nation sources need to be carefully collected. Therefore, the model is as reliable as the data collected and its validation depend on the representativeness of the population. The model would ideally need rates on both hip fracture and MOF, but the latter are only available in a small number of countries, so most models use hip fractures and calculate other rates using ratios derived from Swedish data [25]. FRAX outputs are calibrated to the fracture and death rates in individual country models, so that if all the population underwent assessment by FRAX, the number of fractures predicted in the next 10 years would be equal to the observed number.

The FRAX tool was validated in the UK in a prospective cohort of 454,499 women aged 40–85 years and 424,336 men from 357 general practices and was found to be well calibrated, as the incidences of fractures predicted by FRAX were similar to those observed in the cohort. The area under the receiver-operating characteristic curve (ROC) for FRAX in hip fracture prediction was 0.85 for women and 0.82 for men [19]. FRAX without BMD was also evaluated in Norway; the study found a generally good level of agreement between the observed number of hip fractures and the predicted ones [AUC was 0.81, 95% confidence intervals (CI) 0.78–0.83 for women and 0.79 (0.76–0.83) for men] [26]. Similar numbers for hip fractures were observed in studies from Israel [27, 28] and Canada [29].

The use of FRAX for the treatment of patients at increased risk of fractures

FRAX and the use of thresholds

The importance of FRAX is reflected by its inclusion in many international guidelines [30]. There are more than 150 guidelines published and FRAX is the tool used in more than half of them [31]. However, the way this tool is used for deciding whether to treat a patient or not varies among countries. In general, there are two main approaches. Thus, many guidelines use fixed probability thresholds as intervention

Table 1 Different scenarios of gradients of risk per standard deviation change (95% confidence intervals) in risk score. Examples are given for when only bone mineral density is available, clinical factors only or the combination of the two. From [21] with kind permission from Springer Science and Business Media

| Age	BMD only	Gradient of risk	
		Clinical risk factors alone	Clinical risk factors + BMD
(a) Hip fracture			
50	3.68 (2.61–5.19)	2.05 (1.58–2.65)	4.23 (3.12–5.73)
60	3.07 (2.42–3.89)	1.95 (1.63–2.33)	3.51 (2.85–4.33)
70	2.78 (2.39–3.23)	1.84 (1.65–2.05)	2.91 (2.56–3.31)
80	2.28 (2.09–2.50)	1.75 (1.62–1.90)	2.42 (2.18–2.69)
90	1.70 (1.50–1.93)	1.66 (1.47–1.87)	2.02 (1.71–2.38)
(b) Other osteoporotic fractures			
50	1.19 (1.05–1.34)	1.41 (1.28–1.56)	1.44 (1.30–1.59)
60	1.28 (1.18–1.39)	1.48 (1.39–1.58)	1.52 (1.42–1.62)
70	1.39 (1.30–1.48)	1.55 (1.48–1.62)	1.61 (1.54–1.68)
80	1.54 (1.44–1.65)	1.63 (1.54–1.72)	1.71 (1.62–1.80)
90	1.56 (1.40–1.75)	1.72 (1.58–1.88)	1.81 (1.67–1.97)

thresholds, applied to both sexes and irrespective of age. This approach used in USA and Canada incorporates a 20% FRAX 10-year probability of a major osteoporotic fracture as the intervention threshold. Such probability thresholds vary from 4 to 20% for a major osteoporotic fracture and 1.3–5% for hip fracture, and in some cases, a 20% threshold appears to have been used principally on the basis that it is the threshold chosen in USA, rather than being appropriate for the background population fracture probability of that country [30]. The second approach is to use age-dependent thresholds, as espoused by European guidance from the International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases [32], and incorporated in other country-specific recommendations [30, 33]. Finally, there are countries that used hybrid thresholds, i.e., a combination of age-dependent thresholds and fixed thresholds. Countries following this approach include the UK National Osteoporosis Guideline Group guideline (NOGG), the Lebanon osteoporosis guideline, and the Chilean guideline [34].

The USA guidelines have affected other countries [30]. The National Osteoporosis Foundation (NOF) [now known as Bone Health and Osteoporosis Foundation (BHOF)] guidelines recommend initiation of treatment in patients with hip or vertebral fractures, patients whose T-score is in the osteoporotic range at the femoral neck, total hip or lumbar spine as assessed by DXA, and in postmenopausal women and men older than 50 years with osteopaenia and a 10-year major osteoporosis fracture probability assessed by the appropriate FRAX tool of $\geq 20\%$ or a hip fracture probability $\geq 3\%$ [35]. The development of these thresholds was based on an economic analysis [36]. As mentioned above, other countries have implemented this threshold without undertaking a similar analysis [30]. In other cases, for example China and Japan, thresholds have been adapted

to (usually lower) mean fracture incidence in the population [37, 38].

Age-dependent thresholds, as espoused by the European guidance, are incorporated in recommendations from the UK National Osteoporosis Guideline Group (NOGG), representing the first national guideline to adopt this approach shortly after FRAX was introduced [39, 40]. Prior to the NOGG guidance, the Royal College of Physicians (RCP) guidance recommended the use of BMD as the basis for intervention in postmenopausal women without fracture. The notion that postmenopausal women with a prior fragility fracture should be considered for treatment without the need for a BMD measurement remains a key recommendation. Indeed, the probability of future fracture at any particular age conferred by a prior fracture, with average body mass index and no other risk factors considered, is set as the intervention threshold in the NOGG approach, as proposed through the European guidance [12]. The intervention threshold for women was also applied to men, since the effectiveness and cost-effectiveness of interventions are generally similar to that in women for equivalent risk [41]. Definition of the intervention threshold also informs the setting of assessment thresholds. The lower assessment threshold, below which BMD measurement was not needed, was based on the previous RCP and European guidelines [41, 42]. An example includes a menopausal woman, with normal BMI with no clinical risk factors. The upper threshold was chosen to minimise the probability that a patient characterised to be at high risk on the basis of CRFs alone would be reclassified to be at low risk with additional information on BMD [23]. The upper assessment threshold was set at 1.2 times the intervention threshold [41]. In the first version of this approach, a patient should first be managed by calculating their fracture probability based on age, sex, BMI, and CRFs and the fracture risk was categorised in three groups: high, low, and intermediate (Fig. 2). The high-risk group consisted

Fig. 2 Updated algorithm for the assessment of the risk of fractures, introducing the concept of very high-risk patients. BMD bone mineral density; CRF: clinical risk factor. From [45] with kind permission from Springer Science and Business Media
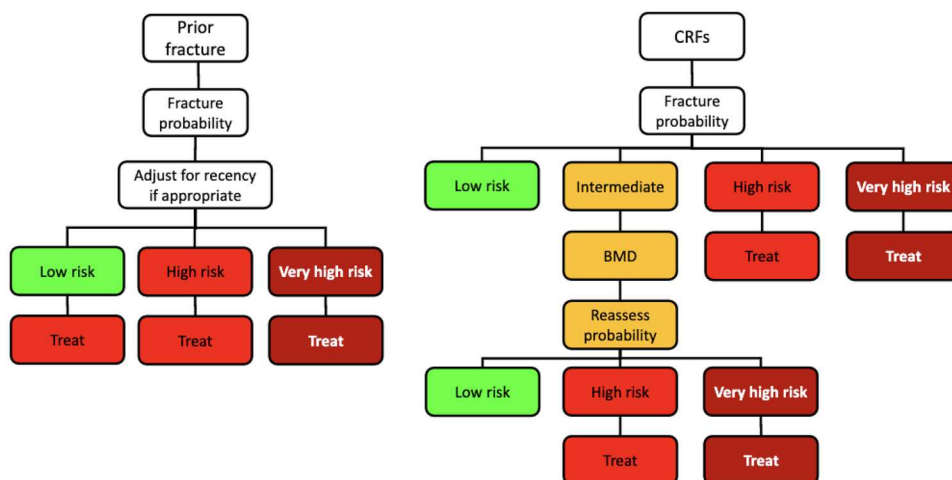
of patients in whom treatment could be initiated without the need for a BMD scan, e.g., a prior fragility fracture. The intermediate group should be then assessed further by BMD to decide on the need for treatment. The RCP and original NOGG guidelines were compared, and it was found that the latter used DXA resources more efficiently. At the age of 50 years, the NOGG guidance required only 3.5 scans to identify one hip fracture, versus the RCP which required 13.9. The respective numbers at age 75 years were 0.9 and 1.5 [43].

Further developments have followed the initial implementation of age-dependent thresholds. For example, in the UK, the threshold was flattened from the age of 70 years and upwards. This was done due to the fact that the previous thresholds required a higher risk of fracture, particularly hip fracture, for treatment to be considered in older women without a prior fracture than those qualifying on the basis of fracture alone [44]. In addition, in 2020, the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis (ESCEO) introduced the concept of 'very high risk' patients (Fig. 2). Examples of the latter include patients with recent fractures, particularly of the spine or hip, or a combination of multiple risk factors, i.e., age > 70y, prior fracture, and family history of hip fracture (Fig. 2). In these cases, osteoanabolic treatment should be considered [32, 45]

Baseline fracture risk and treatment efficacy

One important issue to consider is whether the baseline fracture risk defines the treatment efficacy. To respond to this question, a series of post hoc analyses of clinical trials of anti-osteoporosis medications have been performed. From some medications, there was no interaction between treatment and baseline fracture risk, meaning that treatment is effective irrespective of the baseline FRAX probability. These studies included medications like abaloparatide [Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) study [46]], raloxifene [Multiple Outcomes of Raloxifene Evaluation (MORE) [47]], teriparatide [[48]; Teriparatide Once-Weekly Efficacy Research (TOWER) [49]], alendronate [Fracture Intervention Trial (FIT) [50]], hormone replacement treatment [51], and strontium ranelate [Spinal Osteoporosis Therapeutic Intervention (SOTI) and Treatment of Peripheral Osteoporosis (TROPOS) [52]]. Medications which showed greater efficacy with higher baseline risk included the oral bisphosphonate, clodronate [53], studied in a population sample of older women; there was a significant interaction between baseline FRAX without BMD and treatment efficacy on osteoporotic fractures, $p = 0.043$, with a weakening of this interaction when FRAX included BMD ($p = 0.10$). In this analysis, there was also a significant interaction of treatment with clodronate and

BMI, which could be the major driver of the interaction with FRAX [53]. Denosumab [Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM)], showed no significant interaction between treatment effect and baseline FRAX probability ($p = 0.72$); however, a cubic spline function was found to give a significantly ($p < 0.001$) better fit with a greater effect at higher probabilities [54]. Bazedoxifene showed no overall interaction between treatment and FRAX with BMD ($p > 0.30$), but when the 10-year probability of major osteoporotic fracture is greater than 16% (80th percentile), the treatment was associated with a significant decrease in the risk of all clinical fractures [55]. Finally, significant interactions were observed between romosozumab and baseline FRAX for clinical fractures, osteoporotic fractures, and MOF ($p = 0.064–0.084$), but not vertebral fractures ($p > 0.30$) [FRActure study in postmenopausal women with ostEoporosis (FRAME)] [56]. These observations are of significance when thinking about the cost-effectiveness of treatment. These results have a number of important implications, principally demonstrating the validity of selecting patients for treatment on the basis of fracture probability, potentially improved cost-effectiveness, and the inappropriateness of purely BMD-based thresholds [57]. Importantly, if BMD is not available, high fracture patients as characterised by CRFs and FRAX are likely to respond to treatment. Targeting some medications for high-risk fracture patients would be cost-effective if greater efficacy is assumed from such analyses [58].

Global usage of FRAX

The importance of FRAX in the management of osteoporosis is reflected by its global usage. FRAX is available in 86 models for 78 countries [(https://frax.shef.ac.uk/FRAX/), accessed February 2023]. Over the period ranging from 15 February 2010 to 31 December 2018 inclusive, there were around 4.3 million sessions in the USA, followed by 1.3 million in the UK and 0.3 million in Canada [59]. In February to April 2020 inclusive, the website recorded 460,495 sessions from 184 countries, with the majority (29.2%) coming from USA [60]. Its usage by country model is available on the website; however, this is an underestimation, because there are other portals available to access FRAX, including BMD equipment, smartphone applications, and some healthcare electronic record systems. The COVID-19 pandemic negatively affected access to FRAX (average reduction 58%, with two-thirds of the countries having at least 50% reduction) [60].

The use of FRAX for population screening

Although guidelines in USA and Canada suggest routine DXA assessment in older women, in practice, this tends to

be prompted by the discovery of clinical risk factors rather than a systematic approach to screening. Indeed, the European approach has recommended intervention assessment and intervention on the basis of case finding. However, recent trials of screening and associated health economic analyses have generated an increasingly convincing evidence base, on which to develop approaches to systematic screening for high fracture risk at the population level. The position paper, led by the Epidemiology and Quality of Life Working Group of the International Osteoporosis Foundation has recently considered the recommendations for the adoption of national screening programmes [61]. In the UK, screening for high fracture risk is a key recommendation of the Royal Osteoporosis Society All Party Parliamentary Group in Osteoporosis report into primary prevention (chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://strwebprdmedia.blob.core.windows.net/media/vxuhotlh/appg-on-osteoporosis-and-bone-health-inquiry-report-into-primary-care-2022.pdf, Accessed March 2023).

The first study to address population-based screening was undertaken in the UK. The screening for prevention of fractures in older women (SCOOP) trial was designed to evaluate whether a community screening programme based on FRAX hip fracture probability could reduce the incidence of fractures in older women (70–85 years) over a period of 5 years. This was a pragmatic, unblinded, two-arm, parallel, randomised-controlled trial which recruited women from 100 general practitioner (GP) practices from around Birmingham, Bristol, Manchester, Norwich, Sheffield, Southampton, and York. Women known to be on treatment for osteoporosis (other than calcium and vitamin D) were excluded. Other diseases or factors which could make participants unsuitable for the study were taken into account and patients were excluded on the basis of these (advanced malignancy, dementia, and recent bereavement) [62]. Women were randomised either to the screening arm ($n = 6233$) or to the usual care arm ($n = 6250$) which included opportunistic case finding. In the screening arm, FRAX probabilities were calculated and the 10-year probabilities for a hip fracture were compared with assessment thresholds [63], to determine whether a BMD measurement was needed ($n = 3064$, 49%). FRAX hip fracture probability calculated with BMD was then used to separate patients into high and low fracture risk groups. High-risk patients ($n = 898$, 14%) were invited to discuss treatment options with their general practitioner. By the end of year one, 953 subjects (15%) in the screening arm were given a prescription for an anti-osteoporosis medication. The respective number for the control arm was 264 (4%). There was a steady increase of use of medications in the control arm with time. While the study concluded that screening did not reduce the incidence of all osteoporosis-related fractures [hazard ratio (HR) 0.94, 95% confidence intervals (CI) 0.85–1.03, $p = 0.178$], nor the

overall incidence of all clinical fractures (0.94, 0.86–1.03, $p = 0.183$), the approach led to a 28% relative reduction in hip fractures (prespecified secondary outcome) compared with usual care (2.6% vs 3.5%; HR 0.72, 95% CI 0.59–0.89, $p = 0.002$) [64]. This effect on hip fracture was found to increase significantly with increasing 10-year hip probability at baseline [65], consistent with the treatment effect being mediated through prescription of anti-osteoporosis medications in such women. Women in the screening group showed greater adherence with medication [66]. Screening was found to be cost-effective [67, 68].

Around the same time, the SCOOP trial, the Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study followed a similar approach in women aged 65–80 years in Denmark. Participants were randomised to either screening or control. The difference with SCOOP is that DXA in the screening group, was only performed if the 10-year probability of major osteoporotic fracture was over or equal to 15% and then only those who had osteoporosis as defined by the T-score were offered treatment [69]. As a result, the study failed to show a benefit on the fracture incidence after 5 years of follow-up. However, the screening strategy was found to be beneficial in women with moderate or high risk in the per-protocol analysis (post hoc analysis). In this analysis, women in the screening group who had an FRAX score ≥ 15% and were scanned, were compared to women in the control group who had a FRAX score ≥ 15% but were not scanned. The women in the first group had fewer incident fractures and the risk reduction with a greater effect on hip fractures (adjusted sub-hazard ratio 0.741, $p = 0.007$) [70].

Finally, the SALT Osteoporosis Study (SOS) in the Netherlands assessed women aged 65–90 years having at least one CRF (unlike the SCOOP and ROSE studies which randomised everyone). One of the problems with this study is that the UK FRAX model was used. Treatment was given to women who were found to have high probabilities, but only in combination with a T-score ≤ − 2.0 or a prevalent vertebral fracture. The study failed to show an effect on fracture incidence. A post hoc analysis suggested that screening might be most effective after a recent fracture (HR = 0.65; 95% CI 0.44–0.96 for MOF and HR = 0.38; 95% CI 0.18–0.79 for hip fractures) [71].

A subsequent meta-analysis of all three studies showed that population screening could be effective in reducing major osteoporotic and hip fractures. For MOF, the HR was 0.91, 95% CI = 0.84–0.98, while for hip fractures, HR = 0.80; 95% CI = 0.71–0.91, i.e., a 9 and 20% reduction, respectively [72].

Limitations of FRAX and available adjustments

Over the years, FRAX has been criticised for a number of issues, particularly that it is restricted in the number and

granularity of risk factors. As mentioned above, FRAX was designed to be a simple tool, accessible, and easy to use in primary care. Therefore, only a yes or no answer is accommodated in most questions in the tool. This means that risk factors which are number- or dose-dependent are not fully captured. Examples include the number of prior fractures, the consumption of alcohol and the dose of glucocorticoids. Other concerns include the lack of provision for lumbar spine BMD and the absence of measurements of the material or structural properties of bone. Finally, the age of the parental fracture might be of interest.

Over time, a number of studies have proposed arithmetic adjustments to the conventional FRAX probabilities, to address some of these limitations. To address the issue of glucocorticoids, the guidance shown at Table 2 was proposed [73]. Recently, in the absence of a direct question related to falls history in FRAX and suggested potential adjustments [74], an analysis has provided probability ratios or multipliers that can be applied according to the number of falls over the last year [75, 76].

Probability ratios have also been provided according to the recency of fractures. For example, for a woman at age 50 years, a recent (0–2 years) vertebral fracture is associated with a 1.92-fold higher probability than for a woman of the same age who had a prior fracture at any time [77]. Multipliers have also been provided according to the number of fractures [75]. In the last scenario, a simple solution would be to lower the FRAX-based fracture probability by 5% (i.e., 0.95 × FRAX probability) in the presence of a single prior fracture and to elevate the probabilities by 10, 20, and 30% with a history of 2, 3, and 4 or more prior fractures, respectively.

When BMD at the lumbar spine (LS) is available, and there is discordance between this result and that at the femoral neck (FN), the following rule has been proposed: to increase/decrease FRAX estimate for a major fracture by one-tenth for each rounded T-score difference between LS and FN (10% per SD) [78]. A further study showed that adjustments for large LS/FN discrepancies (> 2SD) only impact to a large extent a relatively small number of people, whereas moderate (1–2 SD) discrepancies only have a small impact [79]. Trabecular bone score (TBS) and hip axis length are sometimes available, and adjustments of fracture probabilities have been provided [80, 81].

A few adjustments have been proposed in cases with type 2 diabetes mellitus, including adjustment with TBS or use of the rheumatoid arthritis (RA) input [82]. A similar approach (using the RA output) has been proposed for Parkinson's disease [83]. Place of origin can also affect FRAX probabilities, as shown in a study in Sweden [84], where the hip fracture incidence for Swedish-born people was approximately double when compared to the one of people born outside the country. Moreover, there was an increase in the hip fracture incidence with time from immigration (0.6% per year). It was suggested that the country of birth should be used when using FRAX [84].

There are variables not incorporated into FRAX, but studies have shown that the fracture probabilities would remain unaffected if these were taken into account. In Canada, FRAX resulted in a robust prediction of fractures regardless of socioeconomic status, given that the competing risk of mortality is taken into account [85]. Moreover, FRAX with and without BMD was found to be unaffected by current or previous osteoporosis treatment [86] and body composition [87].

Although these adjustments can be undertaken by the user to modify the fracture probability output by FRAX, a further website, FRAXplus, will allow the user to incorporate such effect modifiers automatically.

Development of the core FRAX tool

FRAX has been designed as a living tool, hence the adaptation to more countries and territory models, languages,

Table 2 Adjustments (percentage) of the FRAX according to dose of glucocorticoids. From [73] with kind permission from Springer Science and Business Media

Dose	Prednisolone equivalent (mg/day)	Age (years)						
		40	50	60	70	80	90	All ages
Hip fracture								
Low	<2.5	− 40	− 40	− 40	− 40	− 30	− 30	− 35
Medium[a]	2.5–7.5							
High	≥7.5	+25	+25	+25	+20	+10	+10	+20
Major osteoporotic fracture								
Low	<2.5	− 20	− 20	− 15	− 20	− 20	− 20	− 20
Medium[a]	2.5–7.5							
High	≥7.5	+20	+20	+15	+15	+10	+10	+15

[a]no adjustment

etc. In addition to the ability to modify FRAX probability using the new FRAXplus website (https://www.fraxplus.org/), the availability of new cohorts, and longer follow-up in existing cohorts, will underpin the development of the second version of the core FRAX tool itself. This update of FRAX will be informed by analysis of 64 cohorts, including more than 2 million individuals, 69% of them being women [88]. It includes data on 41,015 hip fractures and 113,641 MOF. The expanded numbers will enable more accurate model development and consideration of other risk factors, for example falls and type II diabetes in the risk engine itself.

Conclusion

FRAX is the globally leading tool for assessment of fracture risk, incorporated into over 100 guidelines internationally. In addition to informing treatment decisions, it can also be used to guide assessment with BMD most efficiently. The cost-effectiveness of such approaches has been demonstrated, as has the potential utility of FRAX as the core of approaches to population screening for high fracture risk. The new FRAXplus website will permit modification of FRAX probability to account for a range of additional clinical considerations and the second version of the core FRAX risk engine is under development.

Declarations

Conflict of interest MS: no conflicts of interest in relation to this study. HJ: no conflicts of interest in relation to this study. NCH: reports personal fees, consultancy, lecture fees, and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, UCB, Kyowa Kirin, Servier, Shire, Consilient Healthcare, and Internis Pharma, outside the submitted work. ML has received lecture fees from Amgen, Astellas, Lilly, Meda, Renapharma, UCB Pharma, and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma, and Consilient Health. JAK: Director, Osteoporosis Research Ltd. EVM: Director, Osteoporosis Research Ltd.

Ethical approval All individual cohorts used in the development of FRAX and FRAXplus have been approved by their local ethics committees and informed consent has been obtained from all study participants. General ethics approval for the use of these cohorts is also given by the University of Sheffield. Participant data are stored in coded, de-identified form. Only summary statistics and aggregate data are published, not allowing for identification of individual study participants.

Statement of human and animal rights Neither FRAX nor FRAXplus involve the use of animals.

Informed consent Informed consent has been obtained from all study participants contributing to the development of FRAX and FRAXplus.

References

1. Lewiecki EM, Miller PD, Watts NB (2018) Standard techniques of bone mass measurement in adults. In: Bilezikian JP (ed) Primer on the metabolic bone diseases and disorders of mineral metabolism. Wiley, New York, pp 252–259. https://doi.org/10.1002/9781119266594.ch32
2. Kanis JA (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group (in eng). Osteoporos Int 4:368–381. https://doi.org/10.1007/BF01622200
3. Wylie CD (2010) Setting a standard for a "silent" disease: defining osteoporosis in the 1980s and 1990s (in eng). Stud Hist Philos Biol Biomed Sci 41:376–385. https://doi.org/10.1016/j.shpsc.2010.10.015
4. Looker AC, Johnston CC Jr, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Lindsay RL (1995) Prevalence of low femoral bone density in older U.S. women from NHANES III (in eng). J Bone Miner Res 10:796–802. https://doi.org/10.1002/jbmr.5650100517
5. Looker AC, Wahner HW, Dunn WL, Calvo MS, Harris TB, Heyse SP, Johnston CC, Lindsay R (1998) Updated data on proximal femur bone mineral levels of US adults (in eng). Osteoporos Int 8:468–489. https://doi.org/10.1007/s001980050093
6. Kanis JA, Johansson H, Harvey NC, Mccloskey EV (2018) A brief history of FRAX. Arch Osteoporos. https://doi.org/10.1007/s11657-018-0510-0
7. Cranney A, Jamal SA, Tsang JF, Josse RG, Leslie WD (2007) Low bone mineral density and fracture burden in postmenopausal women. Can Med Assoc J 177:575–580. https://doi.org/10.1503/cmaj.070234
8. Kanis JA, Mccloskey EV, Harvey NC, Johansson H, Leslie WD (2015) Intervention thresholds and the diagnosis of osteoporosis. J Bone Miner Res 30:1747–1753. https://doi.org/10.1002/jbmr.2531
9. Kanis JA, Harvey NC, Johansson H, Odén A, Mccloskey EV, Leslie WD (2017) Overview of fracture prediction tools. J Clin Densitom 20:444–450. https://doi.org/10.1016/j.jocd.2017.06.013
10. Siris ES, Adler R, Bilezikian J, Bolognese M, Dawson-Hughes B, Favus MJ, Harris ST, Jan De Beur SM, Khosla S, Lane NE, Lindsay R, Nana AD, Orwoll ES, Saag K, Silverman S, Watts NB (2014) The clinical diagnosis of osteoporosis: a position statement from the national bone health alliance working group. Osteoporos Int 25:1439–1443. https://doi.org/10.1007/s00198-014-2655-z
11. Paskins Z, Ong T, Armstrong DJ (2020) Bringing osteoporosis up to date: time to address the identity crisis (in eng). Age Ageing 49:329–331. https://doi.org/10.1093/ageing/afaa022
12. Kanis JA, Mccloskey EV, Harvey NC, Cooper C, Rizzoli R, Dawson-Hughes B, Maggi S, Reginster J-Y (2023) The need to distinguish intervention thresholds and diagnostic thresholds in

the management of osteoporosis. Osteoporos Int 34:1–9. https://doi.org/10.1007/s00198-022-06567-9

13. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, Eisman J, Fujiwara S, Garnero P, Kroger H, McCloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A (2004) A meta-analysis of previous fracture and subsequent fracture risk (in eng). Bone 35:375–382. https://doi.org/10.1016/j.bone.2004.03.024

14. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Eisman JA, McCloskey EV, Mellstrom D, Melton LJ, Pols HA, Reeve J, Silman AJ, Tenenhouse A (2004) A family history of fracture and fracture risk: a meta-analysis (in eng). Bone 35:1029–1037. https://doi.org/10.1016/j.bone.2004.06.017

15. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, Fujiwara S, Kroger H, Mccloskey EV, Mellstrom D, Melton LJ, Pols H, Reeve J, Silman A, Tenenhouse A (2005) Smoking and fracture risk: a meta-analysis. Osteoporos Int 16:155–162. https://doi.org/10.1007/s00198-004-1640-3

16. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, Pols H, Tenenhouse A (2005) Alcohol intake as a risk factor for fracture. Osteoporos Int 16:737–742. https://doi.org/10.1007/s00198-004-1734-y

17. De Laet C, Kanis JA, Odén A, Johanson H, Johnell O, Delmas P, Eisman JA, Kroger H, Fujiwara S, Garnero P, Mccloskey EV, Mellstrom D, Melton LJ, Meunier PJ, Pols HAP, Reeve J, Silman A, Tenenhouse A (2005) Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int 16:1330–1338. https://doi.org/10.1007/s00198-005-1863-y

18. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Melton LJ, Tenenhouse A, Reeve J, Silman AJ, Pols HA, Eisman JA, Mccloskey EV, Mellstrom D (2004) a meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 19:893–899. https://doi.org/10.1359/jbmr.040134

19. Hippisley-Cox J, Coupland C (2009) Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores (in eng). BMJ 339:b4229. https://doi.org/10.1136/bmj.b4229

20. Hippisley-Cox J, Coupland C (2012) Derivation and validation of updated QFracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ Br Med J 344:e3427. https://doi.org/10.1136/bmj.e3427

21. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C et al (2007) The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int 18:1033–1046. https://doi.org/10.1007/s00198-007-0343-y

22. Leslie WD, Morin S, Lix LM, Johansson H, Oden A, Mccloskey E, Kanis JA (2012) Fracture risk assessment without bone density measurement in routine clinical practice. Osteoporos Int 23:75–85. https://doi.org/10.1007/s00198-011-1747-2

23. Johansson H, Oden A, Johnell O, Jonsson B, De Laet C, Oglesby A, Mccloskey EV, Kayan K, Jalava T, Kanis JA (2004) Optimization of BMD measurements to identify high risk groups for treatment-a test analysis. J Bone Miner Res 19:906–913. https://doi.org/10.1359/jbmr.2004.19.6.906

24. Mccloskey EV, Harvey NC, Johansson H, Lorentzon M, Liu E, Vandenput L, Leslie WD, Kanis JA (2022) Fracture risk assessment by the FRAX model. Climacteric 25:22–28. https://doi.org/10.1080/13697137.2021.1945027

25. Kanis JA, Oden A, Johnell O, Jonsson B, De Laet C, Dawson A (2001) The burden of osteoporotic fractures: a method for setting intervention thresholds. Osteoporos Int 12:417–427. https://doi.org/10.1007/s001980170112

26. Hoff M, Meyer HE, Skurtveit S, Langhammer A, Søgaard AJ, Syversen U, Dhainaut A, Skovlund E, Abrahamsen B, Schei B (2017) Validation of FRAX and the impact of self-reported falls among elderly in a general population: the HUNT study, Norway. Osteoporos Int 28:2935–2944. https://doi.org/10.1007/s00198-017-4134-9

27. Dagan N, Cohen-Stavi C, Leventer-Roberts M, Balicer RD (2017) External validation and comparison of three prediction tools for risk of osteoporotic fractures using data from population based electronic health records retrospective cohort study. BMJ. https://doi.org/10.1136/bmj.i6755

28. Goldshtein I, Gerber Y, Ish-Shalom S, Leshno M (2018) Fracture risk assessment with FRAX Using real-world data in a population-based Cohort from Israel (in eng). Am J Epidemiol 187:94–102. https://doi.org/10.1093/aje/kwx128

29. Leslie WD, Lix LM, Johansson H, Oden A, Mccloskey E, Kanis JA (2010) Independent clinical validation of a Canadian FRAX tool: Fracture prediction and model calibration. J Bone Miner Res 25:2350–2358. https://doi.org/10.1002/jbmr.123

30. Kanis JA, Harvey NC, Cooper C, Johansson H, Odén A, Mccloskey EV (2016) A systematic review of intervention thresholds based on FRAX. Arch Osteoporos. https://doi.org/10.1007/s11657-016-0278-z

31. El-Hajj Fuleihan G, Chakhtoura M, Cauley JA, Chamoun N (2017) Worldwide fracture prediction (in eng). J Clin Densitom 20:397–424. https://doi.org/10.1016/j.jocd.2017.06.008

32. Kanis JA, Harvey NC, Mccloskey E, Bruyère O, Veronese N et al (2020) Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. Osteoporos Int 31:1–12. https://doi.org/10.1007/s00198-019-05176-3

33. Clark P, Denova-Gutiérrez E, Zerbini C, Sanchez A, Messina O, Jaller JJ, Campusano C, Orces CH, Riera G, Johansson H, Kanis JA (2018) FRAX-based intervention and assessment thresholds in seven Latin American countries. Osteoporos Int 29:707–715. https://doi.org/10.1007/s00198-017-4341-4

34. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D (2019) Pharmacological management of osteoporosis in postmenopausal women: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 104:1595–1622. https://doi.org/10.1210/jc.2019-00221

35. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, Lindsay R (2014) Clinician's guide to prevention and treatment of osteoporosis (in eng). Osteoporos Int 25:2359–2381. https://doi.org/10.1007/s00198-014-2794-2

36. Tosteson ANA, Melton LJ, Dawson-Hughes B, Baim S, Favus MJ, Khosla S, Lindsay RL (2008) Cost-effective osteoporosis treatment thresholds: the United States perspective. Osteoporos Int 19:437–447. https://doi.org/10.1007/s00198-007-0550-6

37. Zhang Z, Ou Y, Sheng Z, Liao E (2014) How to decide intervention thresholds based on FRAX in central south Chinese postmenopausal women. Endocrine 45:195–197. https://doi.org/10.1007/s12020-013-0076-y

38. Orimo H, Nakamura T, Hosoi T, Iki M, Uenishi K, Endo N, Ohta H, Shiraki M, Sugimoto T, Suzuki T, Soen S, Nishizawa Y, Hagino H, Fukunaga M, Fujiwara S (2012) Japanese 2011 guidelines for prevention and treatment of osteoporosis—executive summary. Arch Osteoporos 7:3–20. https://doi.org/10.1007/s11657-012-0109-9

39. Compston J, Cooper A, Cooper C, Francis R, Kanis JA, Marsh D, McCloskey EV, Reid DM, Selby P, Wilkins M, (NOGG) NOGG, (2009) Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK (in eng). Maturitas 62:105–108. https://doi.org/10.1016/j.maturitas.2008.11.022

40. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, Hope S, Kanis JA, McCloskey EV, Poole KES, Reid DM, Selby P, Thompson F, Thurston A, Vine N (2017) UK clinical guideline

for the prevention and treatment of osteoporosis (in eng). Arch Osteoporos 12:43. https://doi.org/10.1007/s11657-017-0324-5

41. Kanis JA, Mccloskey EV, Johansson H, Strom O, Borgstrom F, Oden A (2008) Case finding for the management of osteoporosis with FRAX®—assessment and intervention thresholds for the UK. Osteoporos Int 19:1395–1408. https://doi.org/10.1007/s00198-008-0712-1

42. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D (1997) Guidelines for diagnosis and management of osteoporosis. Osteoporos Int 7:390–406. https://doi.org/10.1007/bf01623782

43. Johansson H, Kanis JA, Oden A, Compston J, Mccloskey E (2012) A comparison of case-finding strategies in the UK for the management of hip fractures. Osteoporos Int 23:907–915. https://doi.org/10.1007/s00198-011-1864-y

44. Mccloskey E, Kanis JA, Johansson H, Harvey N, Odén A, Cooper A, Cooper C, Francis RM, Reid DM, Marsh D, Selby P, Thompson F, Hewitt S, Compston J (2015) FRAX-based assessment and intervention thresholds—an exploration of thresholds in women aged 50 years and older in the UK. Osteoporos Int 26:2091–2099. https://doi.org/10.1007/s00198-015-3176-0

45. Kanis JA, Johansson H, Harvey NC, Lorentzon M, Liu E, Vandenput L, Mccloskey EV (2021) An assessment of intervention thresholds for very high fracture risk applied to the NOGG guidelines. Osteoporos Int 32:1951–1960. https://doi.org/10.1007/s00198-021-05942-2

46. Mccloskey EV, Johansson H, Oden A, Harvey NC, Jiang H, Modin S, Fitzpatrick L, Kanis JA (2017) The effect of abaloparatide-sc on fracture risk is independent of baseline FRAX fracture probability: a post hoc analysis of the ACTIVE study. J Bone Miner Res 32:1625–1631. https://doi.org/10.1002/jbmr.3163

47. Kanis JA, Johansson H, Oden A, McCloskey EV (2010) A meta-analysis of the efficacy of raloxifene on all clinical and vertebral fractures and its dependency on FRAX (in eng). Bone 47:729–735. https://doi.org/10.1016/j.bone.2010.06.009

48. Harvey NC, Kanis JA, Odén A, Burge RT, Mitlak BH, Johansson H, Mccloskey EV (2015) FRAX and the effect of teriparatide on vertebral and non-vertebral fracture. Osteoporos Int 26:2677–2684. https://doi.org/10.1007/s00198-015-3173-3

49. Harvey NC, Kanis JA, Odén A, Nakamura T, Shiraki M, Sugimoto T, Kuroda T, Johansson H, Mccloskey EV (2015) Efficacy of weekly teriparatide does not vary by baseline fracture probability calculated using FRAX. Osteoporos Int 26:2347–2353. https://doi.org/10.1007/s00198-015-3129-7

50. Donaldson MG, Palermo L, Ensrud KE, Hochberg MC, Schousboe JT, Cummings SR (2012) Effect of alendronate for reducing fracture by FRAX score and femoral neck bone mineral density: the fracture intervention trial. J Bone Miner Res 27:1804–1810. https://doi.org/10.1002/jbmr.1625

51. Lorentzon M, Johansson H, Harvey NC, Liu E, Vandenput L, Crandall CJ, Cauley JA, Leboff MS, Mccloskey EV, Kanis JA (2022) Menopausal hormone therapy reduces the risk of fracture regardless of falls risk or baseline FRAX probability—results from the Women's Health initiative hormone therapy trials. Osteoporos Int 33:2297–2305. https://doi.org/10.1007/s00198-022-06483-y

52. Kanis JA, Johansson H, Oden A, Mccloskey EV (2011) A meta-analysis of the effect of strontium ranelate on the risk of vertebral and non-vertebral fracture in postmenopausal osteoporosis and the interaction with FRAX®. Osteoporos Int 22:2347–2355. https://doi.org/10.1007/s00198-010-1474-0

53. Mccloskey EV, Johansson H, Oden A, Vasireddy S, Kayan K, Pande K, Jalava T, Kanis JA (2009) Ten-year fracture probability identifies women who will benefit from clodronate therapy—additional results from a double-blind, placebo-controlled randomised

study. Osteoporos Int 20:811–817. https://doi.org/10.1007/s00198-008-0786-9

54. Mccloskey EV, Johansson H, Oden A, Austin M, Siris E, Wang A, Lewiecki EM, Lorenc R, Libanati C, Kanis JA (2012) Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX. J Bone Miner Res 27:1480–1486. https://doi.org/10.1002/jbmr.1606

55. Kanis JA, Johansson H, Oden A, McCloskey EV (2009) Bazedoxifene reduces vertebral and clinical fractures in postmenopausal women at high risk assessed with FRAX (in eng). Bone 44:1049–1054. https://doi.org/10.1016/j.bone.2009.02.014

56. Mccloskey EV, Johansson H, Harvey NC, Lorentzon M, Shi Y, Kanis JA (2021) Romosozumab efficacy on fracture outcomes is greater in patients at high baseline fracture risk: a post hoc analysis of the first year of the frame study. Osteoporos Int 32:1601–1608. https://doi.org/10.1007/s00198-020-05815-0

57. Kanis JA, Compston J, Cooper C, Harvey NC, Johansson H, Odén A, Mccloskey EV (2016) SIGN guidelines for Scotland: BMD versus FRAX versus QFracture. Calcif Tissue Int 98:417–425. https://doi.org/10.1007/s00223-015-0092-4

58. Kanis JA, Harvey NC, Johansson H, Liu E, Vandenput L, Lorentzon M, Leslie WD, Mccloskey EV (2020) A decade of FRAX: how has it changed the management of osteoporosis? Aging Clin Exp Res 32:187–196. https://doi.org/10.1007/s40520-019-01432-y

59. Chotiyarnwong P, Harvey NC, Johansson H, Liu E, Lorentzen M, Kanis JA, Mccloskey EV (2019) Temporal changes in access to FRAX® in Thailand between 2010 and 2018. Arch Osteoporos. https://doi.org/10.1007/s11657-019-0613-2

60. Mccloskey EV, Harvey NC, Johansson H, Lorentzon M, Vandenput L, Liu E, Kanis JA (2021) Global impact of COVID-19 on non-communicable disease management: descriptive analysis of access to FRAX fracture risk online tool for prevention of osteoporotic fractures. Osteoporos Int 32:39–46. https://doi.org/10.1007/s00198-020-05542-6

61. Chotiyarnwong P, Mccloskey EV, Harvey NC, Lorentzon M, Prieto-Alhambra D et al (2022) Is it time to consider population screening for fracture risk in postmenopausal women? A position paper from the International Osteoporosis Foundation Epidemiology/Quality of Life Working Group. Arch Osteoporos. https://doi.org/10.1007/s11657-022-01117-6

62. Shepstone L, Fordham R, Lenaghan E, Harvey I, Cooper C, Gittoes N, Heawood A, Peters TJ, O'Neill T, Torgerson D, Holland R, Howe A, Marshall T, Kanis JA, Mccloskey E (2012) A pragmatic randomised controlled trial of the effectiveness and cost-effectiveness of screening older women for the prevention of fractures: rationale, design and methods for the SCOOP study. Osteoporos Int 23:2507–2515. https://doi.org/10.1007/s00198-011-1876-7

63. Kanis JA, Borgstrom F, Zethraeus N, Johnell O, Oden A, Jönsson B (2005) Intervention thresholds for osteoporosis in the UK (in eng). Bone 36:22–32. https://doi.org/10.1016/j.bone.2004.08.018

64. Shepstone L, Lenaghan E, Cooper C, Clarke S, Fong-Soe-Khioe R et al (2018) Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial. The Lancet 391:741–747. https://doi.org/10.1016/s0140-6736(17)32640-5

65. Mccloskey E, Johansson H, Harvey NC, Shepstone L, Lenaghan E, Fordham R, Harvey I, Howe A, Cooper C, Clarke S, Gittoes N, Heawood A, Holland R, Marshall T, O'Neill TW, Peters TJ, Redmond N, Torgerson D, Kanis JA (2018) Management of patients with high baseline hip fracture risk by FRAX reduces hip fractures-a post hoc analysis of the SCOOP study. J Bone Miner Res 33:1020–1026. https://doi.org/10.1002/jbmr.3411

66. Parsons CM, Harvey N, Shepstone L, Kanis JA, Lenaghan E, Clarke S, Fordham R, Gittoes N, Harvey I, Holland R, Redmond

NM, Howe A, Marshall T, Peters TJ, Torgerson D, O'Neill TW, Mccloskey E, Cooper C (2020) Systematic screening using FRAX® leads to increased use of, and adherence to, anti-osteoporosis medications: an analysis of the UK SCOOP trial. Osteoporos Int 31:67–75. https://doi.org/10.1007/s00198-019-05142-z

67. Söreskog E, Borgström F, Shepstone L, Clarke S, Cooper C, Harvey I, Harvey NC, Howe A, Johansson H, Marshall T, O'Neill TW, Peters TJ, Redmond NM, Turner D, Holland R, Mccloskey E, Kanis JA (2020) Long-term cost-effectiveness of screening for fracture risk in a UK primary care setting: the SCOOP study. Osteoporos Int 31:1499–1506. https://doi.org/10.1007/s00198-020-05372-6

68. Turner DA, Khioe RFS, Shepstone L, Lenaghan E, Cooper C, Gittoes N, Harvey NC, Holland R, Howe A, Mccloskey E, O'Neill TW, Torgerson D, Fordham R (2018) The cost-effectiveness of screening in the community to reduce osteoporotic fractures in older women in the UK: economic evaluation of the SCOOP Study. J Bone Miner Res 33:845–851. https://doi.org/10.1002/jbmr.3381

69. Rubin KH, Holmberg T, Rothmann MJ, Høiberg M, Barkmann R, Gram J, Hermann AP, Bech M, Rasmussen O, Glüer CC, Brixen K (2015) The Risk-Stratified Osteoporosis Strategy Evaluation study (ROSE): a randomized prospective population-based study. design and baseline characteristics. Calcif Tissue Int 96:167–179. https://doi.org/10.1007/s00223-014-9950-8

70. Rubin KH, Rothmann MJ, Holmberg T, Høiberg M, Möller S, Barkmann R, Glüer CC, Hermann AP, Bech M, Gram J, Brixen K (2018) Effectiveness of a two-step population-based osteoporosis screening program using FRAX: the randomized Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study. Osteoporos Int 29:567–578. https://doi.org/10.1007/s00198-017-4326-3

71. Merlijn T, Swart KM, Schoor NM, Heymans MW, Zwaard BC, Heijden AA, Rutters F, Lips P, Horst HE, Niemeijer C, Netelenbos JC, Elders PJ (2019) The effect of a screening and treatment program for the prevention of fractures in older women: a randomized pragmatic trial. J Bone Miner Res 34:1993–2000. https://doi.org/10.1002/jbmr.3815

72. Merlijn T, Swart KMA, Van Der Horst HE, Netelenbos JC, Elders PJM (2020) Fracture prevention by screening for high fracture risk: a systematic review and meta-analysis. Osteoporos Int 31:251–257. https://doi.org/10.1007/s00198-019-05226-w

73. Kanis JA, Johansson H, Oden A, Mccloskey EV (2011) Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int 22:809–816. https://doi.org/10.1007/s00198-010-1524-7

74. Masud T, Binkley N, Boonen S, Hannan MT, Members FPDC (2011) Official positions for FRAX® clinical regarding falls and frailty: can falls and frailty be used in FRAX®? from joint official positions development conference of the international society for clinical densitometry and international osteoporosis foundation on FRAX® (in eng). J Clin Densitom 14:194–204. https://doi.org/10.1016/j.jocd.2011.05.010

75. Kanis JA, Johansson H, Harvey NC, Gudnason V, Sigurdsson G, Siggeirsdottir K, Lorentzon M, Liu E, Vandenput L, Mccloskey EV (2022) Adjusting conventional FRAX estimates of fracture probability according to the number of prior fractures. Osteoporos Int 33:2507–2515. https://doi.org/10.1007/s00198-022-06550-4

76. Leslie WD, Morin SN, Lix LM, Martineau P, Bryanton M, Mccloskey EV, Johansson H, Harvey NC, Kanis JA (2019) Fracture prediction from self-reported falls in routine clinical practice: a registry-based cohort study. Osteoporos Int 30:2195–2203. https://doi.org/10.1007/s00198-019-05106-3

77. Kanis JA, Johansson H, Harvey NC, Gudnason V, Sigurdsson G, Siggeirsdottir K, Lorentzon M, Liu E, Vandenput L, Mccloskey EV (2020) Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures. Osteoporos Int 31:1817–1828. https://doi.org/10.1007/s00198-020-05517-7

78. Leslie WD, Lix LM, Johansson H, Oden A, Mccloskey E, Kanis JA (2011) Spine–hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. Osteoporos Int 22:839–847. https://doi.org/10.1007/s00198-010-1461-5

79. Johansson H, Kanis JA, Odén A, Leslie WD, Fujiwara S, Glüer CC, Kroger H, Lacroix AZ, Lau E, Melton LJ, Eisman JA, O'Neill TW, Goltzman D, Reid DM, Mccloskey E (2014) Impact of femoral neck and lumbar spine BMD discordances on FRAX probabilities in women: a meta-analysis of international cohorts. Calcif Tissue Int 95:428–435. https://doi.org/10.1007/s00223-014-9911-2

80. Mccloskey EV, Odén A, Harvey NC, Leslie WD, Hans D, Johansson H, Kanis JA (2015) Adjusting fracture probability by trabecular bone score. Calcif Tissue Int 96:500–509. https://doi.org/10.1007/s00223-015-9980-x

81. Leslie WD, Lix LM, Morin SN, Johansson H, Odén A, McCloskey EV, Kanis JA (2016) Adjusting hip fracture probability in men and women using hip axis length: the manitoba bone density database (in eng). J Clin Densitom 19:326–331. https://doi.org/10.1016/j.jocd.2015.07.004

82. Leslie WD, Johansson H, Mccloskey EV, Harvey NC, Kanis JA, Hans D (2018) Comparison of methods for improving fracture risk assessment in diabetes: the Manitoba BMD registry. J Bone Miner Res 33:1923–1930. https://doi.org/10.1002/jbmr.3538

83. Schini M, Bhatia P, Shreef H, Johansson H, Harvey NC, Lorentzon M, Kanis JA, Bandman O, McCloskey EV (2022) Increased fracture risk in Parkinson's disease-an exploration of mechanisms and consequences for fracture prediction with FRAX (in eng). Bone. https://doi.org/10.1016/j.bone.2022.116651

84. Johansson H, Odén A, Lorentzon M, Mccloskey E, Kanis JA, Harvey NC, Karlsson MK, Mellström D (2015) Is the Swedish FRAX model appropriate for Swedish immigrants? Osteoporos Int 26:2617–2622. https://doi.org/10.1007/s00198-015-3180-4

85. Brennan SL, Williams LJ, Berk M, Pasco JA (2013) Socioeconomic status and quality of life in population-based Australian men: data from the geelong osteoporosis study (in eng). Aust N Z J Public Health 37:226–232. https://doi.org/10.1111/1753-6405.12063

86. Leslie WD, Lix LM, Johansson H, Oden A, Mccloskey E, Kanis JA (2012) Does osteoporosis therapy invalidate FRAX for fracture prediction? J Bone Miner Res 27:1243–1251. https://doi.org/10.1002/jbmr.1582

87. Leslie WD, Orwoll ES, Nielson CM, Morin SN, Majumdar SR, Johansson H, Odén A, Mccloskey EV, Kanis JA (2014) Estimated lean mass and fat mass differentially affect femoral bone density and strength index but are not FRAX independent risk factors for fracture. J Bone Miner Res 29:2511–2519. https://doi.org/10.1002/jbmr.2280

88. Vandenput L, Johansson H, Mccloskey EV, Liu E, Åkesson KE et al (2022) Update of the fracture risk prediction tool FRAX: a systematic review of potential cohorts and analysis plan. Osteoporos Int 33:2103–2136. https://doi.org/10.1007/s00198-022-06435-6