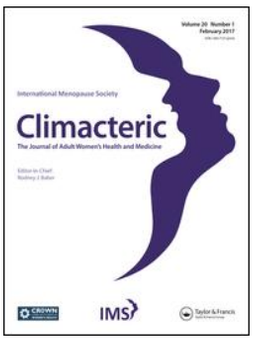

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REVIEW

Osteoporosis and fractures in women: the burden of disease

M. Lorentzon[a,b,c], H. Johansson[a,c], N. C. Harvey[d,e], E. Liu[a], L. Vandenput[a,c], E. V. McCloskey[f,g] and J. A. Kanis[c,f]

[a]Sahlgrenska Osteoporosis Centre, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden; [b]Region Västra Götaland, Department of Geriatric Medicine, Sahlgrenska University Hospital, Mölndal, Sweden; [c]Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Australia; [d]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK; [e]NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK; [f]Centre for Metabolic Bone Diseases, University of Sheffield Medical School, Sheffield, UK; [g]MRC and Arthritis Research UK Centre for Integrated Research in Musculoskeletal Ageing, Mellanby Centre for Bone Research, University of Sheffield, Sheffield, UK

ABSTRACT

Osteoporosis is a disease characterized by impaired bone microarchitecture and reduced bone mineral density (BMD) resulting in bone fragility and increased risk of fracture. In western societies, one in three women and one in five men will sustain an osteoporotic fracture in their remaining lifetime from the age of 50 years. Fragility fractures, especially of the spine and hip, commonly give rise to increased morbidity and mortality. In the five largest European countries and Sweden, fragility fractures were the cause of 2.6 million disability-adjusted life years in 2016 and the fracture-related costs increased from €29.6 billion in 2010 to €37.5 billion in 2017. In the European Union and the USA, only a small proportion of women eligible for pharmacological treatment are being prescribed osteoporosis medication. Secondary fracture prevention, using Fracture Liaison Services, can be used to increase the rates of fracture risk assessment, BMD testing and use of osteoporosis medication in order to reduce fracture numbers. Additionally, established primary prevention strategies, based on case-finding methods utilizing fracture prediction tools, such as FRAX, to identify women without fracture but with elevated risk, are recommended in order to further reduce fracture numbers.

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Postmenopausal osteoporosis

Osteoporosis is a disease characterized by impaired bone microarchitecture and reduced bone mineral density (BMD) resulting in bone fragility and increased risk of fracture [1,2]. BMD measured using dual-energy X-ray absorptiometry to a large extent reflects bone strength [3], and for each standard deviation (SD) decrease in femoral neck BMD, the fracture risk is increased two-fold to three-fold [4] in postmenopausal women. In 1994, the World Health Organization (WHO) defined osteoporosis using a BMD threshold of −2.5 SDs or lower than the mean value for young adult women, referred to as a *T*-score of −2.5 SD or less. A measurement of BMD at the femoral neck, and derivation of the *T*-score using the National Health and Nutrition Examination Survey (NHANES) III reference database with women aged 20–29 years, has been proposed as the reference standard for describing osteoporosis. However, other sites such as the total hip, lumbar spine and radius are frequently used in clinical practice [5,6]. Aging leads to bone loss, and, particularly, the first few years after menopause represent a period of accelerated bone loss [7]. Thus, the prevalence of osteoporosis increases with age [2].

Densitometric osteoporosis is asymptomatic, as the patients affected are unaware of the disease until they sustain a fragility fracture. Common fractures associated with low BMD include fractures of the spine, hip, forearm, proximal humerus, ribs, sternum, pelvis, sacrum and clavicle, whilst fractures of the ankle, hands, feet and skull are to a lesser extent associated with BMD and generally not considered osteoporotic [8,9]. Overall, however, the majority of fractures in postmenopausal women are low-trauma fractures and fall into the osteoporotic category [2].

In western societies, one in three women and one in five men aged 50 years or older will sustain an osteoporotic fracture in their remaining lifetime [10]. Many of these fractures have clinically important and sometimes severe consequences. Fractures, especially those of the spine and hip, often lead to functional decline, disability, chronic pain, reduced quality of life and increased morbidity and mortality [11–13]. Thus, osteoporotic fractures are common and have severe

CONTACT Mattias Lorentzon mattias.lorentzon@medic.gu.se Geriatric Medicine, Institute of Medicine, Sahlgrenska University Hospital, University of Gothenburg, Mölndal, 43180, Sweden

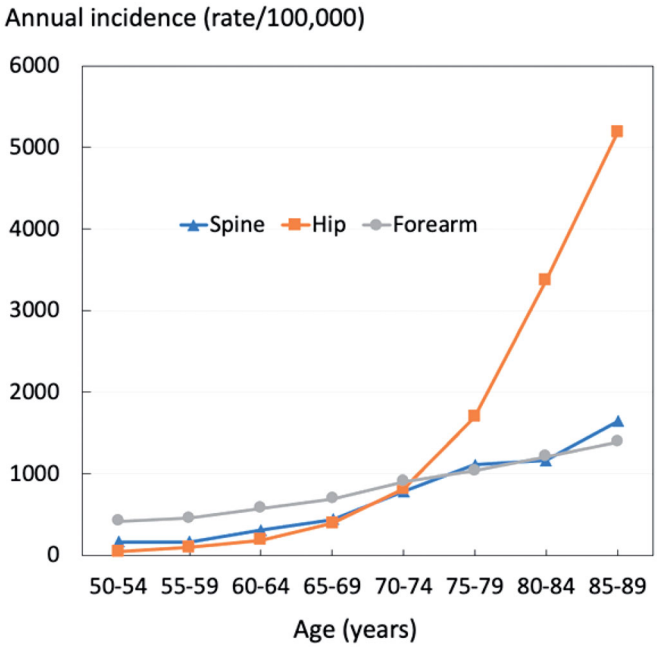

Figure 1. Age-specific incidence of vertebral, hip and forearm fractures in women from Sweden. Figure compiled from data presented in Kanis et al. [8].

long-term consequences, and therefore constitute a major public health concern.

Prevalence of osteoporosis

Using the femoral neck BMD definition of osteoporosis, a *T*-score of −2.5 SD or below, approximately 200 million women have osteoporosis globally [5,14]. As a result of BMD declining with age, the proportion of women having osteoporosis increases with age. At age 60 years about 10% are affected, at age 70 years about 20%, at 80 years approximately 40% and at age 90 years as many as two-thirds of all women have osteoporosis [15].

Epidemiology of fractures

In 2000, there were approximately 9 million new osteoporotic fractures worldwide, of which 1.7 million were forearm fractures, 1.4 million were clinical vertebral fractures and 1.6 million were hip fractures [16]. In total, 51% of these fractures occurred in Europe and the Americas, and most of the remainder occurred in Southeast Asia and in the Western Pacific. In general, nearly twice as many fractures occur in women than in men, and in the case of hip fractures, nearly 75% affect women [17].

As a result of age-dependent decline in BMD, increasing prevalence of sarcopenia, frailty and falls, the risk of fracture increases with age [2,18]. The incidence of vertebral fracture in women starts to rise at around age 60 years and accelerates to reach the highest levels after age 80 years. For hip fractures, the incidence in women starts to rise sharply after age 70 years with peak incidence rates above 80 years of age (Figure 1) [19].

Substantial differences in fracture rates between countries have been observed. The age-standardized annual hip

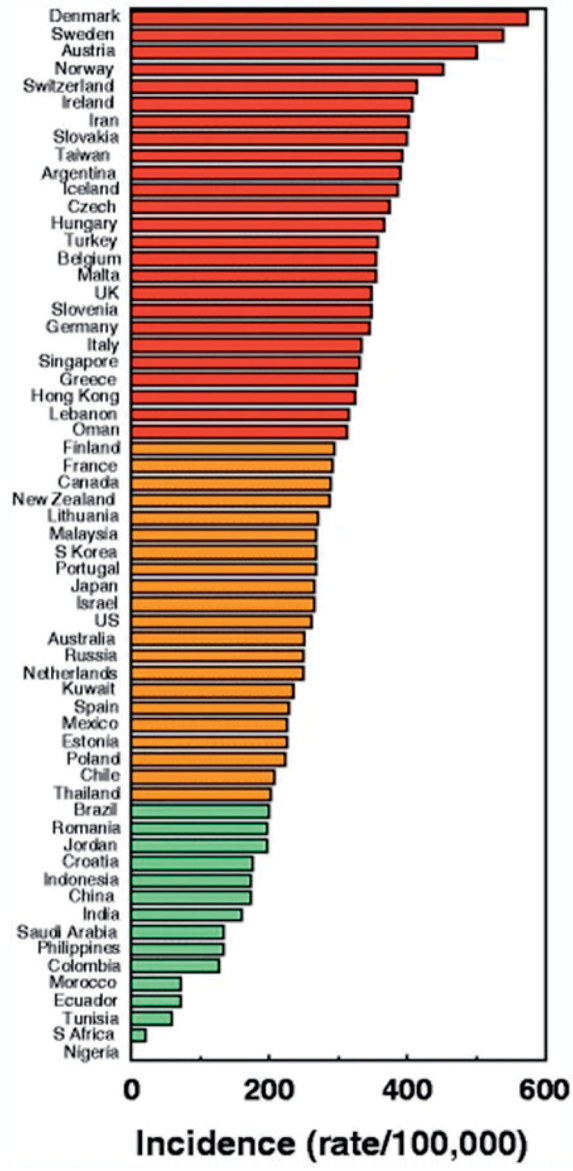

Figure 2. Age-standardized annual incidence of hip fractures in women (per 100,000) according to country together with the color codes to denote moderate, high and very high risk [20].

fracture rate per 100,000 women is the highest in the Scandinavian countries, reaching nearly 600 cases, as compared to the much lower rates around 300 cases in the USA and far fewer cases in many African countries [20] (Figure 2). The reason for the large difference in incidence between countries cannot be explained by differences in BMD; proposed contributing factors include differences in body composition, levels of physical activity, socioeconomic status, calcium intake and differences in sunlight exposure [21,22].

The lifetime risk of fracture also varies considerably according to country. For example, in Sweden, the lifetime probability of hip fracture has been estimated to be 22.8% in women after age 50 years. The corresponding probabilities for hip fracture for women in the UK, France, Spain and Germany are considerably lower, ranging from 10% to about 17% [23].

In comparison to other diseases and conditions, the health and social care burden consequent to osteoporotic

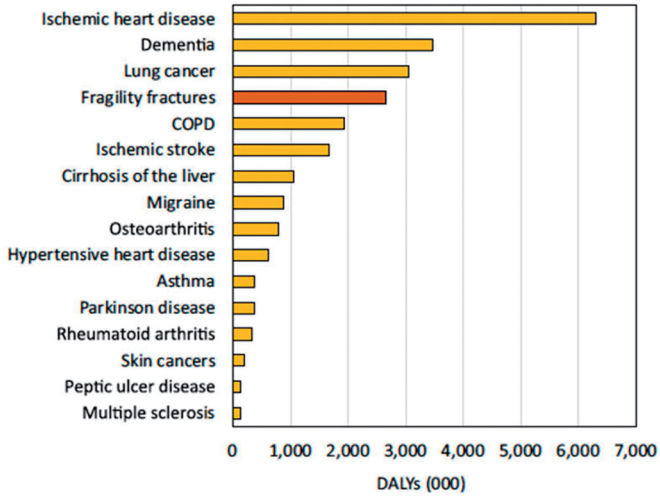

Figure 3. Disability-adjusted life years (DALYs) by disease in the five largest European countries and Sweden (EU6) in 17 selected non-communicable diseases [23]. COPD, chronic obstructive pulmonary disease.

fractures is substantial. Interestingly, the lifetime probability of major osteoporotic fracture for women in Europe is comparable to that of cardiovascular disease, which affects 29% of European women [24].

Patient burden

Fragility fractures in older women often lead to functional decline, disability, decreased quality of life, chronic pain and increased risk of morbidity and mortality [25–28]. As a consequence of most hip fractures occurring in often fragile women at an advanced age, usually after age 80 years, a considerable proportion of affected women need to move to residential care facilities due to increased frailty and functional loss after the hip fracture, leading to loss of autonomy [29].

The WHO's standard method to measure burden of disease uses disability-adjusted life years (DALYs), which include both the sum of years of life lost and the years lost due to disability. The sum of DALYs in the entire population yields the gap (or burden) between the present health status of the population and an ideal disease-free population [30]. In the five largest European countries and Sweden (EU6), fragility fractures were the cause of 2.6 million DALYs in 2016. Average years lost due to disability per 1000 people were much greater (15.1 years) than years of life lost (5.5 years), suggesting that disability due to fracture is the major contributor to DALYs lost in osteoporosis [23]. The number of DALYs due to fragility fractures in the EU6 countries was compared to 16 other non-communicable diseases and was outranked only by ischemic heart disease, dementia and lung cancer (Figure 3) [23,31].

Patient burden can also be assessed using quality-adjusted life years (QALYs) as the outcome, which quantify a year of an individual's life in relation to the average health-related quality of life during a year. As a point of reference, 1 QALY is equal to 1 year spent in perfect health and 0.5 QALYs can be defined either as 6 months spent in perfect health or as 12 months lived at 50% of perfect health. QALYs are particularly useful in health-economic analyses and can be used to compare societal burden across many diseases. In 2017, QALYs lost per capita due to fragility fractures varied considerably within the EU6 countries, and ranged from 4.2 per 1000 people in Sweden to 2.1 per 1000 people in France [23]. For all EU6 countries together, the total health burden caused by fragility fractures was 1.02 million QALYs in 2017 [23].

Fracture-related costs

The cost for fragility fractures is dependent on the need for surgical treatment, admission to hospital, length of stay and need for rehabilitation. Both short-term and long-term costs are incurred by fragility fractures. The length of stay after hip fracture varies considerably by country within the EU6, ranging from 11.6 days in Sweden to 20.5 days in the UK [23]. In the EU6, the fracture-related costs, both direct and indirect, increased from €29.6 billion in 2010 to €37.5 billion in 2017 [23]. Hip fractures are the cause of the greatest disutility and highest costs of all fractures [32]. In a systematic review including 130 studies globally, with over 670,000 hip fracture patients with patient-level hip fracture costs, the total costs covering healthcare costs and social costs the first year after a hip fracture were evaluated. The total 12-month cost was $43,669 per hip fracture patient. of which inpatient costs ($13,331) followed by rehabilitation care ($12,020) contributed the most [33].

Projections

Assuming that the current trends in fracture prevention will continue and the general population increases, with an aging demographic, the hospital and societal cost of fragility fractures will continue to increase. In Asia and South America, both the age-standardized incidence rates of hip fractures and the number of hip fractures are increasing [34]. In many western countries, the age-specific incidence of hip fracture has decreased during recent years but, due to the aging population, the absolute number of hip fractures has increased and is expected to continue to rise over the next decades [34]. A recent study of the Norwegian population concluded that health lost to hip fractures will nearly double, from 32,850 DALYs in 2020 to 60,555 DALYs in 2040, leading to an increase in the overall cost of 65%, despite a continued decline in the age-specific hip fracture rate. In the EU6, the total number of new fractures between 2017 and 2030 was, in a recent analysis, projected to increase from 2.7 million per year to 3.3 million in 2030, which equals an increase of 23.3%. In the same region, fracture-related costs are projected to increase to €47.4 billion in 2030, which would equal a 27% increase from the 2017 estimate [23].

Preventing fractures

Osteoporosis medication

Since the 1990s, a wide range of therapeutic options to treat osteoporosis and reduce fracture risk in postmenopausal

Table 1. Antifracture efficacy of the most frequently used treatments for postmenopausal osteoporosis when given with calcium and vitamin D, as derived from randomized controlled trials.

	Effect on vertebral fracture risk		*Effect on non-vertebral fracture risk*	
Treatment	*Osteoporosis*	*Established osteoporosis*[a]	*Osteoporosis*	*Established osteoporosis*[a]
Alendronate	+	+	NA	+ (including hip)
Risedronate	+	+	NA	+ (including hip)
Ibandronate	NA	+	NA	+[b]
Zoledronic acid	+	+	NA	+[c]
HRT	+	+	+	+ (including hip)
Raloxifene	+	+	NA	NA
Teriparatide	NA	+	NA	+
Denosumab	+	+[c]	+ (including hip)	+[c]

Table updated from Kanis et al. [77], distributed under a Creative Commons license (Attribution-Noncommercial). HRT, hormone replacement therapy; NA, no evidence available; +, effective drug.
[a]Women with a prior vertebral fracture.
[b]In subsets of patients only (post-hoc analysis).
[c]Mixed group of patients with or without prevalent vertebral fractures.

women has been introduced (Table 1). Generic bisphosphonates taken once weekly (alendronate and risedronate) or once yearly (zoledronic acid) are most commonly used; they reduce the relative risk of hip and spine fracture by approximately 40% and 50–70%, respectively, and are available at a low cost [35–38]. Denosumab, a monoclonal antibody against receptor activator of nuclear factor-κB ligand (RANKL), given as biannual injections, increases BMD more than bisphosphonates and, over longer time periods, is at least equally effective in reducing the risk of fractures at the hip and spine, and is generally well tolerated [39,40].

In more recent years, anabolic agents, including teriparatide, abaloparatide and romosozumab, have been shown to provide greater increases in spine and hip BMD as well as more effective fracture prevention than that which can be achieved with bisphosphonates in postmenopausal women with vertebral fracture and low BMD [41–44]. In this group of patients, teriparatide for 24 months and romosozumab for 12 months (followed by alendronate for 12 months) reduced the risk of vertebral fractures over 24 months by 56% and 48% compared to risedronate and alendronate, respectively [45,46]. Based on these findings, recent guidelines suggest that women at very high fracture risk should be considered for sequential treatment; that is, a treatment starting with an anabolic agent, followed by an antiresorptive agent [47,48]. Thus, with adequate identification of women at high or very high risk and with appropriate pharmacological intervention, a substantial proportion of fragility fractures could be prevented.

The discrepancy between eligible patients and patients actually treated is known as the treatment gap. In the European Union and in the USA, only a small proportion of women eligible for pharmacological treatment are being prescribed osteoporosis medication. In the EU6 countries, the average treatment gap (percent of eligible patients not treated) was 73% for women and 63% for men in 2017 [23]. In the USA, the use of osteoporosis medications in patients following a hip fracture declined from over 40% in 2002 to about 20.5% in 2011 [49]. A recent population-based Swedish study of older women 75–80 years old revealed that less than 22% of women with treatment indication according to national guidelines were being treated with osteoporosis medication [50].

Secondary fracture prevention

Large meta-analyses have shown that individuals who have sustained a fracture have about double the risk of a subsequent fracture as compared to their fracture-free peers [51,52]. Postmenopausal women with vertebral fractures have a particularly high risk of subsequent fractures and, for new additional vertebral fractures, the risk is increased over four times [53]. Of those with hip fracture, about half have previously sustained another fracture [54], suggesting that preventive measures targeted at patients with other fractures could be a valuable option to prevent the most serious fracture, the hip fracture.

The risk increase after fracture is not constant over time, but is markedly elevated (by about four to five times) in the first 2 years following the index fracture, emphasizing the importance of identifying fracture patients and intervening to reduce the risk of subsequent fracture early after the index fracture [55,56].

Secondary prevention programs called Fracture Liaison Services (FLS) have to some extent been implemented worldwide with the aim of reducing the treatment gap after a fragility fracture. To facilitate implementation and to uphold adequate care quality, Clinical Quality Standards for FLS have been developed in the UK, New Zealand and Canada [57–59]. Internationally endorsed clinical standards have also been developed by the International Osteoporosis Foundation (IOF) in the Capture the Fracture Program [60]. Patients included in FLS services have higher rates of evaluation with BMD assessment and treatment initiation as well as better adherence to pharmacological treatment [61,62]. However, data on the effect of FLS on rates of recurrent fractures have been very limited. A large study investigating the risk of subsequent fracture after a first fragility fracture in patients treated at hospitals, with and without an FLS, in western Sweden was recently presented. Patients cared for at hospitals with an FLS were much more likely to be evaluated with BMD testing and receive osteoporosis medication, and had 18% lower risk of recurrent fracture, than historic controls and patients treated at hospitals without FLS during the same time period [63].

Primary fracture prevention

The proportion of women who might be targeted for primary prevention differs substantially by country, due to the

large differences in prevalence of fragility fracture in women 50 years or older in different countries. For example, 90% of women in this age group would be eligible for screening in France while the corresponding proportion in Sweden would only be 77% [64,65]. Different case-finding strategies to identify women at high risk, due to the presence of risk factors such as use of oral glucocorticoids, heredity for osteoporosis or fracture, smoking or diseases causing secondary osteoporosis, who have not yet suffered fracture have been proposed [66–69]. The fracture risk assessment tool FRAX is the most widely used such model globally [70], and incorporates several important risk factors, with or without femoral neck BMD, for fracture and provides the 10-year probability of major osteoporotic fracture and hip fracture in women and men 40–90 years old. The FRAX tool can be used to identify women and men at high risk for fracture so that further evaluation with BMD testing and preventive measures can be instituted.

The UK National Osteoporosis Guideline Group (NOGG) has based its guidance on FRAX, with utilization of a FRAX intervention threshold at a fracture probability equal to the probability of a woman with a previous fracture [71]. The National Osteoporosis Foundation in the USA recommends osteoporosis medication for postmenopausal women with: a previous hip or spine fracture; a *T*-score of -2.5 SDs or less at the hip, femoral neck or spine; and a *T*-score at these sites of -1 to -2.5 SDs (osteopenia) and a 10-year probability of major osteoporotic fracture or hip fracture of $\geq$20% or $\geq$3%, respectively, according to the US-adapted FRAX tool [72].

Until recently, the effectiveness of risk-assessment strategies in which samples of the general population might be evaluated for risk factors and BMD estimation to derive individual estimates of absolute fracture risk, with targeting of anti-osteoporosis therapy on the basis of these estimates, remained uncertain. Publication of the Medial Research Council (MRC) SCreening of Older wOmen for the Prevention of fractures (SCOOP) trial provides strong support for such a strategy [73]. Over 5 years, compared to standard clinical care, the screening program reduced the number of hip fractures by 28%. Similar results were observed in a study from Denmark [74] but with lesser effects observed in a further study in the Netherlands [75]. A meta-analysis of the three trials showed that screening reduced the hip fracture risk by 20% [76].

Concluding remarks

Bone fragility and the resulting fractures are very common in postmenopausal women and projections indicate that, due to the aging population, an increase in the number of osteoporotic fractures, accompanied by substantially increased DALYs and financial costs, is to be expected globally. Secondary fracture prevention, orchestrated via implementation of FLS, so that a growing proportion of women at risk are evaluated and treated with osteoporosis medications is a crucial step in reducing fracture numbers. In addition, established primary prevention strategies, based on case-finding methods utilizing fracture prediction tools, such as FRAX, to identify women without fracture but with elevated risk, could be increasingly used in order to further reduce fracture numbers.

Potential conflict of interest M. Lorentzon has received lecture fees from Amgen, Astellas, Lilly, Meda, Renapharma and UCB Pharma, and consulting fees from Amgen, Radius Health, UCB Pharma, Renapharma and Consilient Health. N. C. Harvey has received consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, Servier, Shire, UCB, Kyowa Kirin, Consilient Healthcare, Radius Health and Internis Pharma outside the scope of the submitted work. E. McCloskey has received consultancy, research funding, lecture fees and/or honoraria from AgNovos, AgNovos, AstraZeneca, Consilient Healthcare, Fresenius Kabi, GSK, Hologic, Internis, Lilly, ObsEva, Synexus and UCB outside the scope of this work. All other authors have no conflicts of interest.

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