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POSITION PAPER

Race-specific FRAX models are evidence-based and support equitable care: a response to the ASBMR Task Force report on Clinical Algorithms for Fracture Risk

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Abstract

Task Force on 'Clinical Algorithms for Fracture Risk' commissioned by the American Society for Bone and Mineral Research (ASBMR) Professional Practice Committee has recommended that FRAX® models in the US do not include adjustment for race and ethnicity. This position paper finds that an agnostic model would unfairly discriminate against the Black, Asian and Hispanic communities and recommends the retention of ethnic and race-specific FRAX models for the US, preferably with updated data on fracture and death hazards. In contrast, the use of intervention thresholds based on a fixed bone mineral density unfairly discriminates against the Black, Asian and Hispanic communities in the US. This position of the Working Group on Epidemiology and Quality of Life of the International Osteoporosis Foundation (IOF) is endorsed both by the IOF and the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO).

Keywords Fracture probability · FRAX adjustment · Race and ethnicity · Racism

The findings of a Task Force on 'Clinical Algorithms for Fracture Risk' commissioned by the American Society for Bone and Mineral Research (ASBMR) Professional Practice Committee have recently been published [1]. The aim of the ASBMR Task Force was to determine the impact of race and ethnicity adjustment in the USA Fracture Risk Assessment Tool (FRAX®). This followed a general concern, well-articulated in an editorial by Vyas et al. [2], that clinical assessment algorithms which include race or ethnicity may discriminate against individuals of Black, Asian and minority ethnicity (BAME—also described as the global majority, hereinafter termed non-White which specifically includes Black, Hispanic and Asian communities) [3]. Subsequent publications variously argued that the ethnic-specific FRAX models do [4] or do not discriminate against the non-White community [5–9] or were agnostic [10, 11]. The conclusions of the Task Force were that there is little justification for estimating fracture risk while incorporating race and ethnicity adjustments and recommended that fracture prediction models do not include adjustment for these attributes.

The Task Force reviewed the extensive evidence for discrimination in the field of osteoporosis and fracture management. The question arises whether racial discrimination in the US is furthered by the ethnic and race-specific FRAX models. For the reasons articulated below, we firmly believe that this is not the case.

Extended author information available on the last page of the article

Epidemiology

It is well established the Black, Asian and Hispanic communities in the US have a lower hip fracture rate than White communities [11–14]. The task force confirms this in their systematic review [15]; indeed, in the cohorts studied, there were far fewer fractures in Black and Hispanic women than in White women. The lowest fracture rates were observed in the Black community, who, where reported, had rates of hip fracture 70% lower than in White women and rates of major osteoporotic fractures between 49 and 67% lower. African Americans on average also have higher femoral neck bone mineral density (BMD) than White Americans [11, 16, 17], but higher BMD only partly explains the lower fracture risk [18]. For the same BMD, African Americans have a hip fracture probability that is half that of White individuals of the same age and sex [8, 18]. Indeed, differences in BMD between countries vary by approximately 1 SD and cannot account for the greater than tenfold variations in hip fracture rates worldwide [19, 20]. In this context, the statement of the Task Force 'As demonstrated by the systematic review, …. there is little justification for estimating fracture risk while incorporating race and ethnicity adjustments' is both illogical and unjustified.

A component of the argument of the Task Force was that despite reasonably good calibration of FRAX according to ethnicity in postmenopausal women aged 50–64 years, FRAX discriminated poorly between women who do and do not experience fracture in the Women's Health Initiative (WHI). Indeed, the area under the receiver operating characteristic curve (AUC) ranged from 0.53 to 0.57 for a major osteoporotic fracture and from 0.54 to 0.66 for hip fracture [21]. In a further study of WHI in women age 50–79 years, the AUC was higher (0.64 and 0.61 for MOF in White and Black women, respectively, and 0.75 and 0.81 for hip fracture in White and Black women, respectively) [22]. The improvement in AUCs with a wider age range is expected since the AUC will be smaller the narrower the age range that is studied, illustrating but one of the many fallacies in comparing AUCs within and across studies [23]. We have had the opportunity to assess AUCs in Black and White men and women with a near identical age range (68–80 years) in the Aging and Body Composition (Health ABC) study [24] given in Table 1. The important finding is not so much the absolute value of the AUC but the finding that there is no difference in AUC between Black and White individuals.

It is important to reemphasise that the significance of ethnicity will vary by geography. For example, although Black individuals in the US have on average, lower FRAX 10-year fracture probabilities than White individuals, the probability of fracture in the US Black population is much higher than in African Black populations, in part due to the higher fracture rates and lower mortality risks in those from the US [25]. Ethnically Chinese individuals from Hong Kong, mainland China and Singapore provide a further example of location-specific differences [7]. First-generation immigrants to Sweden (with high fracture rates in Swedes) have an incidence of hip fracture that is markedly lower than that observed in Swedish-born individuals. Although there is a small rise in incidence with time after immigration, the incidence remains much lower [26]. Thus, ratios of fracture incidence between ethnic and racial groups in the US are unlikely to apply elsewhere.

Inequity of care

The Task Force rightly notes that there is inequity of care in the non-White community in the US. This is widely documented both generally [27] and in the context of osteoporosis [6, 16, 28], but it is unclear how it would be rectified by risk assessment that did not take ethnicity or race into account. Indeed, the converse is more likely. Because fragility fractures in the US are much less common in the Black than in the White community, the US FRAX calculator returns a lower fracture risk for Black women by a factor of 0.43 compared to that for White women (0.50 for Asian and 0.53 for Hispanic women), consistent with the Task Force findings and those presented in Table 1. These differences are substantial and rank as highly as or greater than the other strong risk factors such as a prior fragility fracture (Fig. 1).

Thus, their omission would decrease the performance characteristics of FRAX by as much as or more than omitting a prior fracture as an input variable. Moreover, in applying the ASBMR approach into clinical care, a large proportion of the non-White community will be exposed to anti-resorptive treatments that are unnecessary, and risk adverse events without clinical gain. An obvious example

Table 1 Performance of FRAX for incident fractures in the Health ABC study in men and women according to race and ethnicity

	White ($n=1775$)			Black ($n=1268$)		
	Fractures	AUC	95% CI	Fractures	AUC	95% CI
MOF	392	0.700	0.672–0.729	123	0.692	0.645–0.738
Hip fracture	176	0.724	0.684–0.764	58	0.721	0.654–0.787

MOF, major osteoporotic fracture; *AUC*, area under the receiver operating characteristic curve

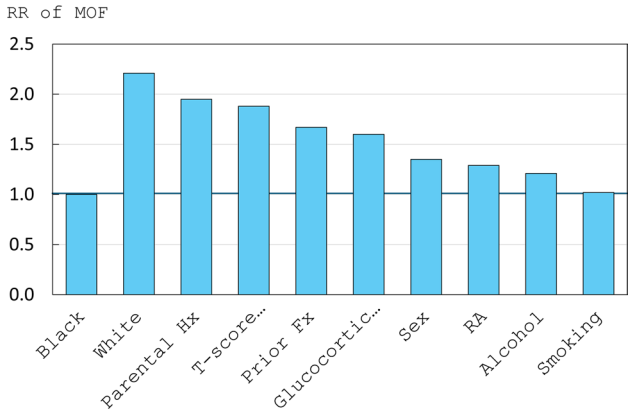

Fig. 1 Ethnic-specific 10-year probabilities of a major osteoporotic fracture in Black women from the US at age 65 years with a body mass index set at 25 kg/m^2. The first bar on the left, set at 1, denotes the risk ratio for a major osteoporotic fracture (MOF) with no additional indices of risk. The impacts of additional indices of risk that are used in FRAX are shown in order of weight in subsequent bars. The probability ratio for sex is female/male ratio. RA, rheumatoid arthritis; Prior Fx, prior fracture; Parental Hx, parental history of hip fracture

is the increase in risk of atypical femoral fracture in the Asian community and less clinical gain following exposure to anti-resorptive medication compared with White patients [29–32].

The wider context

It is instructive to consider other input variables which could be construed as discriminatory. For example, under the Task Force's logic, future iterations of FRAX may need to be gender-neutral to avoid discrimination by sex. The irony of the *reductio ad absurdum* is that omitting sex from FRAX adjustments would have less impact than the Task Force's current recommendations to omit ethnicity (see Fig. 1). On average, hip fracture rates are 1.65 higher in women than men [7]. Mean hip fracture rates are 2.33 higher in White than in Black individuals from the US, as are fracture probabilities (Fig. 2). The difference is such that, on average, White men in the US have a fracture probability that is greater than that of non-White women. In other words, race and ethnicity are more important than sex in improving the accuracy of FRAX and failure to calibrate for ethnicity would have adverse consequences greater than failure to consider sex in fracture risk assessment.

FRAX is the wrong ASBMR target

The appeal of personalised absolute probability-based assessment is that treatments can be applied in an equitable manner that is neither sexist nor racist. For example, treatment is commonly recommended in the US in women with osteopenia when the 10-year probability of a major osteoporotic fracture exceeds 20% or that for hip fracture exceeds 3% [33]. Thus, the same probability threshold is applied irrespective of race and ethnicity or age. Similarly, in the case of ethnicity-specific models in Singapore, a single threshold is applied to all ethnicities [34, 35]. In many countries, particularly within Europe, Eurasia, the Middle East and Latin America [36–39], intervention thresholds are based on a fracture probability that is equivalent to a woman with a prior fragility fracture since treatment is widely recommended in women with a prior fragility fracture [40]. The logic is applied irrespective of sex.

Prior fracture apart, FRAX is the principal gateway for risk assessment in many countries; in others, including the US, bone mineral density (BMD) is most usually the primary access route [40]. Treatment is recommended in postmenopausal women where the T-score is – 2.5 or lower, FRAX being reserved for those with a T-score between – 1 and – 2.5 (osteopenia) [33]. With the use of a T-score threshold, non-White individuals will be treated at a much lower risk than White individuals with less benefit and a higher risk–benefit profile. The effect is not trivial. For example, White women at age 65 years from the US with a femoral neck T-score of – 2.5 (no other risk factors and body mass index of 25 kg/m^2) have a 10-year probability of a major

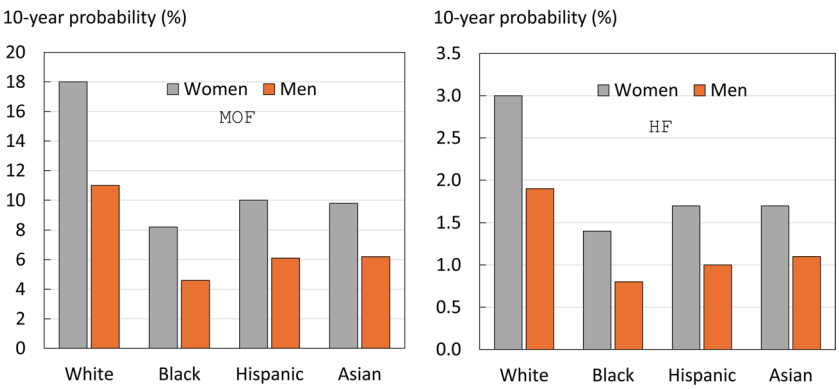

Fig. 2 Ethnicity-specific 10-year probabilities of a major osteoporotic fracture in men and women at age 65 years who have had a prior fragility fracture in the US. Body mass index set at 25 kg/m^2. MOF, major osteoporotic fracture; HF, hip fracture

osteoporotic fracture of 18%. Black women of the same profile have a probability of only 7.5%. No single additional clinical risk factor would redress the disparity but a T-score of − 4.4 would.

Similarly, if one accepts the notion of equity for intervention thresholds based on probability, then the BMD threshold is in fact discriminatory by race and ethnicity. For example, if the intervention threshold is set at 20%, then the equivalent T-score at age 65 years is − 2.8 for White women but − 3.7 for Asian women, − 3.8 for Hispanic women and − 4.2 for Black women [7]. Thus, the use of FRAX generating an individualised absolute probability as a gateway for intervention helps to resolve, rather than exacerbate, current ethnic/racial inequalities. Where appropriate information exists, other countries have opted to take advantage of race- and ethnic-specific models (Brunei, Malaysia, Singapore and South Africa) [34, 41–43].

Considering ethnicity

It has been argued that even if race or ethnicity does associate with clinical outcomes, this does not necessarily justify its inclusion in diagnostic or predictive tools [2]. The rationale is that most adjustments assume that genetic difference tracks reliably with ethnicity and race. While the aspiration that consideration of genetic architectures might replace the need for race or ethnicity is worthy [44], its potential contribution to osteoporosis management is presently limited [45] and restricted to only a small component of fracture risk (bone mineral density) [46–48]. The counter argument is that risk factors should be chosen according to established criteria irrespective of our understanding of their basis or their accuracy [7]. A good example is consumption of alcohol, which is notorious for being inaccurately reported. In general, people who drink alcohol tend to underestimate their alcohol consumption [49, 50]. It matters not whether the return is accurate—only that it provides a consistent indication of risk, which it does [51]. Thus, we are more interested in association than causality, and in consistency of input variable ascertainment between generation of the tool and use of that tool in clinical practice. The same considerations clearly also apply to race, geographic location and ethnicity.

Considering FRAX

FRAX is a computer-based algorithm (http://www.shef.ac.uk/FRAX and http://www.fraxplus.org) developed by the then World Health Organization Collaborating Centre for Metabolic Bone Diseases at Sheffield, UK, and first released in 2008. The algorithm, intended for use in primary care, calculates fracture probability from easily obtained clinical risk factors (CRFs) in men and women [52, 53]. The output of FRAX is the 10-year probability of a major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture. Fracture probability varies markedly in different regions of the world [20]. Thus, the FRAX models need to be calibrated to those countries where the epidemiology of fracture and death is known. Models are currently available for 85 countries across the world. The performance of FRAX can be assessed by the increase in risk of fracture per SD unit increase in risk score. The use of CRFs in conjunction with BMD and age improves the sensitivity of fracture prediction without adversely affecting specificity. At the age of 70 years, for example, the risk of hip fracture increases by 1.84 (95% CI 1.65–2.05) for each SD change in risk score when BMD is not entered. The gradient of risk increases to 2.91 (2.56–3.31) when BMD is included [54]. Overall, the predictive value of FRAX compares favourably with other risk engines such as the Gail score for breast cancer [55].

Notwithstanding, FRAX is far from perfect. Since FRAX is calibrated using national or regional estimates of fracture and death rates, it is axiomatic that FRAX is only as good as the source epidemiology. In this regard, we agree with the ASBMR Task Force that updated representative information is required on the incidence of fracture and death in all ethnicities including American Indians and those of mixed race and ethnicity who are not included in the current iteration of FRAX [13]. Nevertheless, since its launch in 2008, FRAX has proven to be well calibrated in diverse populations from Canada, Israel, Japan, Norway, Taiwan, the UK and US [56–63]. In the recent ASBMR review, analysis of calibration (expressed as observed/expected ratios) reported that FRAX (without BMD) modestly overestimated hip fracture probabilities but that the ethnicity and race-adjusted ratios were similar for different race and ethnicity groups (range mostly 0.8–0.9) [15]. What is not fully explored is whether the clinical risk factors that are input into FRAX have the same weight in racial/ethnic subgroups in the US. The available evidence suggests that this is likely to be the case. Thus, a prior fragility fracture, a given BMD or a history of falls has a similar significance on fracture risk in the White as in the non-White community [8, 64, 65].

While appreciated for its simplicity, an important limitation of FRAX is that several of the input variables do not account for degree of exposure, such as the increase in fracture risk with increasing dose and duration of oral glucocorticoids, the recency and number of prior fractures and magnitude of tobacco and alcohol exposure [66]. Concerns regarding the lack of provision for lumbar spine BMD (commonly recommended in treatment guidelines) and the absence of measurements of the material or structural properties of bone have also been highlighted. To address some of these limitations, a number of exploratory analyses have been conducted in population cohorts

to examine the impact of factors outside of those included in FRAX, with access to these adjustments now being provided via the FRAXplus web-based platform (www.fraxplus.org) [52]. These additions are expected to further improve fracture risk assessment whereas deletions such as adjustments for race and ethnicity will have the opposite effect.

Conclusions and next steps

We agree that race and ethnicity discrimination in the US (and elsewhere} make this an important issue to address. In their editorial, Vyas et al. [2] proposed three questions that should be asked regarding clinical algorithms that include race and ethnicity: 'Is the need for race correction based on robust evidence and statistical analyses? Is there a plausible causal mechanism for the racial difference that justifies the race correction? And would implementing this race correction relieve or exacerbate health inequities?' As outlined above, the answer in the case of FRAX favours race and ethnicity responsive models for all three questions. We consider that the lower probability of fracture in the non-White community appropriately reflects the well-documented lower fracture hazards in non-White individuals compared with White individuals. As noted by the Agency for Healthcare Research and Quality, intentional consideration of race to reduce disparities can be beneficial [67] and as echoed by the British Medical Journal, the thoughtful use of race and ethnicity can help identify and address health inequalities [68]. A single race-agnostic FRAX model for the US would decrease the performance characteristics of FRAX by at least as much as omitting a prior fracture as an input variable. Is it equitable to use a knowingly inaccurate calculator? Moreover, it would disadvantage the non-White community who would consequently be exposed to unnecessary treatments, some with adverse events. This is a view also endorsed by the International Osteoporosis Foundation [7] and now by its Working Group on Epidemiology and Quality of Life and by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO).

We are informed that the FRAX team is always willing to respond to requests to update FRAX models and has done so frequently, usually as a result of updated fracture epidemiology. On the assumption that the Task Force recommendations are accepted by the ASBMR, if other stakeholders in the US including the Bone Health and Osteoporosis Foundation, the Endocrine Society, Menopause Society and the American Association of Clinical Endocrinologists were of the same mind as the ASBMR Task Force, then the FRAX team would reluctantly accommodate the request.

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The Board of the IOF comprise Nicholas C Harvey (President), Cyrus Cooper, Bess Dawson-Hughes, Famida Jiwa, John A Kanis, Eugene V McCloskey, Jean-Yves Reginster, Rene Rizzoli and the following regional representatives:

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	Daniel Pinto (USA)
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Declarations

Ethics approval and consent to participate This position paper contains no original data or personal information and thus issues of ethics, informed consent, and patient confidentiality do not apply.

Conflict of interest JA Kanis led the team that developed FRAX as director of the WHO Collaborating Centre for Metabolic Bone Diseases at Sheffield; he is a director of Osteoporosis Research Ltd that maintains FRAX. EV McCloskey, M Lorentzon, NC Harvey, M Schini, E Liu, L Vandenput and H Johansson are members of the FRAX team. JA Kanis, NC Harvey and EV McCloskey are members of the advisory body to the National Osteoporosis Guideline Group.
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