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The Epidemiology of Osteoporosis

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Abstract

Introduction—With a worldwide ageing population, the importance of the prevention and management of osteoporotic fragility fractures is increasing over time. In this review, we discuss in detail the epidemiology of fragility fractures, how this is shaped by pharmacological interventions and how novel screening programmes can reduce the clinical and economic burden of osteoporotic fractures.

Sources of data—PubMed and Google Scholar were searched using various combinations of the keywords ‘osteoporosis’, ‘epidemiology’, ‘fracture’, ‘screening’ ‘FRAX, and ‘SCOOP’.

Areas of agreement—The economic burden of osteoporosis-related fracture is significant, costing approximately $17.9 billion and £4 billion per annum in the USA and UK.

Areas of controversy—Risk calculators such as the web-based FRAX® algorithm have enabled assessment of an individual’s fracture risk using clinical risk factors, with only partial consideration of BMD.

Growing points—As with all new interventions, we await results of long-term use of osteoporosis screening algorithms and how these can be refined and incorporated into clinical practice.

Areas timely for developing research—Despite advances in osteoporosis screening, a minority of men and women at high fracture risk worldwide receive treatment. The economic and societal burden caused by osteoporosis is a clear motivation for improving the screening and management of osteoporosis worldwide.

Keywords

Osteoporosis; epidemiology; fracture

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Introduction

Osteoporosis is a disease of the skeleton, characterised by micro-architectural deterioration of bone tissue and loss of bone mass. Osteoporosis (meaning 'porous bone') increases bone fragility and susceptibility to fracture [1]. However, due to significant advances in osteoporosis management over the last 50 years – including widespread availability of various effective pharmacological therapies – it is no longer considered an inevitable consequence of ageing. Clinical diagnosis of osteoporosis is challenging: fracture-based criteria may exclude populations-at-risk who would benefit from treatment, whilst the original 1994 World Health Organisation definition by bone mineral density (BMD) alone (2.5 standard deviations below the young adult female mean) may not take account of other risk factors[2]. More recently, risk calculators such as the web-based FRAX® algorithm[3] have enabled assessment of an individual's fracture risk using clinical risk factors such as age and alcohol consumption, with only partial consideration of BMD. The economic burden of osteoporosis-related fracture is significant, costing approximately $17.9 billion and £4 billion per annum in the USA and UK, respectively (Table 1 summarises fracture impact across the European Union) [45].

Methods

The data sources used for this review were all from published literature. PubMed and Google Scholar were searched using various combinations of the keywords 'osteoporosis', 'epidemiology', 'fracture', 'screening' 'FRAX, and 'SCOOP'.

Fracture Epidemiology

According to a report by the US Surgeon General [4], approximately 10 million Americans over the age of 50 have osteoporosis, with a further 34 million at risk of the disease. Osteoporotic fractures in the USA are extremely common, with an estimated 1.5 million suffering fragility fractures each year. A similar burden of disease has been observed in the UK, with epidemiological studies hypothesising that one in two women and one in five men aged over 50 years will suffer an osteoporotic fracture in their lifetime [6]. Bone mass is an established determinant of bone strength, and the bone mass of an individual in later life depends upon peak skeletal growth attained during the fourth decade and the subsequent rate of bone loss thereafter [7]. Logically, fracture risk should be highest when bone mass (and therefore bone strength) is lowest; indeed, fracture incidence by age has a bimodal distribution, with peaks in the young and the elderly [8]. In the young, fractures occur more frequently in males, whereas from the age of 50 years onwards, fractures in females predominate and the rates become approximately twice those in men. Long bone fractures, as a result of substantial trauma, are the most common type of fracture seen in the young. However, studies suggest that (in addition to the extent of trauma) bone mass is nonetheless a relevant and important risk factor for fracture in this demographic [9]. In older individuals, the forearm, hip and vertebrae are the sites most susceptible to fracture [10].

Hip Fracture

In 1990, the number of hip fractures worldwide was estimated to be 1.66 million [11], comprising around 1.19 million in women and 463,000 in men. Approximately 90% of these fractures occurred in individuals aged over 50 years, predominantly as the result of falls from standing height [12]. In most populations, there is typically an exponential increase in the incidence of hip fracture with advancing age; above 50 years, hip fractures in women outnumber those in men with a ratio of two to one [8]. With an ageing population the socioeconomic burden of hip fracture is likely to increase. In the UK around 79,000 individuals suffer hip fractures each year, with a cost in 2010 estimated at £3.5 billion projected to rise to £5.5 billion per year by 2025 [5]. In temperate climates, the number of hip fractures varies by season, with an increase in incidence during winter months. As a high proportion of these occur indoors, the cause is likely multifactorial and not simply due to slipping on icy surfaces. Factors such as fewer winter daylight hours and slowed neuromuscular reflexes may be relevant. Furthermore, the direction of fall is an important consideration, as falling sideways –resulting in a direct impact on the hip– is more likely to result in fracture than falling forwards [12].

The mortality burden of hip fracture is significant, with a rate of approximately 8% in men and 3% in women aged above 50 years and hospitalised following fracture. In the USA, approximately 31,000 annual deaths occur within 6 months of hip fracture. In the UK, observed 12-month survival rates post- hip fracture are significantly lower than expected (63.3% observed vs. 90.0% expected for men, and 74.9% observed vs. 91.1% expected for women) [6]. Co-existing illnesses and poor pre-fracture functional status are key determinants of post-fracture mortality risk, which is greatest immediately post-fracture, gradually decreasing over time [13]. Note, however, that an elevated risk of death has been shown to persist for up to 10 years post-fracture [14]. Death following hip fracture is not solely attributable to the fracture itself; instead, prior exacerbation of other chronic comorbidities has likely contributed to reduced life expectancy and indeed, to occurrence of the hip fracture. Of all fracture types, hip fractures are associated with the highest levels of morbidity. Post-fracture complications such as bronchopneumonia, urinary tract infections and pressure sores are common. Furthermore, approximately half of those individuals who were ambulatory prior to hip fracture are unable to mobilise independently post-fracture. Notably, 55% of individuals above 90 years of age are unable to live independently following fracture and are subsequently discharged to nursing homes [15].

Vertebral Fracture

Age-standardised prevalence of vertebral fracture across Europe has been estimated to be 12.2% for men and 12.0% for women aged 50-79 years, according to data from the European Vertebral Osteoporosis Study (EVOS) [16]. More recently, a UK study using GP records demonstrated an incidence rate for vertebral fracture of 7.1 per 10,000 person years in adults aged over 50 (4.6 for men, 9.4 for women) [8]. For both sexes, vertebral fracture prevalence increases with age, ranging from 3% in female participants below 60 years (7.5% in men) to 19% in female participants over 70 years (20% in men) according to data from the Norwegian Tromso Study [17]. The majority of vertebral deformities in men occur at

younger ages, likely as a result of trauma. In elderly women, vertebral fractures usually occur due to normal activities such as lifting and bending over, as opposed to direct trauma from falling. Note that the prevalence of vertebral fracture may be underestimated as many such fractures are asymptomatic and therefore individuals do not seek medical attention. Vertebral fractures are associated with significant morbidity including back pain, kyphosis and height loss. This results in a marked reduction in quality of life as assessed by quality of life scores, which decrease as the number of vertebral fractures increases [18]. In contrast to hip fractures, the risk of death following a vertebral fracture increases with time post-fracture. Data from the UK GPRD study showed that observed survival 12-months post-vertebral fracture in women was 86.5% vs 93.6% expected. At 5 years, survival was 56.5% observed and 69.9% expected [6]. Like hip fractures, co-morbid conditions contribute significantly towards the risk of mortality post- vertebral fracture [14].

Distal forearm fracture

There is a gradual increase in rate of distal forearm fracture with advancing age, with occurrence higher in women than men at older ages. The incidence of distal forearm fracture has been shown to be 39.7 per 10,000 person-years in women and 8.9 per 10,000 person-years in men in the UK for individuals aged 50 years or greater [8]. In contrast to both hip and vertebral fractures, distal forearm fractures do not appear to be associated with an increase in mortality [6]. Distal forearm fractures also appear to have a lesser impact on activities of daily living, with few patients reporting loss of independence post-fracture. That said, approximately half of individuals report only fair- to poor- function six months post-fracture [8].

Clustering of Fractures in Individuals

There are data to suggest that if an individual suffers a fragility fracture, their risk of subsequent fracture at a different site increases. A meta-analysis conducted by Kanis and colleagues, using a population of 11 cohorts, showed that prior fracture history was associated with an 86% increase in the risk of further fracture at any new site [19]. Furthermore, data from EVOS has shown that vertebral deformity has a high predictive value for future hip fracture [20] with the risk being highest immediately post- index fracture [21].

Effect of co-morbidities on osteoporosis risk

There is a well-established association between co-morbid disease and osteoporosis risk. Indeed, the FRAX algorithm asks the investigator to provide information on the presence of rheumatoid arthritis (RA), and to consider whether a number of conditions associated with “secondary osteoporosis” are present. Examples given include inflammatory bowel disease, insulin-dependent diabetes, and diseases associated with reduced mobility, such as stroke and Parkinson's disease [22]. A study using participants from the Global Longitudinal Study of Osteoporosis in Women (GLOW) has demonstrated that hypertension, heart disease, asthma, chronic obstructive pulmonary disease (COPD), arthritis (reported osteoarthritis or RA), stroke, inflammatory bowel disease, Parkinson's disease, multiple sclerosis, and type I

diabetes were all associated with an increased fracture risk [23]. Additionally, a recent study comprising just under 20,000 adults in Germany demonstrated that 95% of the adults with osteoporosis had at least one coexisting disease, and that the odds for arthrosis, arthritis, chronic low back pain, depression and chronic heart failure, were greater for adults with osteoporosis [24]. The reason for the increased propensity for individuals with co-morbid diseases to develop osteoporosis is likely multifactorial. Co-morbidities such as RA and Crohn's disease are inflammatory conditions and studies have shown that pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 are associated with bone resorption [25, 26]. Furthermore, several epidemiological studies have shown negative correlations between BMD and C-reactive protein (CRP) which is a marker of active inflammation [27–32]. Additionally, bone loss in conditions such as RA, osteoarthritis, stroke and multiple sclerosis is contributed to by the decline in functional capacity and lack of exercise associated with these conditions [33].

Fracture trends over time

Worldwide, the proportion of individuals living to older age is increasing rapidly, with the United Nations predicting that by 2050 all major areas of the world, with the exception of Africa, will have approximately a quarter of their populations aged above 60 years [35]. This ageing population demographic will likely have a significant impact on the number of hip fractures, with a conservative estimate being an increase from 1.66 million in 1990 to 6.26 million in 2050 [11, 36]. The number of individuals at high fracture risk worldwide is also projected to increase, the largest relative increases predicted for Africa (Figure 1). Worldwide, the incidence of age- and sex-specific vertebral, forearm and hip fractures is continuing to increase [5, 37]. Conversely, the incidence of hip fracture in developed countries has stabilised over the last one to two decades (Figure 2), but is still rising in transitioning populations, likely secondary to the adoption of Westernised lifestyles [37]. The reason for the stabilisation and often reduction in hip fracture incidence in developed countries is likely multifactorial. For example, the introduction of bisphosphonates in North America and Europe, the increasing prevalence of obesity in the general population and incidence and alterations in tobacco consumption might also have contributed [37].

Geography

Fracture incidence varies widely by geography, ethnicity and socioeconomic status [38]. This has been demonstrated to be the case both internationally [39] and within individual countries [8]. A threefold difference in the incidence of vertebral fracture between countries was demonstrated in the EVOS study, with Scandinavian countries having the highest rates, although some of these differences may be accounted for by differences in body mass index (BMI) and levels of physical activity [16]. Geographical differences in hip fracture incidence are even more profound: an approximately 11-fold variation was demonstrated within Europe, which could not be accounted for by differences in activity levels, smoking, obesity, alcohol consumption, or migration status [40].

The explanation for global variation in fracture incidence is likely multifaceted, with ethnic differences in BMD, bone geometry and bone micro-architecture thought to contribute to

these differences [8]. Furthermore, as fracture incidence is typically higher in countries with a more northerly latitude (Figure 3), vitamin D status may be implicated [41].

Early life Influences on Adult Bone Health

Osteoporosis is one of a number of diseases (including hypertension, coronary heart disease, osteoarthritis and type 2 diabetes) where low birth weight is a precursor to disease development in adulthood [42]. Although variation in adult bone mass is largely attributable to genotype, evidence is accruing that interactions between genome and environment (during the intra-uterine period and early childhood) are critical for setting growth trajectory, and therefore bone mass and fracture risk in later life [42]. This phenomenon has been termed 'programming'. The link between development of osteoporosis and weight in infancy was first demonstrated in a study of 153 women born in Bath (UK) between 1968 and 1969 who were then traced and studied at 21 years of age [43]. In this study, data detailing childhood growth was obtained from linked birth and school records, and associations were found between bone mineral content (BMC) at the lumbar spine and femoral neck, and weight at one year. Furthermore, these relationships were independent of adult weight and BMI. The association between an individual's weight in infancy and their bone mass in adulthood was again observed in the UK Hertfordshire Cohort Study [44]. Following this, associations between birth weight, or weight at one year, and BMC in later-life have been confirmed internationally across a range of studies, and summarised in a systematic review and meta-analysis [44]. Recent findings suggest that an important early determinant of skeletal development is maternal 25(OH)-vitamin D status. The Maternal Vitamin D Osteoporosis Study (MAVIDOS) was a multicentre, double-blinded, randomised, placebo-controlled trial that recruited pregnant women from three study sites in the UK (Southampton, Oxford, and Sheffield). The findings from MAVIDOS suggest that maternal vitamin D supplementation was associated with greater bone mass at birth in babies delivered in the winter months [45]. Epigenetic studies have demonstrated that sites within the retinoid X-receptor-A (RXRA) gene (important for the action of $1,25(OH)_2$-vitamin D and other nuclear hormones) are associated with both maternal free 25(OH)-vitamin D status and offspring bone mass [46]. Maternal vitamin D supplementation in the MAVIDOS trial was associated with reduced methylation at the RXRA locus in offspring umbilical cord tissue in comparison with placebo [47].

Pharmacological Interventions for Osteoporosis

Over the past half-century, there have been rapid and marked advancements in pharmacological interventions for osteoporosis. These include calcium and vitamin D supplementation, hormonal replacement therapy, and bisphosphonates [5]. Studies have shown that these interventions are effective at reducing the incidence of osteoporotic fragility fracture [48–50]. The drugs most commonly used in the treatment of osteoporosis are in the bisphosphonate (formerly diphosphonates) class, which have been shown to reduce all fractures by 35%, vertebral fractures by 50% and non-vertebral fractures by 25% [49, 51]. The human monoclonal antibody denosumab, which targets RANKL (receptor activator of NFκB ligand), was shown to reduce the risk of new radiographic vertebral fractures by 68% and hip fractures by 40% in the original 36-month FREEDOM trial [52]. Extension of the

FREEDOM trial has subsequently found that this reduction in fracture risk is sustained for at least 10 years of denosumab treatment [53]. A more recent medication called teriparatide, a parathyroid hormone analogue which promotes bone formation, has been shown in clinical trials to be extremely efficacious in reducing fracture risk. For example, Kendler and colleagues showed in a multicentre, double-blinded, double-dummy, randomised controlled trial that teriparatide was more effective than risedronate, with a reduction in the risk of vertebral fractures by 64% and pooled clinical fractures by 52% over a two-year treatment period [54]. The anti-sclerostin antibody romosozumab was approved for medical use in the United States and Canada in 2019. Romosozumab is a humanized monoclonal antibody which blocks sclerostin from inhibiting osteoblast maturation and function. Phase III clinical trials have demonstrated romosozumab's ability to increase BMD at the lumbar spine and hip and reduce the risk of vertebral and clinical fractures [55]. However, as blocking sclerostin leads to Wnt (wingless/integrated) activation and therefore participation in the cardiovascular remodelling process, use of romosozumab may potentially lead to adverse cardiovascular events [56]. Indeed, clinical trials have demonstrated an increased risk of serious cardiovascular events among patients that received romosozumab, which warrant further investigation [55]. Another new approach for the treatment of osteoporosis is the parathyroid hormone–related peptide analog abaloparatide, which was approved to treat postmenopausal osteoporosis in the United States in 2017. The ACTIVE (Abaloparatide Comparator Trial in Vertebral Endpoints) trial showed that treatment with abaloparatide (80 μg daily) for 18 months reduced new morphometric vertebral fractures (RR 0.14; $p < 0.001$), nonvertebral fractures (HR 0.57; $p = 0.049$), major osteoporotic fractures (HR 0.45; $p = 0.03$), and clinical fractures (RR 0.30; $p < 0.001$) compared to placebo [57].

The Osteoporosis Treatment Gap

Although treatment strategies for osteoporosis have been shown to be highly effective, there is evidence to suggest that only a minority of osteoporosis patients receive treatment, and therefore the personal and societal burden of fragility fractures remains high [5]. A recent report issued by the US National Osteoporosis Foundation estimated that 2 million Americans had 2.3 million osteoporotic fractures in 2015 with only 9% undergoing bone mineral density testing within 6 months of the fracture. In the first 2–3 years post fracture, a second fracture occurred in 307 000 of these individuals incurring a cost of in excess of $6·3 billion [58]. This untreated population of individuals with osteoporosis is referred to as 'The Osteoporosis Treatment Gap' and recent studies have sought to introduce interventions to reduce this. For example, fracture risk assessment tools (such as FRAX), which utilise clinical variables to provide a measure of fracture risk, have been developed to assist clinicians in identifying 'at risk' individuals [22]. There is, however, a wide variation in the use of fracture assessment tools worldwide (1000-fold) which may be a reflection of the lack of cohesion in local guidelines or difficulty in accessing the assessment tools online or in paper format[59]. Despite the introduction of fracture risk assessment tools, there has been a reduction in the number of 'at risk' individuals receiving treatment for osteoporosis in some developed countries including the UK and USA [60, 61]. This trend may reflect disproportionate highlighting in the lay-media of rare adverse events associated with bisphosphonate use, such as osteonecrosis of the jaw and atypical femoral fractures [62]. There

is, however, little evidence to suggest that the risk of these adverse events is significantly higher in individuals taking bisphosphonates for 10 years, compared to age-matched controls [63].

Osteoporosis screening programmes

To increase identification of individuals at risk of fracture, and therefore reduce the aforementioned osteoporosis treatment gap, robust screening programmes are required. The WHO recommends that individuals be identified as either at high, medium or low risk of fracture. Following this, they recommend that high-risk individuals be considered for treatment, low-risk individuals not be recommended for treatment and medium-risk individuals be further assessed with a measurement of BMD [64]. One of the first studies to examine the effectiveness of an osteoporosis screening programme recruited a total of 4,800 women aged 45-54 years in Aberdeen, Scotland, who were subsequently randomised in equal numbers to screening or no-screening (i.e. control) groups. Post-screening, those in the lowest quartile of BMD were advised to consider hormone replacement therapy. Nine years later, the effect of screening (on the uptake of treatment and fracture incidence) was assessed by postal questionnaire. They found a 25.9% reduction in risk of fracture (any site) in the screened group [65]. To identify older women with prevalent osteoporotic vertebral fractures, the Cohort for Skeletal Health in Bristol and Avon (COSHIBA) study –a randomized controlled trial of a primary-care–based screening program– was conducted. The trial comprised a total of 3,200 women aged 65 to 80 years from 15 general practices within Bristol in the UK. The major findings were that allocation to screening increased the prescription of osteoporosis medications by 124% and also reduced fracture incidence at 12-month follow-up, although this did not reach statistical significance (OR for new fracture 0.60; 95% CI, 0.35–1.03; p = 0.063) [66]. The Danish Risk Stratified Osteoporosis Study Evaluation (ROSE) study found no overall effect on fracture incidence of a screening programme, but in those individuals with a FRAX ≥15%, major osteoporotic fractures, hip fractures and all fractures were reduced[67]. More recently, the SCreening Of Older women for the Prevention of fractures (SCOOP) trial was established to test whether a community-based screening intervention could reduce fractures in older women. The SCOOP trial was an unblinded randomised controlled trial of women aged 70-85 years in the UK. It was based in seven centres in the UK (including Birmingham, Bristol, Manchester, Norwich, Sheffield, Southampton and York) from which a total of 12,483 participants were recruited [65]. Study participants were stratified into blocks according to age (70-74, 75-79, 80-85) and location of general practice. Participants were then either randomised into the control or screening arm of the study, with control arm participants receiving ‘usual care’, and the participants in the screening arm having their 10-year probability of fracture calculated using FRAX. If participants in the screening arm were assessed as having a moderate- or high-risk of fracture, a Dual-energy X-ray absorptiometry (DXA) scan was performed to calculate BMD. BMD was subsequently incorporated into the FRAX algorithm to inform primary-care treatment decisions. There was no significant difference between the two groups with respect to the proportion of individuals sustaining fragility fractures (p=0.178, HR 0.94 (0.85-1.03)), nor regarding the rate of all clinical fractures (p=0.83, HR 0.94 (0.86-1.03) (as shown in Table 2). There was, however, a reduction in the rate of hip fracture in the

screening arm (p=0.002, HR 0.72 (0.59-0.89) [68]. The absolute reduction in hip fracture risk was 0.9%, i.e. 111 women between the ages of 70-85 should be screened to avert a single hip fracture. Furthermore, osteoporosis medication use was significantly higher in participants in the treatment arm compared to the control arm (15% and 4% respectively) with 78% of participants in the treatment arm on anti-osteoporotic medication 6-months post-screening [68].

Conclusion

Osteoporosis and the resultant fragility fractures have a profound impact in terms of mortality and morbidity on individuals, healthcare systems and communities as a whole. Whilst there is some evidence that in Western countries fracture incidence rates are falling, the combination of an ageing population and the adoption of a Western lifestyle in developing countries is resulting in an increase in the burden of osteoporosis worldwide. In the past quarter-of-a-century, many risk factors for loss of bone mass (and therefore fracture) have been identified, and several effective pharmacologic therapies for osteoporosis have been introduced. Nevertheless, only a minority of individuals with osteoporosis are treated and therefore resources should be focused on the identification and treatment of those at highest fracture risk.

Biography

Biographical details:

Dr Michael A. Clynes (BSc (hons), MBchB, PhD, MRCP) is a Clinical Lecturer in Rheumatology. Research interests include the developmental origin of musculoskeletal diseases.

Prof. Nicholas C. Harvey (MA, MB, BChir, PhD, FRCP) is a Professor of Rheumatology and Clinical Epidemiology. His work incorporates a lifecourse approach towards the epidemiology and determinants of osteoporotic fracture.

Dr Elizabeth M. Curtis (MA, MB, BChir, PhD, MRCP) is a Clinical Lecturer in Rheumatology. Her research interests include the early life influences on musculoskeletal health, including maternal vitamin D and epigenetic mechanisms.

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Prof. Elaine M. Dennison (MA, MB BChir, MSc, PhD) is a Professor of Musculoskeletal Epidemiology. Her research interests include the epidemiology of musculoskeletal disease, particularly those conditions common in later life (osteoporosis and osteoarthritis).

Cyrus Cooper (OBE, DL, FMedSci) is Professor of Rheumatology and Director of the MRC Lifecourse Epidemiology Unit; Vice-Dean of Medicine at the University of Southampton; and Professor of Epidemiology at the Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford. Professor Cooper leads an

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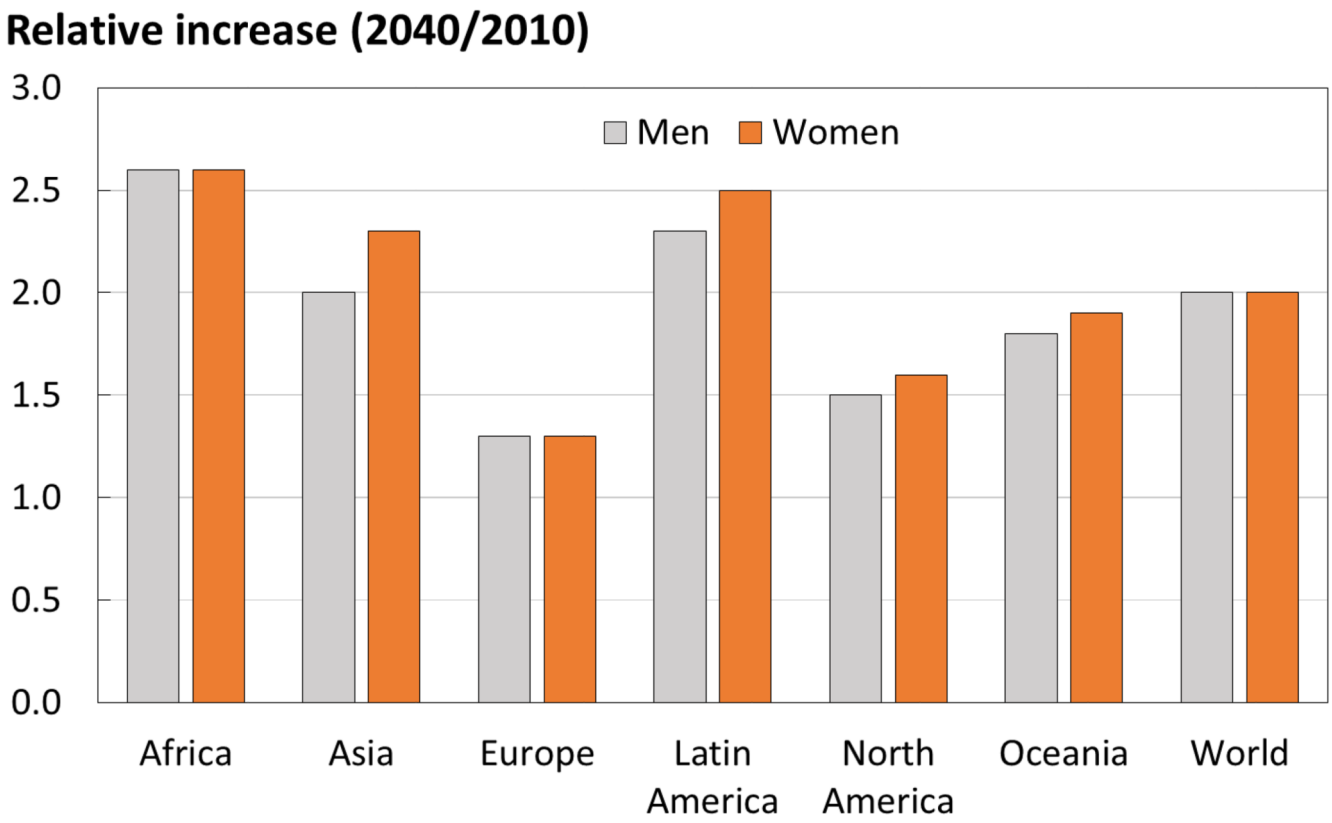

Figure 1. Number of men and women at high fracture risk in 2040 relative to 2010, by world region. (With permission from Oden et al, Osteoporosis International 2015 [34]).

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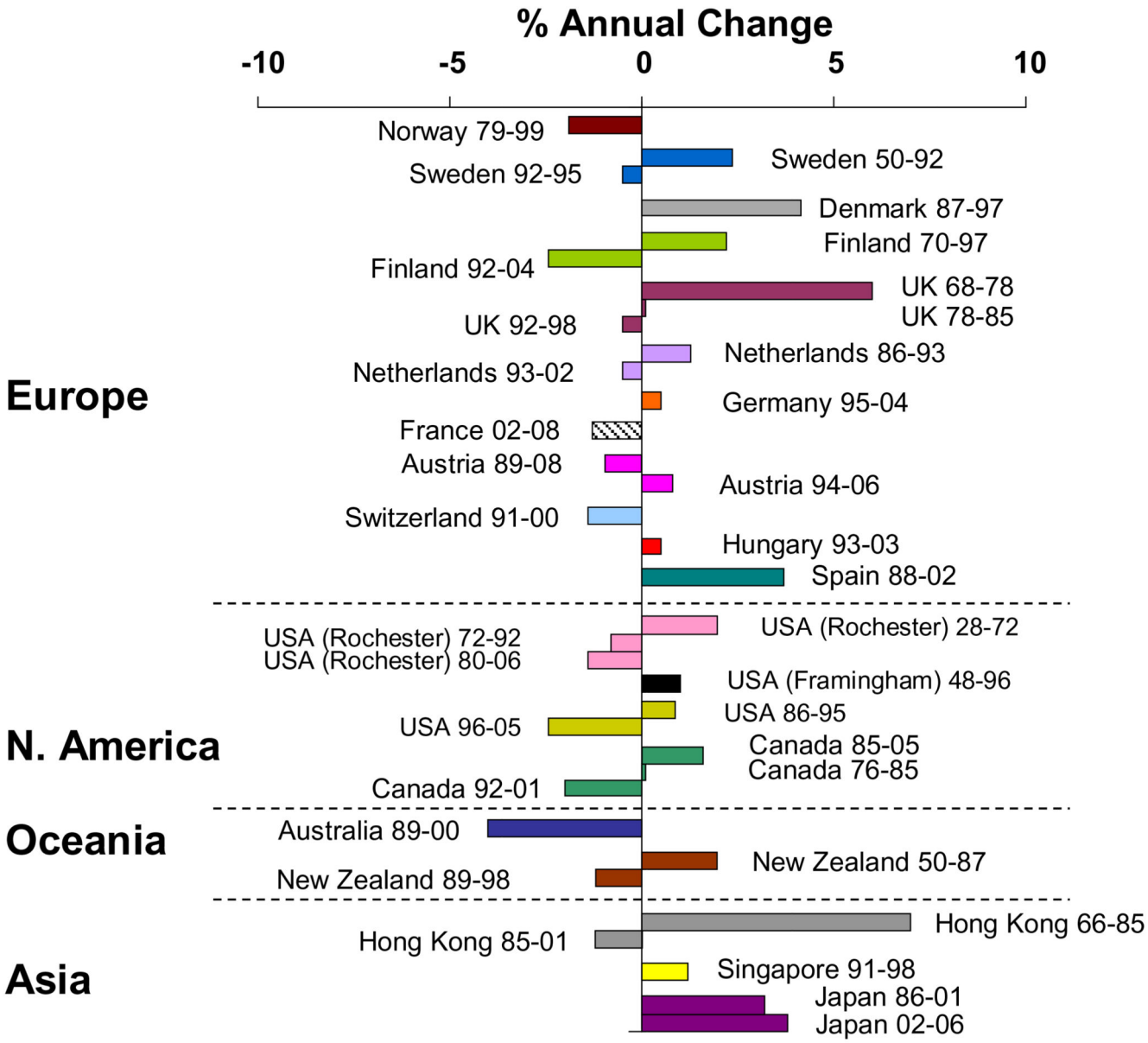

Figure 2. Trends in hip fracture worldwide over time: annual change in age- and sex-adjusted hip fracture incidence (Reproduced with permission from Cooper et al, Osteoporosis International 2011 [37])

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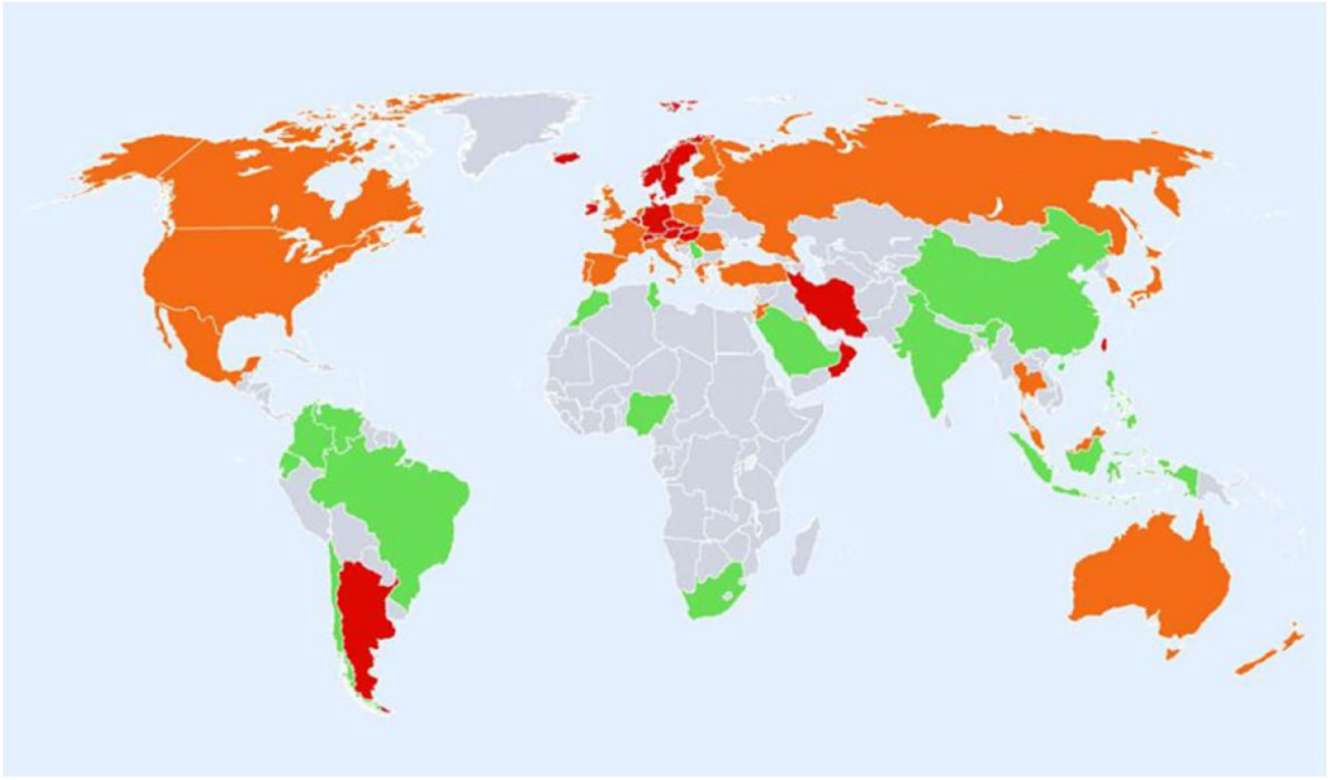

Figure 3. Hip fracture rates for men and women combined in different countries of the world, categorised by risk. Countries are coded red (annual incidence >250/100,000), orange (150-250/100,000) or green (<150/100,000) where estimates are available. (Reproduced with permission from Kanis et al, Osteoporosis International 2012 [39])

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Table 1

Impact of osteoporosis-related fractures across Europe. Data derived from Hernlund et al, Archives of Osteoporosis, 2013.

	Hip	Spine	Wrist
Lifetime risk in Women (%)	23	29	21
Lifetime risk in Men (%)	11	14	5
Cases / year	620,000	810,000	574,000
Hospitalization (%)	100	2-10	5
Relative survival	0.83	0.82	1.00
Costs: All sites combined ~ €37 billion			

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Table 2

Efficacy outcomes for the screening of older women for prevention of fracture (SCOOP) study (Shepstone et al., 2018).

	Control (n=6250)	*Screening (n=6233)*	*Hazard ratio (95% CI)*	*p value*
Osteoporosis-related				
No Fracture	5398 (86.4%)	5428 (87.1%)	-	-
Fracture	852 (13.6%)	805 (12.9%)	0.94 (0.85-1.03)	0.178
Hips				
No Fracture	6032 (96.5%)	6069 (97.4%)	-	-
Fracture	218 (3.5%)	164 (2.6%)	0.72 (0.59-0.89)	0.002
All clinical				
No Fracture	5248 (84.0%)	5282 (84.7%)	-	-
Fracture	1002 (16.0%)	951 (15.3%)	0.94 (0.86-1.03)	0.183
Mortality				
Survived	5725 (91.6%)	5683 (91.2%)	-	-
Died	525 (8.4%)	550 (8.8%)	1.05 (0.93-1.19)	0.436