Published in final edited form as:

Joint Bone Spine. 2016 October ; 83(5): 477–478. doi:10.1016/j.jbspin.2016.03.007.

Editorial for Joint Bone Spine: Use of FRAX® in men

Nicholas C Harvey¹, Eugene McCloskey², and John A Kanis²

¹MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton SO16 6YD, UK

²Centre for Metabolic Bone Diseases, University of Sheffield, Beech Hill Road, Sheffield S10 2RX

According to John Gray, author of “Men are from Mars, Women are from Venus” [1], there are fundamental psychological differences between men and women, which impact on relationships in daily life. In a medical context, osteoporosis was viewed historically in the same way as a disorder of women rather than men, and the majority of studies covering assessment and treatment have focused on women [2]. In recent decades, it has become increasingly appreciated that fragility fractures are also common in men. Indeed, whilst 50% of women will experience a fracture in their remaining lifetime after the age of 50 years, 20% of men will also experience such an event [3]; it has been estimated that 5.5 million men had osteoporosis in Europe in 2010 [4], with 10% of 75 to 79-year-old and 17% of 80 to 84-year old men in Sweden found to have bone mineral density (BMD) in the osteoporotic range [5]. The impact of fragility fracture is similar in men and women, in terms of fracture site, associated comorbidity and reduced survival [3, 6, 7]. This raises the question of whether there are intrinsic differences between men and women, which impact on the assessment of fracture risk.

Men generally have larger bones than women, and since DXA BMD is highly size-dependent, men usually have higher BMD values at the femoral neck than do women of the same overall body size. This observation has sparked debate about what should constitute the reference range for BMD-defined osteoporosis, specifically whether the T-score reference range should be sex-specific. This issue has been reviewed in detail and published as a consensus document in 2011 [2]. Important considerations are whether the gradient of risk (the change in risk of fracture per standard deviation change in BMD) differs between men and women, and whether the absolute risk of fracture at a given T-score also differs. Although there are disparities between studies, as a result of variable age ranges, populations and sex adjustment, a comprehensive meta-analysis demonstrated that the gradient of risk appears to be similar in both sexes [8]. Interestingly, the absolute incidence of hip fracture and of all fractures by femoral neck T-score also appears similar in men and women. This is perhaps surprising given that male and female bones age differently, with men tending towards thinning trabeculae and women towards trabecular perforation, and sex-dependent differences in deterioration of cortical structure [9]. As DXA integrates information from density, structure and size, it may simply be that these various components happen to come together such that the measure acts similarly at these sites in both sexes. Whether fortuitous

or not, these data support the consensus that the NHANES III reference range in healthy women aged 20-29 years at the femoral neck is appropriate for both men and women when assessed by DXA.

With the development of the FRAX[®] algorithm, DXA BMD has moved from being the basis of the operational definition of osteoporosis to become one of several factors considered in fracture risk assessment [10, 11]. FRAX was released in 2008 by the World Health Organization (WHO) Collaborating Centre at Sheffield, UK, designed for estimating individualized 10-year probability of hip and major osteoporotic fracture (hip, clinical spine, distal forearm, and proximal humerus) [11]. The FRAX tool integrates eight clinical risk factors (CRFs: prior fragility fracture, parental hip fracture, smoking, systemic glucocorticoid use, excess alcohol intake, body mass index, rheumatoid arthritis, and other causes of secondary osteoporosis), which, in addition to age and sex, contribute to a 10-year fracture risk estimate independently of BMD. BMD from the femoral neck is an optional input variable when FRAX is used to calculate 10-year fracture probability. FRAX is based on meta-analyses of 12 international cohorts comprising 59,644 individuals and validated in a further 11 cohorts comprising 230,486 individuals. Given the historical focus of osteoporosis on women rather than men, it is not surprising that men make up a minority of participants in the original FRAX cohorts (25%). In relation to potential male-female disparities, important questions are whether there are differences between men and women in terms of the gradient of risk between the risk factor and the fracture outcomes, the threshold for intervention derived from FRAX, e.g. those of the UK National Osteoporosis Guideline Group (NOGG) [12], and the efficacy of medications aimed at fracture prevention.

In terms of the clinical risk factors included in FRAX, adiposity is a particular characteristic which has complex interactions with BMD and fracture risk, and which may vary by sex. Although increasing BMI has historically been associated with reduced fracture risk, a recent study has demonstrated the complex nature of these relationships. Thus in a meta-analysis comprising 398,610 women (mean age 63 years), increasing BMI was protective for osteoporotic fractures, but after adjustment for BMD, obesity became a risk factor for such events [13]. Associations varied by individual fracture types. Fewer data exist for men, and in the US MrOS cohort, the majority of men were overweight or obese, reflecting the very high prevalence in the US, as is becoming the case in many Western populations. Findings in this group suggested that despite the increased loads imposed on the skeleton, BMD was not appropriately increased to compensate for the greater fat mass [14] such that fracture risk was substantially greater in obese than non-obese men when adjusted for BMD. Furthermore, obese men may have poorer physical function than normal weight men, and potentially be at increased risk of falling [14]. Finally hip tissue thickness may not protect men in the same way as women, possibly because of differences in weight distribution [15] between waist and hips. With regard to other clinical risk factors which are incorporated in the FRAX calculator, where it is possible to assess sex differences in the gradient of risk, for example smoking and alcohol consumption, these appear similar in men and women [11].

FRAX is central to the current approach of the UK National Osteoporosis Guideline Group (NOGG) to intervention, which has evolved from the original UK Royal College of

Physicians guidance, and which is based on the notion that an individual with a prior fragility fracture should be considered for treatment, particularly at older ages [12]. Thus in the NOGG guidance, the age-dependent intervention threshold is set at the probability of future fracture equivalent to that of a female with average BMI and who has had a previous fragility fracture, but who has no other risk factors, and without inclusion of BMD. A similar age-dependent threshold is recommended for postmenopausal women in France [16] and elsewhere[17]. Given that the background risk of fracture is lower in men than women, a smaller proportion of men than women will be found to warrant treatment. Furthermore the cost-effectiveness of this approach appears similar in men and women [18, 19]. The global burden of high fracture probability, derived using these principles, has been recently documented, and suggests that worldwide 3.1% of men and 18.2% women had a fracture probability above the intervention threshold in 2010, equating to around 21 million men and 137 million women aged 50 years or more [20]. Using population projections, these numbers are set to approximately double over the next 30 years, with increases most marked in Asia. Although male fracture risk assessment has advanced substantially in recent years, information on the efficacy of many drugs in men has come from the use of surrogate endpoints such as bone mineral density and bone turnover markers [2], with the primary studies in women using fracture outcomes. Thus for many treatments direct evidence of efficacy for fracture reduction in men is lacking (although fracture data are available for men treated with zoledronic acid); changes in BMD and bone turnover markers appear comparable in men and women, and although they do not fully account for anti-fracture efficacy in women, the similar changes by sex are reassuring [2].

In conclusion, over the last 3 decades, the perception of osteoporosis has been transformed from one of an inevitable consequence of ageing in women, to that of a serious and devastating non-communicable chronic disease which also affects men, and for which effective assessment and therapeutic strategies exist. Over recent years, our understanding of the pathophysiology of bone loss in men as well as in women has been refined, partly due to advances in imaging technology, such as high-resolution pQCT scanning, and due to increased inclusion of men in cohorts and trials. Although the lower number of men than women in the FRAX cohorts means that male-specific estimates are likely to be of reduced precision compared with those for females, the available evidence suggests that for the majority of considerations, relationships between risk factor and fracture risk are similar in men and women, and that current approaches are cost-effective in both sexes. Returning to the thoughts of John Gray, it is interesting, and perhaps somewhat ironic, that the gravitational fields of Mars (3.7 m/s^2) and Venus (8.9 m/s^2), being key determinants of skeletal strength, are rather at odds with the sex-specific epidemiology of osteoporosis.

References

1. Gray, J. Men are from Mars, Women are from Venus. Harper Collins; London, UK: 2012.
2. Kanis JA, Bianchi G, Bilezikian JP, Kaufman JM, Khosla S, Orwoll E, Seeman E. Towards a diagnostic and therapeutic consensus in male osteoporosis. *Osteoporos Int.* 2011; 22:2789–2798. [PubMed: 21509585]
3. Harvey N, Dennison E, Cooper C. Osteoporosis: impact on health and economics. *NatRevRheumatol.* 2010; 6:99–105.

4. Hernlund E, Svedbom A, Ivergard M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jonsson B, Kanis JA. Osteoporosis in the European Union: medical management, epidemiology and economic burden : A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Archives of osteoporosis*. 2013; 8:136. [PubMed: 24113837]
5. Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A. Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. *Bone*. 2000; 27:585–590. [PubMed: 11062343]
6. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *OsteoporosInt*. 2004; 15:897–902.
7. Johnell O, Kanis JA, Oden A, Sernbo I, Redlund-Johnell I, Pettersson C, De Laet C, Jonsson B. Mortality after osteoporotic fractures. *OsteoporosInt*. 2004; 15:38–42.
8. Johnell O, Kanis JA, Oden A, et al. Predictive value of BMD for hip and other fractures. *JBone MinerRes*. 2005; 20:1185–1194.
9. Seeman E. Structural basis of growth-related gain and age-related loss of bone strength. *Rheumatology (Oxford)*. 2008; 47(Suppl 4):iv2–8. [PubMed: 18556646]
10. Kanis JA, Hans D, Cooper C, et al. Interpretation and use of FRAX in clinical practice. *OsteoporosInt*. 2011; 22:2395–2411.
11. Kanis, JA. Assessment of osteoporosis at the primary health care level. WHO Scientific Group Technical Report. World Health Organization; Geneva: 2007.
12. Compston J, Bowring C, Cooper A, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. *Maturitas*. 2013
13. Johansson H, Kanis JA, Oden A, et al. A meta-analysis of the association of fracture risk and body mass index in women. *J Bone Miner Res*. 2014; 29:223–233. [PubMed: 23775829]
14. Nielson CM, Marshall LM, Adams AL, LeBlanc ES, Cawthon PM, Ensrud K, Stefanick ML, Barrett-Connor E, Orwoll ES. BMI and fracture risk in older men: the osteoporotic fractures in men study (MrOS). *J Bone Miner Res*. 2011; 26:496–502. [PubMed: 20814955]
15. Freitas SS, Barrett-Connor E, Ensrud KE, Fink HA, Bauer DC, Cawthon PM, Lambert LC, Orwoll ES. Rate and circumstances of clinical vertebral fractures in older men. *Osteoporos Int*. 2008; 19:615–623. [PubMed: 18038109]
16. Briot K, Cortet B, Thomas T, et al. 2012 update of French guidelines for the pharmacological treatment of postmenopausal osteoporosis. *Joint Bone Spine*. 2012; 79:304–313. [PubMed: 22521109]
17. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int*. 2013; 24:23–57. [PubMed: 23079689]
18. Lippuner K, Johansson H, Borgstrom F, Kanis JA, Rizzoli R. Cost-effective intervention thresholds against osteoporotic fractures based on FRAX(R) in Switzerland. *Osteoporos Int*. 2012; 23:2579–2589. [PubMed: 2222755]
19. Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M. Treatment of established osteoporosis: a systematic review and cost-utility analysis. *Health technology assessment (Winchester, England)*. 2002; 6:1–146.
20. Oden A, McCloskey EV, Kanis JA, Harvey NC, Johansson H. Burden of high fracture probability worldwide: secular increases 2010-2040. *Osteoporos Int*. 2015; 26:2243–2248. [PubMed: 26018089]