

Burden of high fracture probability worldwide: secular increases 2010–2040

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Abstract

Summary The number of individuals aged 50 years or more at high risk of osteoporotic fracture worldwide in 2010 was estimated at 158 million and is set to double by 2040.

Introduction The aim of this study was to quantify the number of individuals worldwide aged 50 years or more at high risk of osteoporotic fracture in 2010 and 2040.

Methods A threshold of high fracture probability was set at the age-specific 10-year probability of a major fracture (clinical vertebral, forearm, humeral or hip fracture) which was equivalent to that of a woman with a BMI of 24 kg/m² and a prior fragility fracture but no other clinical risk factors. The prevalence of high risk was determined worldwide and by continent using all available country-specific FRAX models and applied the population demography for each country.

Results Twenty-one million men and 137 million women had a fracture probability at or above the threshold in the world for the year 2010. The greatest number of men and women at high risk were from Asia (55 %). Worldwide, the number of high-risk individuals is expected to double over the next 40 years.

Conclusion We conclude that individuals with high probability of osteoporotic fractures comprise a very significant disease burden to society, particularly in Asia, and that this burden is set to increase markedly in the future. These analyses provide a platform for the evaluation of risk assessment and intervention strategies.

Keywords Burden of disease · Epidemiology · Fracture probability · FRAX · Intervention threshold · Osteoporosis

Introduction

The Global Burden of Disease study demonstrated a massive impact of musculoskeletal conditions on populations worldwide [1–3]. The associated expenditure is equivalent to 3 % of gross national product annually [WHO 2003]. Musculoskeletal illness is the second greatest cause of years lived with disability globally [1] and accounts for 6.8 % of total disability-adjusted life years worldwide; this figure has risen by 45 % since 1990, in contrast to the mean rise of 33 % for other disease areas [2]. The contribution of osteoporosis and associated fractures to the burden worldwide has been characterised in terms of specific fracture sites [4–7], bone mineral density [8], life years lost and disability-adjusted life years lost [6, 7]. Although defining osteoporosis burden by the occurrence of hip, or other fractures, or consequent disability has the merit of being based on discrete events, it may be more helpful for disease prevention to consider the burden in terms of those at high risk of a future fracture, that is, the population to whom treatment might be usefully administered [9].

Historically, the World Health Organization's classification of osteoporosis, based on the measurement of BMD [10], has served as the framework for characterisation of a high fracture risk individual (defined, operationally, as a T-score of –2.5 or below, with BMD at the femoral neck as the international reference standard [11]). Whereas these criteria have commonly provided intervention thresholds for the treatment of osteoporosis, the development of risk assessment algorithms has shown that prevention of fractures is better targeted on the basis of fracture probability using multiple risk factors rather than BMD alone [9, 12]. Probability-based thresholds have

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been recommended by the Committee for Medicinal Products for Human Use (CHMP) and many assessment guidelines [13–15], with FRAX® being the tool most widely used globally to generate fracture probabilities [16].

The advent of FRAX has permitted intervention thresholds to be based on fracture probability, i.e. the probability above which treatment can be recommended, and in many countries (including North America for spine and hip fracture), the view is taken that treatment can be recommended in women with a prior fragility fracture. Thus, the FRAX probability equivalent to that conferred by a prior fracture may be used to categorise a patient as high fracture risk. Indeed, such approach has been adopted in the UK by the National Osteoporosis Guideline Group (NOGG) [17], and in European Guidance [18, 19], country-specific guidelines [17, 20–27] and in Health Technology Assessment of the burden of disease [15, 28, 29]. Thus, the aim of the present study was, using FRAX, to estimate the burden of disease worldwide in terms of high fracture probability.

Methods

Fracture threshold

We defined the threshold of high fracture probability as the age-specific 10-year probability of a major fracture (clinical vertebral, forearm, humeral and hip fracture) which was equivalent to that of a woman with a prior fragility fracture and no other clinical risk factors. For the purposes of this report, this threshold was termed the ‘fracture threshold’. Probabilities at the fracture threshold were calculated from the age of 50 years in 5-year age intervals without the inclusion of BMD, and body mass index was set to 24 kg/m². Note that the threshold varies with age. The identical age-specific

threshold was used for men. The principal reason for using the same probability thresholds in men as used in women is that men at high risk are categorised in guidelines in this manner. The argument for this position is not only that of equity but also that the cost-effectiveness of intervention at any given probability is very similar in men compared with women [30, 31].

Since the risk of fracture varies from country to country, as does the risk of death [32], fracture probability also varies. For this reason, an age- and sex-specific probability-based definition of high risk was calculated for each country where a FRAX model was available using FRAX (version 3.8).

Disease burden

The proportion of men and women who exceed the probability threshold for fracture was computed from the distribution of the risk score among the cohorts used to develop FRAX. The proportion of men and women in each country who exceeded the probability threshold was derived from the independent correlations (calculated mathematically) of the normalised distributions of the risk scores for hip fracture, other major osteoporotic fractures and death. The number of men and women at or above the fracture threshold was determined from the population demography for each country using UN data for 2010 [33] (medium variant) in 5-year age intervals from the age of 50 years with an upper age category of 95+ years.

Countries where a FRAX model was available were categorised by geographical region (Table 1). Where more than one FRAX model was available for a country (the USA and Singapore), the model representing the largest population was used (Caucasian and Chinese, respectively). FRAX models were available for 53 countries (March 2014) that represented 79 % of the world population aged 50 years or

Table 1 Geographical regions and their representation by FRAX

Region	Countries with FRAX model	Proportion of the region represented by FRAX countries (%)
Africa	Morocco, Tunisia	7
Asia	Armenia, China, Hong Kong, India, Indonesia, Japan, Jordan, Lebanon, Palestine, Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, Turkey	84
Europe	Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lithuania, Malta, Netherlands, Norway, Poland, Portugal, Romania, Russia, Slovakia, Spain, Sweden, Switzerland, UK	88
Latin America *	Argentina, Brazil, Chile, Colombia, Ecuador, Mexico	75
North America	Canada, USA	100
Oceania	Australia, New Zealand	87
World	All countries with a FRAX model	79

*includes the Caribbean region

more. The coverage of the regions ranged from 7 % in Africa to 100 % in North America.

To determine the burden of high fracture probability by region, we assumed that the population-weighted proportion of men and women above the fracture threshold in FRAX countries was representative of each region. The number of men and women at or above the fracture threshold was determined from the population demography for each region using UN data for 2010 (medium variant) in 5-year age intervals [33].

Projections beyond 2010

The burden of disease, as measured by the number of men and women at or above the fracture threshold, was estimated from the future population projections up to 2040 in each geographical region using the medium variant of UN projections [33].

Results

The number of men and women at or above the fracture threshold for each region is given in Table 2. Approximately 21 million men and 137 million women aged 50 years or more across the world had a fracture probability at or above the fracture threshold for the year 2010. The highest number of individuals above the fracture threshold was in Asia with more than 11 million men and 73 million women, respectively, comprising 55 and 54 % of all men and women aged 50 years identified at risk. Men and women in Europe accounted for 17

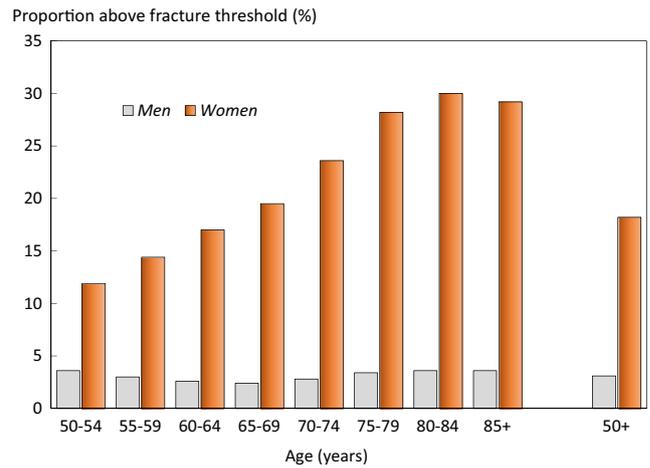


Fig. 1 Proportion (%) of men and women worldwide above a fracture threshold by age calculated without BMD for 2010

and 22 % of the global burden, respectively. In each of the other regions, the global burden was less than 10 % of the total. The proportion of the population above the fracture threshold increased with age. The increase with age was not marked in men but rose progressively with age in women. In the age range 50–54 years, 11.9 % exceeded the threshold and this rose progressively with age to 30 % in the age group 80–84 years (Fig. 1).

Over all ages, the female to male ratio was 6.6 worldwide, ranging from 5.1 in Africa to 8.4 in Europe (Table 3). In all regions, the ratio of female to male at risk increased at older ages, reflecting the greater longevity of women compared with men. This was also reflected in lower geographic

Table 2 Number of individuals (thousands) with a 10-year probability of a major osteoporotic fracture calculated without BMD above the fracture threshold in the year 2010

Region	Age (years)								
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85+	50+
Men									
Africa	652	392	260	205	195	146	85	36	1970
Asia	3706	2835	1654	1122	975	750	395	187	11623
Europe	924	703	508	343	355	316	237	153	3539
Latin America	510	347	255	209	185	160	106	60	1833
North America	523	343	245	158	122	125	103	79	1699
Oceania	44	36	30	23	20	15	12	9	187
World	6359	4655	2953	2058	1852	1512	937	525	20851
Women									
Africa	2009	1929	1745	1473	1209	910	502	231	10007
Asia	12210	13168	11320	9957	9602	8403	5415	3455	73529
Europe	3281	3756	3943	3528	4744	4204	3470	2809	29735
Latin America	1737	1789	1701	1544	1436	1224	877	662	10969
North America	1575	1646	1640	1454	1302	1265	1220	1267	11368
Oceania	128	147	164	137	134	117	100	99	1026
World	20939	22434	20512	18093	18425	16124	11585	8523	136634

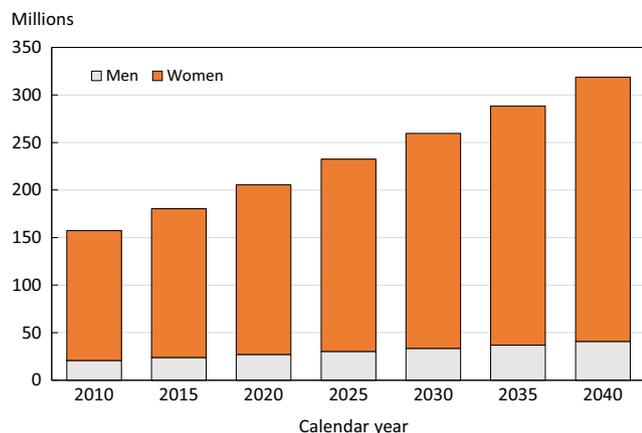
Table 3 Female to male ratios of the number of individuals with a 10-year probability of a major osteoporotic fracture calculated without BMD above the fracture threshold in the year 2010

Region	Age (years)								
	50–54	55–59	60–64	65–69	70–74	75–79	80–84	85–	90–
Africa	3.1	4.9	6.7	7.2	6.2	6.2	5.9	6.4	5.1
Asia	3.3	4.6	6.8	8.9	9.8	11.2	13.7	18.5	6.3
Europe	3.6	5.3	7.8	10.3	13.4	13.3	14.6	18.4	8.4
Latin America	3.4	5.2	6.7	7.4	7.8	7.7	8.3	11.0	6.0
North America	3.0	4.8	6.7	9.2	10.7	10.1	11.8	16.0	6.7
Oceania	2.9	4.1	5.5	6.0	6.7	7.8	8.3	11.0	5.4
World	3.3	4.8	6.9	8.8	9.9	10.7	12.4	16.2	6.6

variation in the female to male ratios at younger ages but a much greater variation in the population aged 85+; here, the ratios ranged from 6.4 in Africa to 18.4 in Europe.

Globally, 3.1 % of men and 18.2 % of women had a fracture probability above the fracture threshold (see Fig. 1). Again, there was some variation by continent with the highest proportion of the female population aged 50 years or more in Oceania and Europe (20.6 and 20.2 %, respectively) and the lowest in Africa and Asia (16.7 and 17.7 %, respectively).

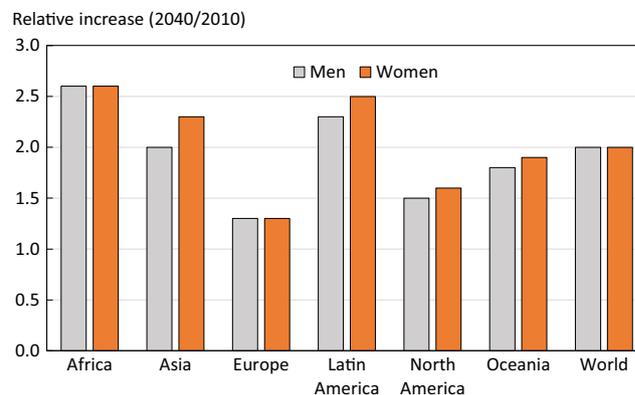
Based on expected demographic changes, the number of men and women exceeding the fracture threshold is expected to increase twofold from 157 million in 2010 to 319 million over a 30-year interval (Fig. 2). Increases were noted for all regions but were particularly marked in Africa and Latin America. The most modest rise (by 30 %) was seen for Europe (Fig. 3). As expected (see Table 2), Asia had the highest proportion of the global burden (59.9 % in women), followed by Europe (14.0 %), Latin America (9.7 %), Africa (9.2 %), North America (6.5 %) and Oceania (0.7 %). The respective share in men was 58.5, 11.2, 10.3, 2.8, 6.3 and 0.8 %.

**Fig. 2** Number of individuals (millions) having a 10-year probability of a major osteoporotic fracture calculated without BMD above the fracture threshold for the years 2010–2040

Discussion

To our knowledge, this is the first attempt to estimate the global burden of disease in terms of fracture probability and complements previous studies which have quantified the burden by hip fracture [4–6], major osteoporotic fracture [7], osteoporosis based on densitometry [8], or disability-adjusted life years and life years lost [6, 7].

We defined the threshold of high fracture probability as the age-specific 10-year probability of a major fracture (clinical vertebral, forearm, humeral or hip fracture), which was equivalent to that of a woman with a BMI of 24 kg/m² and a prior fragility fracture but no other clinical risk factors. As noted in the introduction, the same threshold is used directly or indirectly in many assessment guidelines. Under the assumptions used for this study, we estimated that there were approximately 21 million men and 137 million women worldwide that had a fracture probability at or above this threshold in 2010 of which a majority (55 %) came from Asia. The high prevalence in Asia is consistent with the preponderance of major fractures that are found in Asia [4, 5]. As might be expected, these figures exceed the 56.2 million major osteoporotic fractures estimated worldwide in 2000 [7] which for the year 2010 may be uplifted to 74.2 million, as judged by the population

**Fig. 3** The increase in the number of men and women with a 10-year probability of a major osteoporotic fracture above the fracture threshold between the years 2010 and 2040

growth. Given that major fractures account for 60–65 % of all osteoporotic fractures depending on age [34], the number of fragility fractures in 2010 is likely to exceed 120 million. These considerations indicate that a large majority of individuals at high risk (at or above a fracture threshold) have already sustained a fragility fracture. This view is supported by an analysis in the UK where approximately 93 % of women identified in this way had sustained a prior fragility fracture [35]. The changes in population demography suggest that the numbers at high risk will double over the next 40 years.

The present estimates provide a platform on which to evaluate the impact of assessment strategies. For example, screening of women from the age of say 65 years with FRAX (without a BMD test) would identify 72.8 million women (28 % of all women aged 50 years or more) representing 53 % of the postmenopausal population at high risk (see Table 2). Additionally, the methodology could be extended to assessing the potential impact of intervention using a “high-risk” strategy (targeting intervention to those at high risk) or a global strategy to decrease fracture probability in populations such as in postmenopausal women.

The present study relies on a number of assumptions that may affect the reliability of our estimates. The assessment is based on the availability and adequacy of FRAX models and the assumption that in each region, the available models are representative of the region as a whole. Overall, the countries with a FRAX model cover 79 % of the world population but FRAX models in Africa (Morocco and Tunisia) account for only 7 % of the African population. Moreover, the fracture probabilities in North Africa are likely to overestimate those in the rest of the continent. The global impact is likely to be small because of the low fracture probabilities and modest population size. More complete information is available for high-risk countries in the developed world.

A further consideration relates to the construct of the FRAX models. The majority of the FRAX models rely on the assumption that the age- and sex-specific incidence of clinical spine, forearm and proximal humerus fractures can be derived from hip fracture rates [14]. This assumption seems to be reasonable, at least in the Western world, but it may not hold true for morphometric vertebral fractures [36, 37]. With regard to clinical vertebral fracture, there is a high correlation between hip fracture rates and admission to hospital for vertebral fracture such that vertebral fracture discharges are high in those regions where the incidence of hip fracture is also high [38, 39]. A recent long-term prospective study of the incidence of major fractures in Iceland has shown the reliable prediction of other major fractures from hip fracture rates [40]. Similar data have been reported in a North American cohort [41]. These limitations point to the need for more epidemiological information on fracture rates and their inter-relationships worldwide.

The threshold for high risk that we chose for the present study is intuitively appealing, representing the age-specific probability equivalent to a woman with a prior fracture. Many guidelines suggest that women with a prior fracture (limited to hip or spine fractures in some countries) merit intervention on this basis. Notwithstanding, the threshold is arbitrary. In this regard, it is notable that the threshold used for men was the same as that used in women which resulted in a somewhat stable prevalence of the high-risk category. Other thresholds, such as a fracture probability of 5, 10 and 20 %, are alternatives that have been partially explored [28, 42]. Our projection for the doubling of individuals at high risk depends on the adequacy of the future demographic shifts. Although uncertain, it is relevant to note that all individuals who will be aged 50 years or more in 40 years’ time have already been born. Thus, barring major catastrophes, the population projections are relatively robust. We have, however, not factored in secular changes in fracture probability, which may variously increase, decrease or remain stable over this period.

With these caveats, the present data suggest that individuals with high probability of osteoporotic fractures comprise a very significant disease burden to society, particularly in Asia, and are set to increase markedly in the future.

Conflicts of interest None.

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